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OBSERVATIONS ON DRUG METABOLISM AND LIVER DISEASE

DR. GORDON GRAHAM BIRNIE

M.B.Ch.B. M.R.C.P.

This thesis describes research carried out principally at the University Department of Medicine, Western Infirmary, Glasgow.

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Fortune telling is a game as old as mankind, now it has largely been taken over by our profession. The cards of the sooth-sayers have been replaced by the laboratory sheets, prophecies are called prognoses, but the coverting for knowledge about the future is the same, and the predictions still depend on the interpretation of omens.

N TYGSTRUP 1973

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A P P E N D I C E S

APPENDIX 1 The effect of drugs on antipyrine kinetics

APPENDIX 2 The effect of liver disease on the disposition of drugs

APPENDIX 3 The data for Chapter 10

Report 1 - Clinical details, standard biochemistry

Report 2 - Antipyrine kinetics, histology

Report 3 - Indocyanine green kinetics, drugs

APPENDIX 4 Methods of data collection

- APPLE IIE Microcomputer
    - DB Master database
        - Liver file
        - Reference extraction file
- ACT APRICOT Microcomputer
    - Comsoft delta database
        - Reference storage file
    - Pharmacokinetic programs in Apple and Apricot microcomputers

A B B R E V I A T I O N S

ALA	Aminolaevulinic acid
ALA-S	Aminolaevulinic acid synthetase
ALD	Alcohol related liver disease
ALT	Alanine aminotransferase
AP	Alkaline phosphatase
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
BSP	Bromosulphthalein
C	Plasma concentration
CAH	Chronic active hepatitis
ca	Arterial concentration
CFFT	Critical Flicker Fusion Time
cl	Clearance
cl(h)	Hepatic clearance
cl(int)	Intrinsic clearance
cl(int*)	Fractional intrinsic clearance
co	Concentration at time zero
CRT 1	Recognition Time
CRT 2	Total Reaction Time
cv	Venous concentration
D	Dose
E	Hepatic extraction ratio
E(true)	True hepatic extraction ratio
E(actual)	Actual hepatic extraction ratio
fb	Fraction of drug free in the plasma
fm	Fraction of portal blood flowing through functioning hepatic tissue

GGT	Gamma glutamyl transpeptidase
HPLC	High Pressure Liquid Chromatography
ICG	Indocyanine green.
K	Elimination rate constant
Km	Michaelis-Menton constant
KHZ	Kilohertz
LCAT	Lecethin:Cholesterol acetyl transferase
LD	Lactate dehydrogenase
LogN	Natural logarithms
Log 10	Logarithms to the base 10
mg	milligrams
ml	millilitres
nm	Nanometres
PBC	Primary biliary cirrhosis
PBG	Porphobilinogen
PBG-D	Porphobilinogen deaminase
PSI	Pounds per square inch
PT	Prothrombin time
Q	Total liver blood flow
R	Plasma disappearance rate
SD	Standard Deviation
SEM	Standard error of the mean
t	Time
t1/2	Half life
ul	Microlitres
vd	Apparent volume of distribution
vmax	Maximum rate of removal

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I HAF THREE FUNNY LEEDLE PEOPLE
VOT GOMES SCHUST TO MINE KNEE
DER QUEEREST SCHAP
DER GREATEST ROGUES
AS EFER YOU DIT SEE.

Adopted from Yawcob Strauss
By Charles Follen Adams (1842 - 1918)

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BIRNIE G.G., THOMPSON G.G., COOKE A., BRODIE M.J.
British Pharmacological Society, London, December 1986

8. Impaired drug metabolism in cardiac failure.
BIRNIE G.G., GOUDIE B.M., BRODIE M.J.
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SUMMARY

A summary of the experimental chapters is included at the start of each of these chapters, however for the ease of the reader these are also compiled in this summary. The aim of this thesis is to explore the relationship between hepatic drug metabolism and liver disease and in particular to determine if the parameters of drug elimination provide useful information as liver function tests.

The value of kinetic data as a screening test for liver disease is explored in chapter 9, using patients at risk of developing methotrexate induced liver disease. Standard biochemical liver function tests and the clearances of antipyrine and indocyanine green have been compared in psoriatic patients taking methotrexate, psoriatic patients on topical treatment, patient controls and patients with hepatic cirrhosis. The methotrexate-treated patients showed significant elevations in alkaline phosphatase ($p<0.025$) and gamma glutamyl transpeptidase activities ($p<0.05$) compared to topically treated psoriatics and patient controls. The clearance of antipyrine was reduced in the methotrexate treated group but not significantly ($0.1> p > 0.05$). In contradistinction, the weight-adjusted clearance of indocyanine green was significantly impaired in the methotrexate group in comparison with the topically treated psoriatics ($p < 0.01$). These data suggest that the serial measurement of alkaline phosphatase and indocyanine green clearance may provide a non-invasive indicator of the development and progression of methotrexate-related liver injury.

In chapter 11 the effect of betablockade on portal pressure is assessed. Antipyrine elimination was determined to assess the effect

of nadolol therapy on hepatic drug oxidation. Indocyanine green elimination was measured to see if it accurately reflected changes in portal pressure, thus possibly providing a non-invasive monitor of changes in the portal circulation. The effect of Nadolol 160mg/day on antipyrine and indocyanine green kinetics and wedged hepatic vein pressure was assessed in 6 patients with hepatic cirrhosis and portal hypertension. There was a significant reduction in wedged hepatic vein pressure during treatment with nadolol (Nadolol = 13.1 $\pm$ 3.6 mmHg: Placebo = 19.9 $\pm$ 5.6 mmHg). There were no significant alterations in the standard liver function tests, antipyrine or indocyanine green kinetics. These data show that Nadolol leads to a fall in portal pressure similar to that produced by propranolol. Nadolol is excreted by the kidney so that its elimination should be predictable even in patients with severely compromised liver function, which suggests that it may be a more suitable drug for use in these patients.

Two experiments were performed to assess the value of antipyrine and indocyanine green elimination in predicting the metabolism of other compounds. In chapter 12 the kinetic and psychomotor function were studied after an intravenous dose of 0.075 mg/kg of body weight of Midazolam. A total of 7 patients with alcoholic cirrhosis and 8 patient controls were studied. Four of the 7 cirrhotics died of complications of their liver disease within 6 months of completion of the study. The bioavailability of midazolam was significantly increased in the cirrhotic patients ($p< 0.025$). These patients also had evidence of greater sedation than the control group for up to 6 hours after the dose was administered ($p<0.05$). The clearance of midazolam did not correlate significantly with the serum albumin or

bilirubin or with the kinetics of antipyrine or indocyanine green. This study demonstrates significant delay in the elimination of midazolam and reduction in psychomotor function in patients with severe alcoholic liver disease. Caution should be exercised in using this drug for pre-medication in such patients prior to endoscopic examination.

In chapter 13 kinetic analysis was performed following single intravenous (25mg) and oral (200mg) doses of the novel partial opioid agonist meptazinol (Meptid) in patients with non-cirrhotic liver disease (NCLD) and biopsy-proven cirrhosis. Comparison was made with a group of patients with normal hepatic function. There was no significant alteration in the plasma clearance of the drug (cirrhotics = 83.5 $\pm$ 8.7 L/hr; NCLD = 98.4 $\pm$ 11 L/hr; control = 78.5 $\pm$ 7.3 L/hr). Following the oral dose, 7 out of 15 cirrhotic patients vomited but only 1 patient in each of the other groups was unable to tolerate the drug ($p = 0.06$). This may be explained by very much higher peak meptazinol concentrations in the cirrhotic (n=8; 184 $\pm$ 37ng/ml, $p<0.01$) and NCLD (n=8; 131 $\pm$ 38ng/ml, $p<0.05$) patients than those of the controls (n=7; 53$\pm$ 12ng/ml) reflecting a mean four fold and two fold increase in oral bioavailability respectively (cirrhotics: n=8; 27.9 $\pm$ 5.3%: $p< 0.001$; NCLD: n=7; 13.7 $\pm$3.9%: $p<0.05$; controls: n=7; 6.5 $\pm$ 1.3%). There was no evidence of accumulation following chronic dosing with 200mg meptazinol four times daily for 13 doses in 7 control, 7 NCLD and 6 cirrhotic patients as would be predicted by the lack of change in drug clearance. There was no correlation between the elimination of midazolam and the elimination of either antipyrine or indocyanine green. There were no detectable differences in psychomotor function measured objectively

using the Leeds Psychomotor Tester or subjectively by linear analogue scoring between the groups in all three parts of the study. This study shows that the use of meptazinol in cirrhotic patients is likely to be limited by gastrointestinal intolerance rather that excessive sedation. These two studies provide further evidence that there is little value in the use of probe drugs to predict the elimination of other molecules in a disease state.

In chapter 8 the kinetics of antipyrine elimination were measured in patients with porphyria in attack and remission and a control group. The clearance of antipyrine was significantly lower in patients with acute attacks of porphyria compared to the other two groups (In attack = 0.37 $\pm$ 0.06 ml/min/kg: In remission = 0.55 $\pm$ 0.17 ml/min/kg: controls = 0.63 $\pm$ 0.18 ml/min/kg: $P < 0.02$). There were no significant correlations between the indices of porphyria metabolism and the measurements of antipyrine kinetics. These data show that the elimination of Antipyrine is reduced in acute attacks of porphyria, indicating that there is a reduction in the functional capacity of cytochrome P450 in these patients. The total lack of any correlation between antipyrine kinetics and the markers of porphyrin metabolism suggest that these changes occur as a result of haem deficiency rather than a functional inhibition of the enzyme system.

The disposition of antipyrine and indocyanine green was studied in 11 patients with congestive cardiac failure (CCF) before and after treatment and 32 control patients (chapter 14). The antipyrine distribution was not significantly altered in patients with CCF. The indocyanine green half life was significantly prolonged in patients with CCF (CCF = 10.0 $\pm$ 8.0 min; Control = 4.2 $\pm$ 1.1 mins: $p < 0.01$). The indocyanine green disposition was not significantly altered in a

further 12 patients with valvular heart disease but without evidence of CCF. There was a close correlation between the ICG half life and the clinical assessment ($r = 0.99$; $p < 0.001$). In the 12 patients without CCF there was no correlation between cardiac pressure measurements and the disposition of antipyrine or indocyanine green. This study suggests that changes in liver blood flow may be an important determinant of the changes in drug metabolism seen in patients with CCF.

In chapter 10 the relative value of standard liver function tests, antipyrine and indocyanine green elimination in the assessment of the natural history of chronic liver disease. One hundred and sixteen patients with chronic liver disease were studied. When the patients were divided by diagnostic groups there were similar changes in the standard liver function tests and kinetic parameters in all the groups. The only exception was that patients with primary biliary cirrhosis had a marked reduction in the volume of distribution of antipyrine (controls = 36.3 ± 13.7 l; PBC = 25.4 ± 7.3 l : $p<0.005$). This suggests that these patients have a reduced total body water, which may be a consequence of the hyperlipidaemia seen in this condition. The patients were divided into those with and without the major complications of liver disease - Encephalopathy, ascites and portal hypertension. A reduction in antipyrine clearance of 2, 16 and 14% respectively was found in the patients with these complications. The reductions in indocyanine green clearance were much greater at 44, 48 and 37% respectively. The antipyrine clearance was reduced by 26% in patients with biopsy proven active cirrhosis compared to a reduction of 50% in the indocyanine green clearance. The non-survivors had a 3% reduction in antipyrine clearance, and a 75%

reduction in indocyanine green clearance.

When these data was analysed by multiple regression and Cox's proportional hazard model, the most powerfull of the kinetic parameters was the indocyanine green half-life. When this was included with the patients age in the model all the other biochemical, histological and kinetic data became redundant. These data show that indocyanine green elimination provides important information regarding the severity of liver disease. The greater magnitude of change seen with indocyanine green compared to antipyrine suggests that an important determinant of the complications and survival in liver disease is the functional liver blood flow rather than the hepatic metabolic capacity.

CHAPTER 1

INTRODUCTION AND AIMS

The liver is a highly complex organ which fulfils many different functions. One of these is the biotransformation and elimination of of lipid soluble molecules including many drugs. The relationship between the liver and drug metabolism is complex but is of major clinical importance.

Patients who have liver disease require medication either as treatment for their liver disease or for the treatment of unrelated symptoms and diseases. The response of patients with impaired liver function can be unpredictable. Some patients will be unduly sensitive to sedatives and may become consciousness or suffer from respiratory depression as a result of the administration of standard doses of these drugs. Some patients may be unresponsive to some medications because they have lost the ability to transform these drugs into their active metabolites. It would be clinically useful to be able to detect the patients with liver disease who have an altered capacity to metabolise drugs so that appropriate drugs can be selected for them and the dose of these drugs tailored to the patients own capacity to metabolise them.

The altered drug metabolising capacity which occurs in liver disease may provide important diagnostic information. There are over 50 primary diseases of the liver, and the liver can be secondarily involved in a number of other disease processes. In an attempt to differentiate these diseases hundreds of biochemical tests of varying complexity have been designed. A few of the diseases can be detected and characterised by simple non-invasive tests but for the majority dangerous and invasive liver biopsies are still required. The various forms of liver disease involve different cells and organelles within the liver. Similarly various drugs are primarily metabolised

and excreted by different hepatic structures. It is possible that specific patterns of altered drug metabolism may occur in different liver diseases. So that be chosing specific probe drugs in may be possible to produce a profile of the liver function which may be of diagnostic importance.

Alterations in hepatic drug metabolism may also provide important prognostic information. There is no generally accepted measurement of the severity of liver disease. Advances in the treatment of liver disease has been limited by the lack of objective and repeatable measurements of the severity of liver disease. Alterations in mortality rates have been the major measurement of therapeutic efficacy (CONN & LINDENMUTH 1969, COOK et al 1971). One of the problems in devising a standard liver function test is that there are so many different functions and pathological processes which occur in the liver. Many of these functions and processes impinge on the metabolism of drugs and it may be that measurements of the rate of elimination of some drugs may yield important prognostic information.

The principal aim of the thesis is to explore the relationship between liver disease and the metabolism of drugs. The specific aims are :

1. To review the literature pertaining to drug metabolism and liver function to -
   a) Determine the current value of liver function tests.
   b) To compile a database of information on the alterations in drug metabolism which occur in different disease states.

2. To determine the value in measuring the kinetic parameters of the metabolism of different drugs in -

a) Detecting subclinical liver disease

b) Monitoring alterations in liver function

c) Predicting the natural history of liver disease

d) Predicting the metabolism of other compounds

e) Predicting hepatic histology

C H A P T E R 2

NORMAL LIVER FUNCTION AND THE FUNCTIONAL EFFECTS OF LIVER DISEASE.

2.1 INTRODUCTION

The liver has more functions than any other single organ in the human body, the major functions of the liver are shown in Table 2.1. The extent to which any of the functions becomes disturbed in liver disease depends on the nature of the disease and its severity. These functional variations are important for two reasons. Firstly, the majority of the signs and symptoms of liver disease result from these changes rather than the underlying disease process. Secondly, these changes can be used to produce important diagnostic and prognostic information. Before assessing the value of drug disposition as a test of liver function, the current understanding of the functions of the liver and the functional effects of liver disease will be reviewed.

2.2 METABOLIC FUNCTIONS

2.2.1 Protein

Albumin

The average human body contains about 300 grams of albumin of which 40% is within the intravascular compartment. The normal liver produces 10-12 grams of albumin per day which constitutes about 25% of the total daily hepatic synthesis of protein. The turnover of albumin is slow with a serum half-life of 20 days.

Hypoproteinaemia is a common feature of chronic liver disease. Many factors contribute to its aetiology including

TABLE 2.1 FUNCTIONS OF THE LIVER

1. METABOLIC FUNCTIONS

PROTEIN METABOLISM
- Albumin synthesis
- Globulin synthesis
- Coagulation factor synthesis (11,V,VII,IX,X)
- Amino Acid turnover
- Urea synthesis
- Ammonia synthesis and clearance

CARBOHYDRATE METABOLISM
- Glycogen storage
- Glycogenolysis
- Galactose metabolism
- Fructose metabolism
- Alcohol metabolism
- Gluconeogenesis
- Lactose clearance

LIPID METABOLISM
- Ketogenesis
- Fatty acid turnover
- Triglyceride metabolism
- Lipoprotein production
- Cholesterol synthesis
- Phospholipid metabolism

2. STORAGE FUNCTION
- Vitamin B 12, Iron, Fat, Glycogen

3. HORMONE METABOLISM
- Sex Hormone Metabolism
- Inactivation of Adrenocortical hormones
- Inactivation of Antidiuretic hormone
- Conversion of T4 to T3
- Catabolism of insulin
- Catabolism of growth hormone
- Catabolism of glucagon

3. EXCRETORY FUNCTION
- Bilirubin/Nitrogenous waste products

4. DIGESTIVE FUNCTION
- Bile acid production

5. IMMUNOLOGICAL FUNCTION
- Kupffer cell function/Complement metabolism

6. HAEMATOLOGICAL FUNCTION
- Haemopoesis in the neonate

7. BIOTRANSFORMATION OF DRUGS

decreased synthesis, portosystemic shunting (ZIMMON et al 1969), nutritional deficiency and alterations in the intravascular/ extravascular distribution. Not all these mechanisms may operate in an individual patient and in alcoholic cirrhotics with hypoalbuminaemia the rate of albumin synthesis may even be normal (ROTHSCHILD et al 1969, ROTHSCHILD et al 1970). There is evidence of a compensatory prolongation of the half life of albumin in liver disease (DYKES 1968, STERLING 1951, WILKINSON and MENDENHALL 1963). The serum albumin levels can be increased in chronic liver by the administration of corticosteroids (CAIN et al 1970) suggesting that the depression of albumin may be due, at least partly, to a change in the regulation of production rather than finite changes in the hepatic synthetic capacity.

Globulins

The liver is the site of synthesis of the alpha 1 globulins of which alpha 1 antitrypsin is quantitatively the most important. Deficiency of this protease results in the early occurrence of pulmonary emphysema and is associated with chronic liver disease (SHARP 1976).

Caeruloplasmin is another alpha 1 globulin which is associated with a specific form of liver disease. It is reduced in patients with Wilson's disease, which allows copper to accumulate in the tissues, resulting in damage to the liver and the central nervous system.

Beta globulins synthesised in the liver include transferrin,

haemopexin, some components of complement, plasminogen and fibrinogen. The liver is the only site of fibrinogen production. In mild liver disease the serum level is either normal or slightly elevated (WARDLE 1974). However in severe hepatocellular disease the serum level may fall as low as 1.5 umol/l (RATNOFF 1982). Changes in the Beta globulins are seen in liver disease with increases in viral hepatitis, extrahepatic biliary obstruction and Primary Biliary Cirrhosis (HOBBS 1967).

The alpha lipoproteins are also synthesised in the liver and have a short half life of four days, and reductions in serum levels have been demonstrated in acute viral hepatitis (McINTYRE and HEATHCOTE 1974).

Coagulation factors

All the coagulation factors except for factor VIII are synthesised within the liver. They have short half lives varying from four days for fibrinogen to 2 hours for factor VII.

Following absorption from the gut vitamin K is utilised in the liver in the synthesis of Prothrombin (factor II), factor VII, Stuart factor (IX) and Christmas factor (X). Deficiencies of these factors lead to abnormalities in the intrinsic and extrinsic pathways of coagulation, resulting in prolongations of prothrombin time and the cephalin or partial thromboplastin time. In obstructive jaundice there are reduced levels of these factors because reduction in the delivery of bile salts to the gut results in the malabsorption of vitamin K. The resulting bleeding tendency is responsive to the parenteral administration

of vitamin K. In parenchymal liver disease deficiency of these factors may result from reduced hepatic protein synthesis.

Factor VIII is probably not produced within the liver and elevated levels have been found in acute viral hepatitis (GAZZARD et al 1975), alcoholic cirrhosis (GREEN and RATNOFF 1974) and non alcoholic cirrhosis (OUTRYVE et al 1973). Factor V is synthesised within the liver but it is not dependent on vitamin K and reduced factor V levels are unusual in uncomplicated obstructive jaundice (CEDERBLAD et al 1976) and so theoretically it should be of value in differentiating clotting abnormalities due to hepatocellular failure from those due to vitamin K deficiency. Factor XIII is reduced in hepatocellular disease but not in obstructive jaundice (WALLS and LOSOWSKY 1971).

Abnormal platelet function also occurs in acute liver failure (RUBIN et al 1977) and cirrhosis (THOMAS et al 1967).

Aminoacids

The liver is the major site of amino acid metabolism. Amino acids are broken down within the liver to form components of the carbohydrate and lipid metabolic pathways. Both transamination and deamination lead to the formation of ketoacids and ammonia, glutamate, or glutamine. The ketoacids are metabolised by the Krebs citric acid cycle and ammonia is converted to urea by the Krebs urea cycle. About 85% of human nitrogen excretion is in the form of urea excretion through the kidney. Removal of about 90% of the functioning hepatic mass is required before there are

significant alterations in amino acid metabolism. In both acute and chronic liver disease there is a failure of urea synthesis (SHAMBAUGH 1978). The maximal rate of urea synthesis is reduced in cirrhotic patients from 4.46 mmol (65mg) urea N/hr/kg to 1.93mmol (27mg) urea N/hr/kg. There is a resulting fall in serum urea and a concomitant increase in serum ammonia levels (ROSOFF and ROSOFF 1977). Liver failure is also associated with an accumulation of the straight chain aminoacids with a decrease in the branch chain amino acids (Leucine, Isoleucine, and Valine).

2.2.2 Carbohydrates

One of the major roles of the liver is the maintenance of glucose homeostasis. The liver is responsible for disposing of ingested carbohydrate particularly glucose and fructose. It has the capacity to store glucose as glycogen and lipid, and to create new glucose from glycogen, lipid, aminoacids and glycerol. The normal liver can store 80-100g of glycogen.

Glucose intolerance is common in chronic liver disease (ALBERTI & JOHNSON 1986) although the mechanisms by which it occurs are not well understood. Some of the possible mechanisms are shown in Table 2.2. Impaired insulin production can occur in some forms of liver disease e.g. chronic active hepatitis (ALBERTI et al 1972) and haemochromatosis, but hyperinsulinaemia is more common in most forms of liver disease (CONN and DAUGHADAY 1970; SESTOFT and REHFIELD 1970; FELIG et al 1970). The hyperinsulinaemia is due to defective hepatic clearance of insulin (JOHNSON et al 1977) which results either from parenchymal liver

cell failure or portosystemic shunting (JOHNSON et al 1978). The direct shunting of glucose from the portal circulation into the systemic circulation occurs in liver disease but is probably not quantitatively important because under normal circumstances only about 8% of glucose is extracted on the first pass through the liver (RADZIUK et al 1978).

TABLE 2.2

THE POSSIBLE MECHANISMS OF GLUCOSE INTOLERANCE IN LIVER DISEASE

1. GENERAL FACTORS

   Nutritional deficiency
   Potassium deficiency

2. HEPATIC FACTORS

   Decreased parenchymal mass
   Portosystemic shunting
   Decreased glycogen synthetic capacity
   Impaired action of insulin
   Increased glucagon secretion
   Increased cortisol secretion
   Increased growth hormone secretion
   Haemosiderosis
   Hypoinsulinaemia

3. EXTRAHEPATIC FACTORS

   Peripheral insulin resistance
   Increased non esterified fatty acids
   Circulating antagonists

(After ALBERTI and JOHNSTON 1986)

The impaired ability to synthesise and store glycogen remains a likely cause of carbohydrate intolerance. This may be related to to reduced insulin sensitivity due to either damaged insulin receptors or increased levels of hormones which antagonise insulin (COLLINS et al 1970). Peripheral insulin resistance occurs in alcoholic cirrhotics (HED et al 1977). It is possible that other defects of the action of insulin exist at the receptor and post receptor level.

A number of hormones antagonise the action of insulin by driving gluconeogenesis. These include glucagon, glucocorticoids, and growth hormone. Circulating glucagon levels are elevated in cirrhosis, despite this the production of glucose by the liver in cirrhotics is normal. If the high glucagon levels are suppressed by the infusion of somatostatin the insulin resistance remains (GRECO et al 1974) suggesting that the high glucagon levels are not primarily responsible for the insulin resistance of cirrhosis. Growth hormone levels are elevated in some cirrhotics but this is a very variable finding and elevated levels do not correlate with the finding of insulin resistance, and suppression of elevated levels with somatostatin does not correct the resistance (GRECO et al 1974). Levels of the other insulin inhibitory hormones such as cortisol are usually normal in cirrhosis.

Another possible mechanism of glucose intolerance is the presence of a circulating non-hormonal antagonist (DZURIKOVA et al 1974) or the lack of some "glucose tolerance factor" normally produced by the liver. There is no clear evidence for such a

factor.

The impaired clearance of galactose in liver disease has been demonstrated (SHAY et al 1931, ZIEVE and HILL 1955, TYGSTRUP 1964). The liver removes galactose from the circulation and converts it to glucose by phosphorylation and epimerization. This is discussed further in Chapter 3.

Normally about 70% of fructose is rapidly converted to lactate within the liver. This lactate is then rapidly metabolised but this does not occur in the diseased liver and results in hyperlactataemia and there have been reports of fatal lactic acidosis occuring in patients with severe liver disease given fructose infusions. Sorbitol is also potentially hazardous as it follows the same metabolic pathway.

2.2.3. Lipids

Lipids reach the liver in the form of lymph and as fatty acids in the portal blood. Within the liver the fatty acids are converted by B-oxidation in the mitochondria into acetyl-Coa, which is one of the key molecules in the production of cholesterol, triglyceride, phospholipid and lipoprotein. Under normal circumstances fat makes up about 5% of the liver's weight but in disease this can increase to 40-50% which is mostly in the form of triglyceride. The liver will normally synthesise 1.5 - 2g of cholesterol per day (OLSON 1965). A fall in the liver's ability to synthesise apolipoproteins is thought to predispose to the development of fatty liver.

The first abnormality in lipids noted in liver disease was the elevation in free cholesterol which particularly occurs in obstructive jaundice (EPSTEIN 1932). Decreased levels of Lecethin: Cholesterol Acyltransferase (LCAT) have been demonstrated in human liver disease and the levels have correlated with the percentage of cholesterol present in the esterified form (SABESIN et al 1977, MONROE et al 1983). LCAT catalyses the invitro esterification of cholesterol (GLOMSET 1968). Reduced LCAT activity can result from either a reduced synthesis of the enzyme by the liver or impairment of release from the hepatocytes. In acute viral hepatitis the alpha and pre-beta lipoprotein bands disappear and reappear on recovery (GJONE et al 1971). These abnormalities are also probably due to LCAT deficiency (DAY et al 1978).

Hypertriglyceridaemia may occur in acute or chronic hepatitis and cholestasis (McINTYRE et al 1975). Normally triglycerides are cleared from the blood by peripheral and hepatic lipases, in liver disease the peripheral lipases are normal but there can be a marked reduction in the hepatic lipase activity (BOLOZANO et al 1975, MULLER et al 1974).

Increases in the beta-globulin fraction of the lipoproteins have been shown in primary biliary cirrhosis (KUNKEL and ARHENS 1949). These changes in the lipoprotein pattern were shown to be due to the appearance of an abnormal lipoprotein (EDER et al 1955). By removing the 'normal' low density lipoproteins it was found that a lipoprotein remained which was rich in phospholipid and free cholesterol (SWITZER 1967), this has been called Lipoprotein-X (LP-X) (SEIDEL et al 1970). The accumulation of

this lipoprotein does not appear to be related to LCAT deficiency, and LP-X appears to be virtually specific for cholestasis (SEIDEL et al 1973). It has been claimed that LP-X gives a better differentiation of "medical" from "surgical" jaundice than the other biochemical tests of liver function (MAGNANI and ALAUPOVIC 1976). This has however, been disputed (MILLER and JOHNSON 1976, RITLAND et al 1973) and it has been superceded as a diagnostic test by ultrasound.

The clinical repercussions of these changes are few. In longstanding obstructive jaundice xanthelasma and xanthomas may form, and the high levels of cholesterol may also produce a peripheral neuropathy. The alteration in the lipid content of the red blood cells result in deformity of the red cells producing the characteristic "Target cells" of hepatobiliary disease.

2.3 STORAGE FUNCTIONS

The liver has large stores of iron, vitamin B12, copper, lipid and glycogen. The liver can be damaged by disorders of the storage but with the possible exception of glycogen the measurement of the storage capacities has little relevance to the quantification of liver disease but may be of value in the diagnostic differentiation of the storage disorders.

2.4 HORMONE METABOLISM

The liver is involved in the activation, action and deactivation of a number of hormones. The polypeptide hormones are degraded by interaction with specific cell surface receptors.

2.4.1 Glucagon

Glucagon levels are high in cirrhotic patients, and there is a significant correlation between the level of glucagon and the plasma ammonia (KABADI et al 1985). The increased levels of glucagon may be a physiological response to reduced glycogen stores in chronic liver disease. Glucagon stimulates gluconeogenesis and results in the maintenance of blood glucose levels in these patients.

2.4.2 Testosterone and Oestrogen

The relationship of sex hormones to liver disease has recently been reviewed (JOHNSON 1984). The typical alcoholic cirrhotic has low levels of circulating androgens and high levels of oestrogens. Several mechanisms are responsible for these alterations including malnutrition, vitamin deficiency, liver disease, direct gonadal toxicity of alcohol and inhibition of gonadotrophin production. Gonadal failure can occur in alcoholics before there is evidence of liver dysfunction.

The major androgen in men is Testosterone which is produced by the Leydig cells of the testis and then converted to the more biologically active dihydrotestosterone. Testosterone is degraded, mainly in the liver, by conjugation with sulphuric and glucuronic acid before being excreted in the bile. In alcoholic liver disease the circulating levels of testosterone are reduced (BAKER et al 1976). This is probably due to a combination of the testicular toxicity of alcohol (COBB et al 1978) and an inhibition of gonadotrophin production.

Oestrogens are also metabolised with the liver by conjugation with sulphuric or glucuronic acid. Oestradiol is the most biologically active of the oestrogens and it has been shown to be normal (GALVAO-TELES et al 1973), slightly increased (BAKER et al 1976) or markedly elevated (CHOPRA 1976) in chronic liver disease. Levels of circulating oestrone are elevated in liver disease, however this has only a weak oestrogenic effect being only a fifth as potent as oestradiol. The feminisation of the chronic alcoholic appears to be out of proportion to the elevation of weakly active oestrone. The hypothesis (EDMONSTON et al 1939) that feminisation in chronic liver disease occurred because of a failure of oestrogen degradation is now untenable.

It seems more likely that the feminisation occurs because of an imbalance in the oestrogen/androgen ratio rather an absolute excess of either. However, the oestrogen receptors in the liver are high affinity/low capacity receptors and it appears that even elevations in androgen levels of a factor of 1000 will not lead to displacement of oestradiol from these receptors. It is now suggested that there are altered numbers of oestrogen receptors in the livers of alcoholic men which is probably a result of gonadal failure.

2.4.3 Parathormone

The liver appears to be important in the metabolism of parathormone (FANG & TASHIGIAN 1972). However, the bone thinning and spontaneous fractures which occur in chronic liver disease are multifactorial, with dietary deficiency,

malabsorption, alterations in vitamin D metabolism playing a part.

2.4.4 Adrenocortical hormone

Cortisol is mainly degraded within the liver to tetrahydrocortisone and subsequently conjugated with glucuronic acid. Plasma levels of cortisol tend to be normal or reduced in liver disease although the significance of these results is difficult to interpret because of the marked reductions in plasma albumin and cortisol binding protein (PETERSON 1960, SHOLITON et al 1961).

2.4.5 Antidiuretic hormone

Delayed degradation of antidiuretic hormone is believed to be partly responsible for the hypervolaemia in chronic liver disease.

2.4.6 Thyroid Hormone

The liver has a major role in thyroid hormone metabolism being involved in the conjugation, biliary excretion and deamination of thyroxine and in the deiodination of thyroxine to the highly active tri-iodothyronine.

The majority of patients with chronic liver disease appear to be clinically euthyroid although the biochemical assessment of thyroid status can be confusing.

2.4.7 Insulin - See Carbohydrates 2.1.2

2.4.8 Growth Hormone

The half life of growth hormone is extremely short at about 19 minutes (OWENS et al 1973). The liver and kidneys are the major sites of degradation of growth hormone. Basal growth hormone levels are elevated particularly in cirrhosis and this has been attributed to a reduction in the clearance (GRECO et al 1974). However, the liver is responsible for about 90% of the clearance of growth hormone and normal levels have been found in liver disease (TAYLOR et al 1972).

2.4.9 Other Hormones

Aldosterone is inactivated in the liver and failure of this inactivation is one of the factors that results in the retention of fluid in liver disease.

Prolactin levels are variable in liver disease, 12% of patients have a level above the reference range but there is a poor correlation with gynaecomastia (MORGAN et al 1978).

2.5 EXCRETORY FUNCTION

The principal excretion product of the liver is bilirubin. It is a tetrapyrole pigment mainly derived in the reticulo-endothelial system by the degradation of haem from aging red blood cells and to a lesser extent from catalase, myoglobin, and the cytochromes. Bilirubin is virtually insoluble in water and it is transported in the plasma bound to albumin. The bilirubin is then taken up by the hepatocytes and conjugated with glucuronic acid to the mono- and diglucuronide. These reactions are catalysed by the microsomal enzyme Glucuronyl transferase. The diglycuronide is highly water soluble and is excreted in the bile with little enterohepatic circulation. The hepatic handling of bilirubin has recently been reviewed (SCHMID 1975).

In liver disease changes in the metabolism of bilirubin can occur at five main sites, and all can result in an elevation in the total serum bilirubin concentration:-

1. Increased load of bilirubin presented to the liver cell.
2. Reduced uptake and intracellular transport of bilirubin.
3. Reduced conjugating capacity.
4. Reduced excretion at the cannilicular surface.
5. Reduced biliary flow.

The level of the serum bilirubin is not a particularly sensitive marker of the severity of liver disease with disproportionate elevations occurring in cholestasis.

The liver is responsible for the clearance of a number of other substances which accumulate in liver disease. These

include the weak neural transmitters such as octopamine, and beta phenylethanolamine. Increases in urine and serum octopamine levels have been found in patients with hepatic encephalopathy (FISCHER and BALDESSARINI 1971; MANGHANI et al 1975).

2.6 DIGESTIVE FUNCTION

The liver plays an important part in the digestive processes by the production of bile acids. Bile acids are important because they are involved in four major pathophysiological processes:-

1. The production of bile acids from cholesterol provides the major metabolic pathway in the elimination of cholesterol.
2. The bile acid pool is largely stored in the gall bladder where they enhance solubilisation of cholesterol.
3. Bile acids stimulate hepatic bile production, and they are important determinants of the liver's capacity to eliminate various other endogenous and exogenous metabolites.
4. In the duodenum bile acids act as detergents and emulsify triglycerides and facilitate the absorption of fatty acids, monoglycerides, and lipid soluble vitamins.

The normal human liver converts 0.78-1.29 (300 - 500mg) of cholesterol into bile acids per day. At normal body Ph the bile acids are in the form of salts with sodium as the main cation. The bile salts are large asymmetrical molecules with both hydrophobic and hydrophilic regions this allows them to aggregate as large polymolecular structures (micelles). Following synthesis in the liver the bile salts are conjugated within the

liver with Glycine and Taurine. About 95% of the bile salts secreted by the liver are absorbed in the small bowel and recirculated to the liver. The hepatic uptake of bile acids from the portal vein is highly efficient with a first pass extraction of 62% for Chenodeoxychorate 70% for Cholic acid (GILMORE and THOMSON 1978) and 89% for the unconjugated bile acids (GILMORE and THOMSON 1981).

2.7 IMMUNOLOGICAL FUNCTION

A major part of the bodies reticuloendothelial system lies within the liver. The Kupffer cells clear bacteria and endotoxins from the portal vein by phagocytosis and pinocytosis. The natural portosystemic shunts which occur in liver disease bypass the Kupffer cell and may in part be responsible for the high incidence of infection and endotoxaemia in these patients.

Abnormalities in grannulocyte function, humoral immunity, and lymphocyte function are described in alcoholic liver disease (ZETTERMAN & SORRELL 1981)

The liver also takes up and secretes IgA. The bile contains no IgG or IgM but IgA accounts for 40% of its protein content.

2.8 HAEMATOLOGICAL FUNCTION

The liver is the primary site of erythrocyte production in the foetus from the ninth to the twenty-fourth week when the bone marrow takes over. The potential for haemopoesis remains into adult life and in some circumstances of marrow failure the liver may again become a major haemopoetic organ.

C H A P T E R 3

A REVIEW OF THE STANDARD TESTS OF LIVER FUNCTION

3.1 INTRODUCTION

There are a wide variety of tests available for the investigation of patients with or suspected of having liver disease. These tests are often referred to as "liver function tests", although it is quite clear that many have little or nothing to do with either a liver function or the severity of liver disease. In normal clinical practice these tests are generally considered as having three basic uses.

Firstly, as screening tests they are of value in detecting liver disease. These tests need to be sensitive to changes in liver function but do not necessarily have to be specific for a particular liver disease, as they indicate that further investigation is required.

Secondly, as diagnostic tests they allow the differentiation of the types of liver disease so that appropriate advice and therapy can be given. They must be specific for the individual types of liver disease but their sensitivity is less important. A full description of these tests is outwith the scope of this review but a summary of the major diagnostic tests of liver disease is included in Table 3.1.

Thirdly, as tests of the severity of liver disease they can fulfil four functions:

1) Assessment of Prognosis: An accurate assessment of the prognosis of a patient with liver disease has become more important over the last few years as the therapeutic options have increased. For patients with fulminant hepatic failure various techniques of liver support have been developed, and

for patients with end stage chronic liver disease hepatic transplantation can be considered. The rational use of these expensive and potentially dangerous techniques requires the identification of patients with a very limited prognosis.

However, the use of quantitative liver function tests in the assessment of prognosis makes three assumptions (TYGSTRUP & VILSTRUP 1983). It is unlikely that any of the current liver function tests fulfils these criteria.

a) The function decreases in a predictable way with the progression of the disease.

b) Death is inevitable when the function has deteriorated to a certain degree.

c) The test has a predictable relationship to the function.

It is uncertain whether any liver function test fulfils any or all of these criteria.

2) Drug dosage adjustment: Patients with liver disease may have an altered capacity to metabolise drugs. The extent of these changes depends on the drug involved and the severity of the liver disease. There is no standard method of adjusting the dose of hepatically metabolised drugs to take into account this impairment of metabolic capacity. A simple adjustment would be of value particularly in the prescription of analgesics and sedatives to these patients.

3) Monitoring: Tests of the severity of liver disease should allow the monitoring of the progress of the liver disease and also its response to specific therapies. If accurate

tests of the severity of liver disease were available these tests would presumably reflect the progression of the liver disease towards terminal liver failure, and would then be of value in the assessing whether new therapies altered the progression of liver disease.

4) Detection of complications: Some of the complications of chronic liver disease, for example portosystemic encephalopathy, are notoriously difficult to detect clinically. They lead to a subtle but significant deterioration in the patients performance which could be corrected if detected. The testing of all patients for these complications is difficult and it would be of great value if a subgroup of patients with liver disease who were likely to have these complications could be identified.

The purpose of this chapter will be to review the currently available liver function tests and in particular to try to indentify which tests are of most value in assessing the severity of liver disease.

TABLE 3.1 THE MAJOR DIAGNOSTIC TESTS OF LIVER DISEASE

TEST	HEPATIC DIAGNOSIS
Ferritin	- Haemochromatosis
Hepatitis Bs antigen	- Hepatitis B
Hepatitis A immunoglobulin	- Hepatitis A
Alpha 1 fetoprotein	- Hepatocellular carcinoma
Alpha 1 antitrypsin	- Alpha 1 antitrypsin associated liver disease
Antimitochondrial antibody	- Primary biliary cirrhosis
Smooth muscle antibody	- Chronic active hepatitis
Caeruloplasmin	- Wilsons disease
Leptospira titres	- Leptospirosis
Liver ultrasound	- Extrahepatic obstruction
Isotope liver scanning	- Liver tumours
Computerised axial tomography	- Liver tumours
Bile duct imaging	
- iv cholangiogram	- Gallstones
- E.R.C.P.	- Sclerosing cholangitis
	- Bile duct malignancy
Nicotinic acid test	- Gilbert's syndrome
Liver biopsy	- Parenchymal liver disease

Liver function tests can best be divided into the following categories:

1) Tests of a liver function
2) Tests of hepatocellular destruction
3) Tests of bile duct patency
4) Tests of hepatic fibrosis

3.2 TESTS OF A LIVER FUNCTION

All these tests reflect one of the functions of the liver outlined in Chapter 2.

3.2.1 Serum Albumin

The use of serum proteins to assess liver disease assumes that changes in the serum level of a protein are due to alterations in the capacity of the liver to produce that protein. There are however, two major problems with this interpretation.

Firstly, alterations in the serum proteins may result from changes in the anabolism, distribution, catabolism or loss of protein from the body. Therefore, a reduction in serum protein levels may not represent a true reduction in the capacity of the liver to produce that protein.

Secondly, true reduction in the rate of synthesis of a protein may result from either a reduction in the capacity of the synthetic mechanism or an alteration in the regulation of the synthetic mechanism. Which in turn may result from some extrahepatic manifestation of liver disease.

The relatively long half life of albumin (20 days) make it an insensitive test of acute liver disease (McINTYRE and HEATHCOTE 1974). The daily synthesis of albumin is approximately 3% of the total albumin pool. If albumin production ceased totally for a week then the serum albumin would only fall by 25%. Albumin is the major site of protein binding for acidic drugs (LUNDE et al 1970) and the doses of these drugs may need to be altered in patients with hypoalbuminaemia.

The insensitivity and lack of specificity for liver disease result in albumin having a limited role as a liver function test. However the estimation of serum albumin has the great advantage of simplicity and provides a rough guide to the severity of chronic liver disease provided that other causes of hypo-albuminaemia e.g. nutritional deficiency, nephrotic syndrome, protein losing enteropathy and catabolic states are excluded.

3.2.2 Globulin

Many of the globulins have short half lives and may be abnormal in liver disease when the serum albumin is still within the reference range (SKREDE et al 1973). The estimation of the individual globulins was difficult but a group of liver function tests was available which depended on abnormalities in the ratio of the various globulins to albumin. These tests have been superceded by protein electrothoresis and the immunological measurement of specific protein factors but included:

a) Cephalin-Cholesterol flocculation test. This test reflects an increase in the serum globulins and a decrease in the

serum albumin (BREEN and SCHENKER 1971). The test is more often positive in parenchymal liver disease than in obstruction (HILL and ZIEVE 1957) but it lacks specificity and adds little to the measurement of serum albumin.

b) Thymol tubidity and flocculation tests. These tests are similarly affected by an increase in the globulin concentration and a fall in albumin but are also affected in a major fashion by changes in the lipoprotein and beta globulin fractions. The tests may be positive in hyperlipaemic state.

c) Zinc Sulphate turbidity test is more influenced by isolated changes in globulins than the other two tests.

Alpha feto protein is usually only produced by foetal liver cells, but it has proven to be a sensitive screening test in the detection of hepatocellular carcinoma (ALPERT et al 1971). The serum level of alpha fetoprotein is also elevated in the presence of active hepatic regeneration (WEPSIC & KIRKPATRICK 1979).

Fibrinogen is reduced in liver disease and is associated with a poor prognosis (FINKBINER et al 1959). Fibrinogen deficiency can result either from reduced synthesis or from excessive consumption in disseminated intravascular coagulation.

The acute phase reactants are a group of proteins which either rise or fall in association with tissue necrosis (WEST et al 1964). The changes which occur in liver disease are generally difficult to interpret and they are not of diagnostic or prognostic help.

The concentration of beta 2 microglobulin is elevated in the

majority of patients with chronic active or persistent hepatitis and in alcoholic cirrhotics but is normal in alcoholic fatty liver (HALLGREN 1979).

3.2.3 Pseudocholinesterase

Pseudocholinesterase is an enzyme whose serum level falls when there is protein catabolism and rises during anabolic phases. It has been used in prediction of liver function following portocaval shunting (HUNT and LEHMANN 1960).

3.2.4 Coagulation Factors

The prothrombin time is the most useful test of coagulation in patients with liver disease. It measures the rate at which prothrombin is converted into thrombin in the presence of thromboplastin, calcium ions. It is influenced by factors I, II, V, VII and X. In the absence of a deficiency of vitamin K the prothromin time is only prolonged in severe hepatocellular injury (GREEN et al 1976) and has prognostic value in fulminant hepatic failure. A progressive prolongation of the prothrombin time has particularly ominous significance in acute viral hepatitis or in hepatic damage due to an overdose of paracetamol. Some of the individual clotting factors also have prognostic value. A factor VII of less than 8% of the normal mean value indicates a poor prognosis in acute liver failure (DYMOCK et al 1975).

3.2.5 Urea Synthesis

The rate of urea synthesis in response to an aminoacid load is impaired in patients with cirrhosis (RYPINS et al 1980). A

serum urea approaching zero then this is a sign of a poor prognosis (SHERLOCK 1985).

3.2.6 Aminoacids

In chronic liver disease the pattern of aminoacids in the peripheral blood shows an elevation of the aromatic aminoacids phenylalanine, tyrosine, tryptophan, methionine, glutamate, and aspartate with a reduction in the branch chain aminoacids valine, leucine, isoleucine. No correlation has been found between these changes in aminoacids in chronic liver disease and the severity of the disease as reflected by elevations in the serum transaminases (ROSEN et al 1977) and the presence of portocaval shunts (ZOLI et al 1981). In acute liver disease there is an elevation in all the the aminoacids except the branch chain aminoacids and especially methionine which may increase as much as 27 fold (RECORD et al 1982). There is some correlation between the severity and prognosis of fulminant liver failure and changes in the aminoacid concentration (ZOLI et al 1981). The rise and fall of the serum aminoacids was thought to correlate well with the level of encephalopathy, particularly the ratio of the branch chain aminoacids to the aromatic aminoacids was considered to be important but this measurement is now considered to be of little value (ZEIVE 1979).

3.2.7 Glucose Tolerance

This is often abnormal in liver disease but lacks specificity and does not appear to be of diagnostic value. The coincidence of a high blood sugar and high circulating insulin levels strongly suggests parenchymal liver disease.

3.2.8 Glycogen Reserve

The hepatic reserves of glycogen can be tested by administering 1mg of glucagon intramuscularly or intravenously. The consequent rise in blood glucose then gives an indication of the hepatic glucagon content (FELIG et al 1970). This test lacks specificity and is very dependent on the nutritional status.

3.2.9 Tests of Gluconeogenesis

Alterations in gluconeogenesis can be inferred from alterations in the concentrations of the precursors of gluconeogenesis in the peripheral blood. Blood lactate in particular correlates well with other tests of liver function with the most marked changes occurring in cirrhotic patients. The value of the measurement of lactate is reduced by the stringent requirements for its sampling (no muscle movement and the immediate removal of protein). The measurement of lactate may be of particular value in patients with fulminant liver failure who require parenteral nutrition, these patients are particularly prone to develop lactic acidosis because of the liver's impaired capacity to remove lactate.

3.2.10 Galactose Tolerance

The elimination of galactose by the liver is dependent on liver blood flow and the hepatic metabolic capacity. When galactose is administered in a dose of 30 grams intravenously the metabolic pathway is saturated and the elimination follows zero

order kinetics. Used in this fashion the elimination of galactose is only dependent on liver function. At lower plasma concentrations the metabolic pathway is not saturated and the elimination becomes a first order process with an exponential decline in plasma concentrations. The elimination in these circumstances is dependent on the liver blood flow and the elimination capacity. The application of this test would be as a measurement of liver blood flow but it has not been widely used use of the lack of a sensitive assay for galactose, although one has recently been described (HENDERSON et al 1982).

The standard galactose tolerance test consists of the administration of an intravenous load of 350 - 500 mg/kg body weight of galactose, and utilises zero order kinetics. A marked prolongation of the half life of galactose has been demonstrated in cirrhotic patients with results prolonged by 250-2500% compared to control subject (ZIEVE & HILL 1955, TYGSTRUP 1964, TENGSTROM 1969). The galactose tolerance test discriminates better between cirrhotic patients and normal subjects than serum albumin, alkaline phosphatase, thymol turbidity, or ALT (TENGSTROM 1969) but was not of value in the differentiation of fatty liver from cirrhosis (LINDSKOV 1982). In comparison to the BSP retention test a modified galactose retention test has proved to be less sensitive in the discrimination of cirrhotic patients from healthy controls (ZIEVE & HILL 1955; BIRCHER et al 1973). In cirrhotic patients it correlated with most of the standard biochemical tests of liver function and correlated only poorly with the clinical signs of and the histological severity

of liver disease (LINDSKOV 1982). In rats the elimination of galactose is independent of enzyme inducing agents (KEIDING et al 1973).

In fulminant liver failure the galactose tolerance test has some prognostic value being significantly lower in a group of non-survivors, and it is superior to the standard biochemical tests of liver function (RANEK et al 1976). However, some patients with normal galactose clearances and fulminant hepatic failure die (RAMSOE et al 1980). A marked reduction in the test has also been found in patients who develop encephalopathy after portosystemic shunting (KARDEL et al 1975).

The test has been simplified by validating the use of an oral dose of galactose and by changing the sampling to a breath test. In this test the patient ingests a dose of 14C or 13C labelled galactose and the elimination of labelled carbon dioxide in the breath is measured (SHREEVE et al 1976). The descrimination between cirrhotics and normal subjects was better with the galactose breath test than the serum bilirubin, alkaline phosphatase, and serum albumin.

The major assumption in the use of the galactose elimination capacity is that there is negligible extrahepatic metabolism or excretion. This assumption is now challenged (LINDSKOV et al 1983).

3.2.11 Storage Function

The measurement of serum ferritin and serum iron/total iron binding capacity, caeruloplasmin have some relevance in the diagnosis of haemochromatosis and Wilson's disease but are not a

value in assessing the severity of liver disease.

The only storage function which has been explored as a liver function test is that of glycogen storage which is discussed above under carbohydrate metabolism.

3.2.12 Bilirubin

The handling of bilirubin in the liver involves several different hepatic functions including uptake across the hepatocyte membrane, intracellular transport, conjugation by the microsomal enzymes and excretion into the biliary canaliculus. Bilirubin is measured by the Van den Bergh diazo reaction which splits the bilirubin molecule into two dipyrole azopigments. Unconjugated bilirubin requires to be dissolved in alcohol prior to this reaction and therefore gives an indirect Van den Bergh result. This test is cumbersome and not particularly sensitive. A normal range for serum bilirubin is difficult to define because the distribution curve for control subjects tends to be skewed to the right because of the inclusion of some patients with minor abnormalities the the handling of the pigment. Elevations in the serum bilirubin has significance as a diagnostic test as well as indicating the severity of liver damage.

The total serum bilirubin is generally not a sensitive test of liver dysfunction (GITNICK 1981) as elevations tend to occur late in the natural history of most liver diseases and disproportionate elevations occur in cholestatic liver disease. A major value of the measurement of bilirubin is its specificity for liver disease. Elevated serum bilirubin levels have been found to be of prognostic value in primary biliary cirrhosis,

with a level of >34 micromols indicating a three to six year survival and a level >170 micromols being associated with a survival of <1.5 years (SHAPIRO et al 1979). In alcoholic hepatitis bilirubin levels in excess of 100 umol/l tend to be associated with a poor prognosis (HARDISON & LEE 1966).

The fractionation of the total serum bilirubin into its conjugated and unconjugated components is of diagnostic value especially in the diagnosis of Gilbert's disease, when there are unconjugated hyperbilirubinaemia with less than 20% of the total serum bilirubin in the conjugated form.

3.2.13 Bromosulphthalein

Bromosulphthalein (BSP) is a brominated phthalein dye, sodium phenoltetrabromphthalein disulphonate, which is handled by the liver in a similar fashion to bilirubin. Following intravenous injection BSP is carried in the blood bound to albumin and alpha-1-lipoprotein. BSP is taken up by the liver cells and is conjugated to glutathione. The conjugated BSP is then actively excreted across the canalicular membrane (GITNICK 1981). Retention of BSP is generally considered to be a reliable and sensitive indicator of hepatic dysfunction (SCHOENFIELD 1965), but it is affected by other factors such as fasting (BRADLEY et al 1969).

BSP has been used as a sensitive indicator of hepatic dysfunction in investigations of the mechanisms of intrahepatic cholestasis of pregnancy (REYES et al 1981). In patients with a previous history of this condition there was an exaggerated slowing in the biliary phase of the removal of BSP.

The elimination of BSP has a biexponential pattern. By repeatedly sampling for up to 60 minutes it is possible to calculate the rate of uptake of BSP into the liver cells, of reflux back into the plasma, and of its transfer into bile (BARBER-RILEY et al 1961).

Dibromosulphthalein is a dibromo analogue of BSP, it has a high hepatic extraction of 80-100% but unlike BSP it is not conjugated, it has a major disadvantage as a test of liver function in that there is active renal tubular excretion (MEIJER et al 1983).

3.2.14 Nitrogenous Waste Products

Several of the waste products of nitrogen metabolism have been shown to be altered in hepatic disease. Mercaptans (methanethiol, ethanethiol, dimethylsufide) accumulate in severe disease (McCLAIN et al 1980).

Gamma aminobutyric acid (GABA) is a potent inhibitory neurotransmitter which is generated in the gastrointestinal tract by the action of bacteria and is degraded in the liver by GABA transaminase. The accumulation of GABA in chronic liver disease has been implicated in the genesis of portosystemic encephalopathy (SCHAFER and JONES 1982). There are as yet no data available in human subjects as to the value of GABA in the prediction of prognosis or in the detection of encephalopathy.

3.2.15 Ammonia

The level of ammonia is raised in cirrhosis particularly in patients with a marked degree of portosystemic shunting (ROSOFF & ROSOFF 1977). The role of ammonia in the genesis of

portosystemic encephalopathy remains obscure. The ammonia levels are affected by changes in diet, and colonic production of ammonia and portosystemic shunting. Serum ammonia estimations have been of some discriminating value in patients with fulminant hepatic failure (DEMEDTS et al 1974).

Ammonium Chloride Test: The capacity for ammonia metabolism can be tested by the ammonium chloride test. The patient is given three grams of ammonium chloride with a blood test for ammonia prior to administration and at plus 45 minutes. Normal tolerance is indicated by a return to baseline ammonia levels within 45 minutes of administration. The test is now little used because of improvements in the understanding of the mechanisms of encephalopathy (KORMAN et al 1974).

3.2.16 Bile acids

Bile acids are both produced and metabolised within the liver. Marked elevations in bile acids seen in liver disease are entirely analagous to the changes in serum concentration seen with many highly extracted drugs. Porto-shunting of blood round the liver play an important part in the production of elevated serum levels (OHKUBO et al 1984). There are four main methods of assessing changes in the serum bile acids :-

a) Fasting bile acids. The measurement of fasting conjugated bile acids is a less sensitive test in the detection of hepatic dysfunction than the transaminases (FERRARIS et al 1983). This test has been modified as a breath test using 15N-labelled ammonium chloride (JUNG et al 1985). There is a poor correlation with hepatic histology (MILSTEIN et al

1976, RICKERS et al 1982, LINNET et al 1982, LINNET & RYE ANDERSON 1983). This test is however more sensitive than the serum bilirubin (van BLANKENSTEIN et al 1983). The correlation to serum albumin, bilirubin and BSP retention is poor (HIRAYAMA et al 1979).

b) Post prandial bile acids. The measurement of post prandial bile acids can be considered as an endogenous bile acid tolerance test, in which the patient ingests his own bile acids following a meal. It was suggested that the post prandial measurement is a more sensitive indicator of hepatic dysfunction than the fasting bile acids (KAPLOWITZ et al 1973, BARNES et al 1975, FAUSA 1976). The test has also been found to be more sensitive than indocyanine green and bromosulphthalein clearances in the detection of minimal liver disease (JAVITT 1977) although this is disputed (van BLANKENSTEIN 1981). Initially the results were expressed as a ratio of the trihydroxy to dihydroxy bile acids, however the value of this ratio has been challanged because of its failure to separate patients with liver disease from control subjects. The test has been modified and the results are now expressed as the ratio of cholic to chenodeoxycholic acid. In this form the test is more sensitive for the detection of liver disease than the fasting bile acids or the standard liver function tests (ANGELICO et al 1977). Although in alcoholics the postprandial bile acids were less sensitive than the serum aspartate transaminase in the detection of minimal liver disease (GALIZZI et al 1978).

The test has been used to discriminate between cirrhotic patients, normal subjects and patients with extrahepatic obstruction (PENNINGTON et al 1977).

The first pass metabolism of bile acids is probably not altered in liver disease so that the test no longer has a firm theoretical basis. If it is truely a more sensitive test than the fasting levels then it may be because of changes in extrahepatic factors such as gall bladder storage and portal blood flow (GILMORE & HOFMAN 1980).

c) Bile acid tolerance test. In this test the tolerance to exogenous bile acids is assessed. An intravenous test using cholylglycine (LARUSSO et al 1975) has proved to be insensitive in detecting mild liver disease (THJODLEIFSSON et al 1977, GILMORE & THOMSON 1978), but an oral test has proved to more sensitive (GILMORE & HOFMANN 1980). A test measuring the capacity of the liver to conjugate cholic acid is significantly lower in nonsurvivors with viral hepatitis but there was considerable overlap and a survival limit could not not be defined. Glycine conjugation correlated with the prothrombin time and galactose elimination capacity but not with the serum albumin or the antipyrine clearance (BREMMELGAARD et al 1983).

d) Breath test. The bile acid tolerance test has been modified to a breath test to avoid the need for repeated blood samples. In this test 14C glycocholic acid is administered and the excretion of C14 is measured in the breath. the rate of appearance being proportional to the rate of elimination of the 14C glychocholic acid by the

liver. This test is however less sensitive than the measurement of total serum bile acids (GILMORE & THOMSON 1978, THJODLEIFSSON et al 1977).

Potentially the most useful measurement would be the hepatic extraction of bile acids. This measurement requires catheterisation of the hepatic veins and is therefore not readily available (THOMSON & GILMORE 1981).

3.3 HEPATOCELLULAR DESTRUCTION

The majority of tests which reflect the active destruction of hepatocytes consist of the measurement of hepatic enzymes in the peripheral blood. Why these enzymes appear in the blood in liver disease is not clear. When they do appear they behave like serum proteins being distributed in the plasma and interstitial fluid. The half-lives of elimination are usually measured in days. The mechanism by which these enzymes are cleared is not fully understood but there is some evidence of clearance by the reticuloendothelial system (WATKIN & FLEISCHER 1963).

Four factors are of importance in determining the level of the enzymes in the serum.

a) The concentration of the enzyme in the hepatocytes.

b) The amount of leakage from the hepatocyte.

c) The rate at which the circulating enzyme is cleared from the blood.

d) The number of liver cells damaged.

3.3.1 Aminotransferases

The most commonly measured liver enzymes are the aspartate (AST) and alanine (ALT) aminotransferase, previously known as serum glutamic oxaloacetic transaminase (SGOT) and serum glutamic pyruvate transaminase (SGPT). These enzymes catalyse the conversion of alpha amino acids to alpha-keto acids by the transfer of an amino group. They have negligible and are present in high concentration in the liver cells with AST in the cytoplasm and mitochondria while ALT is found only in the cytoplasm (BOYDE & LATNER 1961). ALT is considered to be a more sensitive and specific test of acute hepatocellular damage, whereas changes in AST occur in chronic damage to the hepatocyte (COODLEY 1971). The half life of AST is 17 hours which is considerably shorter than ALT at 47 hours, they have negligible renal and biliary secretion (DUNN et al 1958).

The total activity of AST consists of different isoenzymes which originate either in the mitochondria or the cytoplasm. In parenchymal liver disease with a raised total AST activity the cytoplasmic isoenzyme is always elevated and the mitochondrial enzymes is high in approximately 50% of cases. The mitochondrial isoenzyme is particularly elevated in patients with metastatic liver disease (SKRHA et al 1978). The ratio of mitochondrial AST to total AST is significantly elevated in alcoholics with and without evidence of liver disease compared to nonalcoholic controls and patients with viral hepatitis (NALPAS et al 1984).

In acute liver disease the ALT and AST are usually markedly elevated and a fall in the enzyme level usually precedes a clinical improvement. A persistent elevation of the amino-

transferase for six or more months following an attack of acute hepatitis is suggestive of progression to chronicity and is an indication for a liver biopsy. The correlation between the transaminases and the histological findings is poor so that attempts to tailor the dose of steroids to the transaminases has not proved to be useful.

The estimation of AST has been found to be a more sensitive measure of minimal liver disease in alcoholics than either postprandial bile acids or the aminopyrine breath test (GALIZZI et al 1978).

3.3.2 Ornithine carbamyl transferase

This measurement of this enzyme is not widely available because of the complicated methodology involved. It is a mitochondrial enzyme and elevated levels are found only in liver disease and are particularly associated with active hepatocellular damage (REICHARD 1961). Measurement of ornithine carbamyl tranferase has been found to be a more sensitive indicator of liver disease than AST and ALT (SKREDE et al 1973).

3.3.3 Lactate dehydrogenase

Many different tissues contain lactate dehydrogenase and elevated levels therefore lack diagnostic specificity. There are five major isoenzymes of which LD1 is predominantly found in liver tissue and the serum activity enzyme is elevated in conditions of hepatocellular damage (MASSEY et al 1971).

3.3.4 Isocitrate dehydrogenase

This enzyme is found in the hepatic cytoplasm as well as in skeletal muscle, the heart and the kidney. Elevated levels are usually indicative of liver disease but the measurement does not appear to have and particular benefit over the measurement of the other enzymes (OKUMURA & SPELLBERG 1950).

3.3.5 Sorbitol dehydrogenase

This enzyme is almost exclusively found in the liver and elevated levels are found in patients with hepatocellular damage but its use is limited by its instability in blood (DeRITIS et al 1965).

3.3.6 Glutamate dehydrogenase

This is a mitochondrial enzyme which is found in the liver, heart, kidney and skeletal muscle. A comparison of glutamate dehydrogenase and AST in alcoholics suggested that the former was the more sensitive indicator of hepatocellular damage (VAN WAES & LIEBER 1977). However a recent study found that elevated levels of glutamte dehydrogenase reflected recent alcohol intake rather than hepatic histology (JENKINS et al 1982).

3.3.7 Guanase

Guanase activities are high in the brain, liver and kidney but are low in the myocardium, pancreas and skeletal muscle. Serum guanase activity is elevated in acute and chronic liver disease and there is a suggestion that it is a more sensitive predictor of liver dysfunction than gammaglutamyl transpeptidase,

ALT, AST (ITO et al 1982).

3.3.8 Aldolase

Fructose 1,6 diphosphate aldolase occurs as three isoenzymes. The A isoenzyme occurs in muscle, aldolase B in the liver and aldolase C in the brain. Elevated levels of aldolase B have been demonstrated in patients with acute and chronic liver disease and hepatic neoplasia. Levels corelated closely with ALT levels but B aldolase has the advantage that it is liver specific (ASAKA et al 1984).

3.4 BILE DUCT PATENCY

In most forms of liver disease there is some degree of hepatocellular destruction and some obstuction to the flow of bile. The relative proportion of each component varies in each type of liver disease. It is of great therapeutic importance to be able to distinguish patients with predominantly biliary obstruction, particularly those with an extrahepatic lesion.

3.4.1 Alkaline phosphatase

The most commonly utilised measurement which is used as an indicator of biliary obstruction is the serum alkaline phosphatase (AP). The term alkaline phosphatase is used for a group of enzymes which catalyse the hydrolysis of a number of organic phosphate esters with the liberation of inorganic phosphate and an organic radical. Different isoenzymes are found in the liver, kidney, bone and intestine. The liver enzyme is found in the microvilli of the bile canaliculus and it may

participate in transport mechanisms but its basic functions remain unknown.

Elevation of alkaline phosphatase are seen in biliary obstruction, metabolic bone disease and diffuse infiltration of the liver with the highest levels being recorded in complete extrahepatic biliary obstruction. The activity in the serum of a patient with obstructive jaundice comprises two components. One derived from the liver cells is identical to the liver isoenzyme and the other only appears in biliary obstruction and is derived from bile (PRICE & SAMMONS 1974). Elevated levels of the enzyme are due to an overspill from the hepatocyte, whose content of the enzyme is increased in biliary obstruction (KAPLAN 1972). Quantitation of the biliary isoenzyme has been suggested as a method of improving the sensitivity of alkaline phosphatase in differentiating total biliary obstruction from partial obstruction (PRICE & SAMMONS 1976), although this is disputed (SORENSEN et al 1981). Intrahepatic cholestasis can not be clearly distinguished from extrahepatic cholestasis on the basis of alkaline phosphatase estimations (GUTMAN 1959). The intestinal isoenzyme may provide a better guide to this differentiation (WARNES et al 1977). The basis for this approach is that the presence of bile in the bowel is necessary for the release of the intestinal isoenzyme, and in biliary obstruction the levels of this isoenzyme will be either reduced or absent.

A further isoenzyme alpha-1 has been claimed to be specific for hepatic metastasis (VIOT et al 1979).

3.4.2 5 Nucleotidase

5-nucleotidase is a phosphomonoesterase that hydrolyses the nucleotide attached to the 5 position of a pentose chain. It is widely distributed in the body and in the liver it is located in the sinusoidal and canalicular membranes. Elevations in the serum occur in patients with liver disease and in women in the third trimester of pregnancy (KATER & MISTILIS 1972). It is not elevated in bone diseases (KAPLAN 1972). Elevated levels are found in all types of liver disease but the most marked changes are found in cholestasis. The changes in 5-nucleotidase activity tend to parallel those seen in the alkaline phosphatase but tend to fall more rapidly on the relief of the obstruction. The alkaline phoshatase tends to be more sensitive, and for this reason it is irrational to use the estimation of 5-nucleotidase as a method of confirmation of liver disease in patients with an elevated alkaline phosphatase (CONNELL & DINWOODIE 1970). The main clinical application of 5-nucleotidase estimations is the confirmation of liver disease in children.

3.4.3 Leucine aminopeptidase

Leucine aminopeptidase is a proteolytic enzyme which hydrolyses amino acids. Elevations of leucine aminopeptidase are found only in patients with diseases of the hepatobiliary system and pancreas (NACHLAS et al 1957). The levels are particularly high in patients with obstructive jaundice due to a carcinoma of the head of the pancreas (RUTENBERG et al 1958). It is also elevated in pregnancy (BRESSLER & FORSYTH 1959), but it is not

increased in patients with bone disease (RUTENBERG et al 1958). It shows a similar sensitivity as alkaline phosphatase and 5 Nucleotidase.

3.4.4 Gamma glutamyl transpeptidase

The serum levels of gamma glutamyl transferase (GGT) are elevated in all forms of liver disease and particularly high levels are found in patients with obstructive jaundice (LUM & GAMBINO 1972). Five isoenzymes have been demonstrated only two of which occur in normal individuals (WENHAM et al 1979). The enzyme is not confined to the liver and high levels are found in some non-hepatic conditions including renal neoplasia, nephrotic syndrome (ORLOWSKI 1963), renal transplant rejection, acute and chronic pancreatitis, congestive cardiac failure (RUTENBERG et al 1963), diabetes mellitus (GOLDBARG et al 1963) and angina pectoris (HEDWORTH-WHITTY et al 1967), but it is not elevated in pregnancy. Elevated levels are also found in patients taking drugs which induce tha hepatic monoxygenase enzymes (ROSALKI et al 1971). It has therefore been suggested that it may be of value in monitoring the abstinence of alcoholics (HORNER et al 1979).

The high serum levels seen in extrahepatic obstruction are not sufficent to confidently differentiate 'medical' from 'surgical' jaundice (KEANE and GARCIA 1973). The levels seen in cirrhotic patients are very variable and an elevation in the enzyme may be the only biochemical abnormality. The serum levels do not correlate closely with the levels in the hepatocyte, suggesting that increased concentrations in the hepatocyte may

not be an important mechanism in the production of high serum levels (SELINGER et al 1982). There is a tendency for the serum levels of the enzyme to fall in the terminal phases of liver disease presumably because of a failure in its synthesis (NOSSLIN et al 1966). The complete absence of the enzyme from bone together with its greater sensitivity in cholestasis (WHITFIELD et al 1972) and its ease of estimation have resulted in the widespread use of the enzyme as a means of confirming that an elevated alkaline phosphatase is of hepatic origin (LUM & GAMBINO 1972).

There is no information available on the prognostic value of GGT but its greater sensitivity for liver disease compared to bilirubin, aminotransferases, and alkaline phosphatase make it a useful screening test.

3.5 HEPATIC FIBROSIS

The normal architecture of the liver is supported by a framework of connective tissue. This consists of collagen which is a heterogeneous class of extracellular proteins with a unique aminoacid composition. Three distinct forms of collagen have been isolated and are designated as collagen I,II,III. In chronic liver disease this framework becomes thickened and distorted. Increased deposition of type III collagen occurs in early fibrosis (PROCKOP et al 1979) and type I collagen is produced in the later stages of fibrosis (ROJKIND 1981). Collagen is formed by the activation of amino acids in the ribosomes. Specific enzymes including prolyl hydrolase, lysyl hydrolase and glycosyltransferase act on the procollagen which is

then secreted into the extracellular space where the procollagen peptidases remove the peptide extensions from the amino and carboxy terminals (PROCKOP et al 1979, FESSLER & FESSLER 1978). The collagen fibrils and possibly procollagen are later degraded by collagenase.

A noninvasive measure of hepatic fibrosis might be of clinical value in distinguishing patients with active cirrhosis and also patients with the committed precursors stages of cirrhosis from those with inactive disease. In cirrhosis the liver content of collagen increases five fold. The mechanism by which collagen accumulates is unknown but four process can be involved (CARTER et al 1982) :-

1. An increased rate of collagen synthesis
2. An increased production of type IV collagen which is resistant to degradation by collagenase
3. An increase in the number of collagen cross links, which also render collagen more resistant to collagenase
4. An alteration in the activity of collagenase

The noninvasive measurements which are used in the assessment of intrahepatic fibrogenic activity are based on three basic principles:-

a) Analysis of metabolic products which are either needed in the synthesis of collagen or are released during its degradation. These include proline, hydroxyproline and the analysis of the amino-terminal peptide for type III collagen.

b) Measurement of serum metabolites which induce or stimulate collagen formation in vitro.

c) Measurement of enzymes involved in the modification of collagen including prolylhydroxylase and galactosyl-hydroxysyl glucosyltransferase.

The concentration of hydroxyproline is increased in patients developing chronic liver disease. Elevated levels of prolyl hydrolase have also been demonstrated in the early stages of cirrhosis (MANN et al 1979).

An alternative approach to the non-invasive detection of hepatic fibrosis is the determination of the aminoterminal propeptide type III. This is elevated in patients with alcoholic cirrhosis compared to controls (ROHDE et al 1979). In another study type III procollagen peptide levels could not be used to differentiate alcoholic cirrhosis from alcohol associated fatty liver, although grossly elevated levels were suggestive of alcoholic hepatitis (NIEMELA et al 1983). There remain considerable methodological problems in the measurement of this peptide (ROJKIND 1984).

3.6 COMBINATION TESTS OF LIVER FUNCTION

The liver has many different functions, it is possibly that the assessment of a combination of functions may yeild more information than the measurent of a single function.

3.6.1 Child's classification

The best known of the combination indices of liver function is the Childs' classification (Table 3.3) which was later modified by PUGH (PUGH et al 1973). This index provides a

scoring system for clinical and biochemical features of liver disease (TABLE 3.4). Those patients who have a total score of 5 or 6 have well preserved liver function and are classified as Child's grade A. Moderate liver function is a score of 7,8,9 (grade B) and severe liver disease is a total score of > 9 (grade C). The original application of this grading was in the selection of patients with bleeding oesophageal varices for portocaval shunts. The two main problems of this grading are that the assessment of ascites and encephalopathy are highly subjective and that the biochemical measurements can be very unstable following an acute gastointestinal bleed, with the bilirubin in particular being disproportionately elevated. Discriminant functional analysis of the Child's classification show that in the prediction of survival there is a high degree of correlation between the individual components, and therefore the index contains redundant information (BARBARE et al 1985). The childs classification has less prognostic value than an index derived by multivariant analysis (CHRISTENSEN et al 1984). Despite these problems the Child's classification remains the standard method for differentiating the severity of liver disease.

TABLE 3.3 CHILD'S CLASSIFICATION OF THE SEVERITY OF LIVER DISEASE

	Grade A	Grade B	Grade C
Serum Bilirubin (umol/l)	< 40	40-50	> 75
Serum Albumin (g/l)	> 35	30-35	< 30
Ascites	None	Easily controlled	Poorly controlled
Neurological Disorder	None	Minimal	Advanced coma
Nutrition	Excellent	Good	Poor

(from CHILD 1964)

TABLE 3.4 PUGH'S MODIFICATION OF CHILD'S CLASSIFICATION OF THE SEVERITY OF LIVER DISEASE.

	POINTS SCORE FOR INCREASING ABNORMALIY		
	1	2	3
Encephalopathy (Grade)	None	1 or 2	3 or 4
Ascites	Absent	Slight	Moderate
Bilirubin (mg/100ml)	1-2	2-3	> 3
Albumin (g/l)	> 35	28 - 35	< 28
Prothrombin time (sec)	1-4	4-6	> 6
Bilirubin in Primary Biliary Cirrhosis	1-4	4-10	> 10

(From PUGH et al 1973)

3.6.2 Simple ratio procedures

Since biochemical tests of liver function were introduced attempts have been made to combine two or more of these tests in a simple ratio to provide a third more sensitive or specific test. Initially it was suggested that an AST/ALT ratio of >1 was suggestive of cirrhosis, hepatocellular carcinoma, metastasis or lymphoma, and a ratio of <1 suggested extrahepatic obstruction, viral hepatitis, or drug induced hepatotoxixity (WROBLEWSKI 1958). More recently interest in the AST to ALT ratio has been revived by the suggestion that a ratio of greater than 2 is highly suggestive of alcoholic hepatitis and cirrhosis (COHEN & KAPLAN 1975). A ratio >2 was found in 70% of patients with alcoholic cirrhosis or hepatitis compared to only 8% of patients with chronic active hepatitis, 4% with viral hepatitis, and no patient with obstructive jaundice. However a ratio of >2 was found in 26% of patients with cryptogenic cirrhosis. AST is predominantly a cytoplasmic enzyme where as ALT originates predominantly from a mitochondria so that an explanation of these findings is that a low AST/ALT suggests some impairment of the cellular membrane and a high ratio suggest mitochondrial damage, as in alcoholic liver disease (SKREDE et al 1973). This explaination is unlikely to be correct because the finding of a high ratio does not correlate with elevated levels of the mitochondrial enzyme ornithine carbamyl transferase. The change in the ratio has been shown to be due to a reduction of the concentration of ALT in the hepatocyte rather than to a differential pattern of release (MATLOFF et al 1980). These

changes may to some extent be due to deficiency of pyridoxal 5-phosphate (DIEHL et al 1984), the biologically active form of vitamin B6. This vitamin is necessary for the activation of the aminotransferases.

3.6.3 Correlation matrices

Correlation matrices have been used to suggest that the standard liver function tests are themselves dependent on four underlying hepatic functions (MILOSZEWSKI et al 1970). These functions were :

1. Disturbance or modification of the hepatocyte membrane. This was most reflected by changes in the zinc sulphate and thymol turbidities and the ALT.
2. Protein synthesis. This is shown by changes in the serum albumin and prothrombin time.
3. Hepatic excretory function. This is best reflected by the alkaline phosphatase and serum bilirubin.
4. Immunological function. This function is reflected in the standard liver function tests by the serum globulins.

3.6.4 Discriminant function analysis

In discriminant function analysis a set of weighting factors are added to the individuals test results. The sum of the weighted test profile is then termed the 'discriminant'

$$d = w1t1 + w2t2 + w3t3 \ldots\ldots\ldots wntn$$

where d is the discriminant , wl.....wn are the weighting factors for test results tl.....tn. The analysis depends on

the definition of prearranged groups in the data for example non-survivor and survivors or diagnostic groups. The weightings are the calculated to minimise any within group variation and to maximise between group variation.

Initial studies of this technique produced results for the differention of six forms of liver disease which were not better than random guessing (BARON 1970). This analysis has now been applied to the diagnostic value of standard liver function tests in large groups of patients with liver disease. It was found that the optimum group of tests for the differentiation of liver diseases was very dependent on which liver diseases were to be separated. On a standard battery of six tests about two thirds of the patients were allocated to the correct disease group. The most significant information was derived from the alkaline phosphatase and either the AST or ALT.

Another application of these methods is a computer based index for the diagnosis of parenchymal liver disease. The system considers 14 pieces of information of which it found 9 to be of value in differentating the diagnosis in an individual case. The system produced the correct diagnosis in 53% of the cases and included the correct diagnosis in a list of two likely diagnoses in 73% of cases. The nine components in order of their effectiveness in producing a diagnosis were :-

1. Plasma disappearance rate of indocyanine green
2. Alanine transaminase
3. Zinc turbidity test
4. Alkaline phosphatase

5. Age
6. Hepatitis Bs Ag
7. Rheumatoid factor
8. AST/ALT ratio
9. AST

Five tests were found to have no discriminant diagnostic value and they included the serum cholesterol, total proteins, total bilirubin, albumin to globulin ratio and the gamma globulin fraction (ITOSHIMA et al 1983). This type of analysis has also been applied to various parameters of BSP elimination to allow the separation of normal subjects from obstructive jaundice from a group with cirrhosis (MOLINO et al 1978).

This analysis has also been used to assess the prognosis in liver disease. In a group of 129 patients with cirrhosis nine prognostic variables were evaluated. These variables included age, ascites, encephalopathy, gastrointestinal bleeding, serum bilirubin, serum albumin, GGT,AST, and prothrombin time. It was found that the serum bilirubin and GGT were of particular prognostic value and a bilrubin/GGT ratio of > 1 was associated with a 12 month survival of only 12% (POYNARD et al 1984).

In a group of 72 patients with mixed liver disease multiple regression analysis showed that the best predictors of histological and clinical severity were Lecithin - cholesterol acyltransferase (LCAT), total plasma cholesterol, alkaline phosphatase, and serum bile acids (SIMKO et al 1985). Discriminant analysis has also been used to construct a simple nomogram for the assessment of the severity of liver disease (HAMILTON 1977). This was based on the total bilirubin, alkaline

phosphatase, Zinc turbidity, and alanine aminotransferase. This nomogram has not been widely applied, probably due to loss in the zinc turbidity test being superceded by other liver function tests.

Multiple regression analysis has been used to evaluate prognostic features in a group of 248 patients with primary biliary cirrhosis. Five variables were found to have independent prognostic significance; serum albumin, serum bilirubin, cirrhosis, age and central cholestasis. These factors were combined as a prognostic index which was validated against independent data (CHRISTENSEN et al 1985(a)). The same group applied similar methods to patients with cirrhosis to predict patients who would benefit from therapy with prednisolone. Four variables had therapeutic value. Antinuclear factor and large piecemeal necrosis were associated with a beneficial effect of prednisolone and ascites and large regenerative nodules were associated with a deleterious effect of prednisolone (CHRISTENSEN et al 1985(b)).

3.6.5 Canonical analysis

Canonical anlysis is a type of descriminant analysis in which there is a transformation applied to the initial vectors to reduce the within sample ellipsoids of scatter to spheres. This technique allows the weighting of the individual liver function tests so that the resulting sums of the liver function test for patients with a specific diagnosis is similar and different from patients with other diagnoses (BARON 1970).

3.6.6 Artificial Intelligence

An system for the functional assessment of liver disease has been constructed based on Artificial Intelligence methodology. The system gives an assessment of four aspects of liver function - biosynthesis, cholestasis, reactivity, cellular destruction. The data used includes albumin, pseudocholinesterase, prothrombin time, bromosulphthalein clearance, bromsulphthalein retention at 45 minutes, ALT, AST, isocitrate dehydrogenase, bilirubin, GGT, rheumatoid factor, immunoglobulin A, immunoglobulin G and immunoglobulin M (LESMO et al 1984).

3.6.7 Numerical Taxonomy and cluster analysis

At any given time a patient has a given set of of liver function test results. These results can be considered as the coordinates of a point in some multidimensional space. As further patients are added to this space so the space becomes crowded and it is likely that certain groups or 'clusters' will appear. The basic problem in this method is the desciption of a cluster. The distance between two patients is called the Mahalanobis D2. A small D2 signifies the close proximity of the patients. The formation of clusters then occurs as follows. First the D2 is calculated for all possible patient pairs. Second the pair with the smallest D2 are clustered. Third the D2 for each nonclustered pair with the cluster is calculated. Fourth the D2s obtained are compared to the D2s obtained in stage 1. The lowest D2 is taken and results in a patient either being added to the original cluster or forming a second cluster with another patient. The process is then repeated from stage three

until the D2s obtain fail to reach some preset level of statistical significance.

The use of cluster analysis has been extensively investigated in the diagnosis of liver disease with disapointing results (BARON & FRASER 1965, FRASER & BARON 1966). One of the early computer models for the diagnosis of liver disease utilised two and three dimensional plotting to allow the recognition of characteristic profiles in specific forms of liver disease (STRANDJORD et al 1973).

3.6.8 Bayes theorem

A medical diagnosis can be considered as an analysis of symptoms. The physician has an almost unconcious awareness of the relative frequencies of any symptom in any disease state, and a diagnosis involves the eliciting of symptoms and an awareness of the relative probabilities of those symptoms. If Sp denotes the patients symptom profile, and D represents one particular disease then the 'conditional probability' is denoted as p(D/Sp). This probability is dependent on two main factors. Firstly the overall statistical chance that a patient has a particular disease for example in alcoholic liver disease has a prevelance of 1 in 10,000 then before the patient divulges any symptom there is a probability of 0.0001 that he has alcoholic liver disease. This is termed the 'population factor' and is denoted as P(D). The second factor determining the conditional probability is the probability that any patient with disease D will have the symptom profile of the presenting patient this is denoted as p(D/sp).

The relationship between these factors is described by the

equation :-

$$p(D/sp) = \frac{1}{k} * P(D)*P(sp/D)$$

k is a constant relating to the experience and practice of the physician involved.

Usually the equation will be used to calculate the conditional probabilities of at least two diseases. The equations are then :-

$$p(D2/sp) = 1/k * P(D2)*P(sp/D2)$$

$$p(D1/sp) = 1/k * P(D1)*P(sp/D1)$$

The relative probability of the two diseases can then be expressed by cancelling k out of the equations as

$$\frac{p(D1/sp) = 1/k}{p(D2/sp) = 1/k} * \frac{P(D1)*P(sp/D1)}{P(D2)*P(sp/D2)}$$

This equation can then be expanded to consider the relative probabilities of a any number of diseases. This technique makes two major assumptions, firstly that each disease state is mutually exclusive of the others and secondly that there is no correlation between the individual components of of the symptom profile.

Discriminant analysis was used by TENGSTROM to evaluate serum bilirubin, thymol turbidity, alkaline phosphatase, ALT and the galactose tolerence test in the differentiation of cirrhosis from viral hepatitis, biliary obstruction and patients with normal liver biopsies (TENGSTROM 1969).

An evaluation of this type of analysis has been applied in a computer based system has been applied to the differential diagnosis of jaundice. This system takes account of 72 pieces of information taken from the history, physical examination,

biochemistry and haematological reports. The accuracy in diagnoses between 11 causes of jaundice was 77% and in the differentiation of surgical from medical jaundice the system was accurate in 95% of cases (STERN et al 1975).

C H A P T E R 4

PHARMACOKINETICS AND PHARMACODYNAMICS

4.1 INTRODUCTION

All therapeutic agents which are absorbed into the body require to be excreted. Some drugs are water soluble and can be directly excreted from the human body in urine, bile, sweat or other body secretions. However the majority of drugs are lipid soluble and require to undergo biotransformation within the body to render them more water soluble. This improves their excretion in two ways. Firstly, the metabolites can be filtered out of the circulation by the renal glomeruli and secondly because they are less able to penetrate lipid membranes therefore they are less likely to be reabsorbed from the renal tubules. The rate at which these transformations to aqueous solubility occur largely dictates the rate of elimination of these drugs from the body. Most of these transformations occur in the liver and are mediated by mitochondrial enzymes.

These transformations are considered to be of two types (WILLIAMS 1971). The Phase 1 reactions involve the hydrolysis, oxidation or reduction of the molecule by the monooxygenase enzymes in the smooth endoplasmic reticulum. This system comprises a large number of enzymes the best studied of which are cytochrome P-450 and cytochrome P-448. The function of the system is to supply oxygen in the form of high energy complexes. These reactions generally decrease the pharmacological activity of the molecule but occasionally a more active molecule is created (azathioprine to 6-mercatopurine and prednisone to prednisolone). These reactions may also result in the production of a more toxic metabolite than the parent compound for example paracetamol.

The second group of transformations (Phase 2) involve the

conjugation of the parent molecule or its metabolites with a small endogenous molecule to render them more water soluble. Conjugation to a variety of molecules including glucuronic acid, sulphates, aminoacids, acetic acid or glutathione may occur. A list of some of the drug metabolising reactions and the enzymes involved is included in TABLE 4.1. It has become clear that many of these enzymes exist in multiple forms whose activity may be affected differently by external agents. For example chlordiazepoxide and diazepam are both primarily metabolised in the liver by N-demethylation but the elimination of chlordiazepoxide is profoundly reduced in the elderly whereas the elimination of diazepam is less affected.

The purpose of this chapter is firstly to examine the factors which determine the elimination of drugs from the body. Secondly, to review the drugs which have been used as indicators of liver disease.

TABLE 4.1 HEPATIC DRUG METABOLISING REACTIONS IN MAN

Reaction	Enzyme	Substrate
Oxidation		
alkyl hydroxylation	cytochrome P-450	pentobarbitone
aromatic hydroxylation	cytochrome P-450	phenytoin
epoxidation	cytochrome P-450	dieldrin
N,S,O-dealkylation	cytochrome P-450	aminopyrine,antipyrine
deamination	cytochrome P-450	amphetamine
	monoamine oxidase	tyramine
N-hydroxylation	cytochrome P-450	aniline
N-oxidation	cytochrome P-450	sparteine,carbamazepine
S-oxidation	cytochrome P-450	chlorpromazine
desulphuration	cytochrome P-450	thiopentone
alcohol oxidation	alc: dehydrogenase	ethanol
aldehyde oxidation	alde:dehydrogenase	acetaldehyde
Reduction		
azo reduction	azo-reductase	prontosil
nitro reduction	nitro-reductase	chloramphenicol
dehalogenation		halothane
ketone reduction	ketone reductase	warfarin
Hydrolysis		
deesterification	esterase	pethidine
deamination	amidase	procainamide
epoxide hydrolysis	epoxide hydratase	styrene oxide
Conjugation		
acylation	acetyltransferase	isoniazid
glucuronidation	glucuronyl transferase	propranolol
sulphation	sulphotransferase	ethinyloestradiol
mercaptopurine acid formation	glutathione transferase	paracetamol
amino acid conjugation	amino acid transferase	acetylsalicylic acid
N,S,O-methylation	methyltransferase	catecholeamines

From PARK 1982

4.2 DEFINITION OF PHARMACOKINETIC PRINCIPLES

Pharmacokinetics involves the study of the distribution and elimination of drugs. Examination of the various pharmacokinetic parameters can be of value in two ways. Firstly it allows the description of a profile of a drug and this information is then of use in determining size and frequency of drug doses. Secondly in the diseased state information can be gained regarding the functional capacity of the elimination mechanisms.

4.2.1 Absorption

When drugs are given by mouth they are mostly absorbed from the small bowel into the portal circulation. The speed of absorption depends on the rate of gastric emptying, small bowel motility, the surface area of the small bowel, the capacity and rate of the transport mechanisms and the intestinal blood flow. When drugs are given intramuscularly they are directly absorbed into the systemic circulation and the rate at which this occurs is dependent on the molecular weight of the drug, its solubility and the blood flow at the site of injection.

4.2.2 Systemic availability

Bioavailability or systemic availability is the fraction of an orally administered dose which reaches the systemic circulation. When a drug is given intravenously it is given directly into the systemic circulation and the whole dose is therefore available to the systemic circulation i.e. it is 100% bioavailable. When a drug is administered orally some of the administered dose may not reach the systemic circulation either because it is not absorbed or because it is metabolised in the

gut wall or liver. This effect is called the presystemic elimination or the "first pass metabolism" of the drug. The systemic availability of a drug can determined by measuring the area under the drug concentration/time curve following intravenous and oral administration. Drugs which are undergoing a major degree of presystemic elimination are listed in TABLE 4.2. Alterations in the presystemic elimination of drugs can lead to large changes in the amount of orally administered drugs which reach the systemic circulation.

TABLE 4.2 DRUGS THAT UNDERGO SUBSTANTIAL FIRST PASS ELIMINATION.

Acetylsalicylic acid	Methyltestosterone
Alprenolol	Metoprolol
Aminosalicylic acid	Morphine
Amitriptyline	Nalorphine
Chlormethiazole	Nortriptyline
Chlorpromazine	Oral contraceptives
Dextropropoxyphene	Oxprenolol
Doxepin	Paracetamol
Glyceryl trinitrate	Pentazocine
Hydralazine	Pethidine
Imipramine	Prazosin
Indoramin	Propranolol
Isoprenaline	Propoxyphene
Isosorbide dinitrate	Quinidine
Labetalol	Salbutamol
Levodopa	Terbutaline
Lignocaine	Triazolam
Lorcainide	Verapamil

From BRODIE 1983

In man the factors affecting the presystemic elimination of drugs are the size and frequency of the dose, the metabolic capacity of the liver and the degree of portal-systemic shunting.

4.2.3 Distribution

The relationship between the amount of drug in the body to the concentration in the plasma is expressed as the apparent Volume of distribution (Vd). This is influenced by many factors including the affinity of the drug for different tissues and the degree of binding of the drug to protein.

The apparent volume of distribution can be calculated from the equation :-

$$Vd = \frac{D}{Co} \qquad (1)$$

where D is the administered dose and Co is the blood concentration back extrapolated on the concentration/time curve to the time of administration (time zero).

4.2.4 Half-life

The half life is defined as the time taken for the concentration of the drug to decrease by 50% following absorption and distribution. It can be expressed by the equation

$$t\ 1/2 = \frac{(\ 0.693\ Vd\ )}{cl} \qquad (2)$$

It can be seen from this equation that the half-life is dependent both on the volume of distribution and on the clearance of the drug. Either of these variables may alter in liver disease and it is therefore invalid to assume that alterations in half life reflect alterations in the elimination of the drug unless the volume of distribution is known.

4.2.5 Clearance

The clearance of a substance is defined as the volume of blood from which the substance is irreversibly removed in unit time. For drugs which follow single compartment kinetics the clearance (cl) is calculated by the equation :

$$cl = \frac{0.693.Vd}{t1/2} \qquad (3)$$

where t1/2 is the plasma half life.

If the drug shows multicompartment kinetics then the clearance should be calculated according to the equation :

$$cl = \frac{DOSE}{AUC} \qquad (4)$$

where AUC is the area under the concentration/time curve.

The total clearance of a drug can also be considered as the sum of the clearances of the drug by individual organs. For some drugs the equation would be :

$$cl = \text{renal cl} + \text{hepatic cl} \qquad (5)$$

For many lipid soluble drugs the plasma clearance is effectively the same as their hepatic clearance because they cannot be filtered through the glomerulus. For an individual organ the clearance can be calculated from the concentration of drug entering (ca) and leaving (cv) the organ and the organ blood flow (Q).

$$cl = Q \ \frac{[\ ca - cv\ ]}{ca} \qquad (6)$$

The arteriovenous difference is refered to as the extraction ratio (E).

$$E = \frac{[\ ca - cv\ ]}{ca} \qquad (7)$$

Therefore the clearance can also be expressed as

$$cl = Q \cdot E \qquad (8)$$

As the extraction ratio approaches unity then the clearance becomes dependent on the blood flow. Conversely when E is small then the clearance is dependent on the hepatic extraction and independent on the blood flow. This relationship can be used to divided into two groups :-

1. Flow-limited drugs have a high hepatic extraction ratio (>.7) and their clearance is then dependent on the rate of delivery of the drug to the liver i.e. liver blood flow. These drugs have a large presystemic elimination and can be recognised because they are either not recommended for oral use or the recommended oral dose is much larger than the intravenous dose to make allowance for the large presystemic elimination. They can be used to monitor changes in the liver blood flow but this technique assumes that the hepatic extraction ratio remains constant.

2. Capacity limited drugs have a low hepatic extraction ratio (<.3) and their clearance is primarily dependent on the rate at which the liver can extract them from the portal blood. Examples of this type of drug include phenytoin, diazepam, tolbutamide, warfarin , quinidine , digitoxin , and clindamycin. These drugs are particularly suitable as models for the demonstration of alterations in the hepatic metabolic capacity. This technique assumes that the rate limiting step in their extraction is hepatic metabolism and not the uptake across the hepatocyte membrane.

4.2.6 Intrinsic clearance

The intrinsic clearance of a drug is the clearance of the drug if the organ blood flow was not a limiting factor. The intrinsic clearance is therefore dependent only on the protein binding and the activity of the eliminating mechanism.

The intrinsic clearance can be deduced if one assumes that the concentration of the free drug in the hepatic vein (fbcv) is equal to the concentration in the hepatic water. Where fb is the fraction of the drug unbound to plasma protein. The rate of removal of free drug from liver water will then be

$$cl(int).fbcv$$

But this is also given by $Q(ca-cv)$

Thus $$cl(int).fbcv = Q(ca-cv)$$

$$cl(int) = \frac{Q(ca-cv)}{fbcv} \qquad (9)$$

since $$E = \frac{ca-cv}{ca}$$

then $$cl(int) = \frac{QE}{fb(1-E)} \qquad (10)$$

then $$QE = cl(int).fb - cl(int).fb.E \qquad (11)$$

then $$QE + cl(int).fb.E = cl(int).fb$$

and $$E = \frac{fb.cl(int)}{Q+fbcl(int)} \qquad (12)$$

therefore $$cl = Q \cdot \frac{fb.cl(int)}{Q+fbcl(int)} \qquad (13)$$

This proof is derived from ROBERTS et al 1979

The intrinsic clearance can also be considered in terms of Michaelis-Menton enzyme kinetics.

$$cl(int) = \frac{Vmax}{Km + C} \qquad (14)$$

where C is the drug concentration, Vmax the maximal rate of metabolism, and Km is the Michaelis-Menton dissociation constant.

4.2.7 Protein binding

Drugs exist in the circulation either as the free unbound form or bound to a constituent of the blood, the majority of the binding occurs with albumin. A reduction in the degree of binding results in an increase in the concentration of the free pharmacologically active drug and this results in an enhanced effect but also may lead to an increased rate of excretion.

The elimination of drugs may be influenced by the drug binding and drugs can be subdivided on ability of the liver to extract the drug from the binding sites. Drugs are then subclassified as :

a) Restrictive drugs where only the free unbound fraction is available for extraction .

b) Nonrestrictive drugs where both the bound and unbound drug are available for extraction.

Drugs can be classified into groups, from which it may be possible to predict how their systemic availability would alter in disease states (TABLE 4.3).

TABLE 4.3 CLASSIFICATION OF DRUGS ACCORDING TO INTRINSIC CLEARANCE AND PROTEIN BINDING.

GROUP	FREE INTRINSIC CLEARANCE	PROTEIN BINDING
I	HIGH	HIGH
II	LOW	LOW
III	LOW	HIGH

(Drugs with a hepatic extraction ratio of >30% are classified as having a high intrinsic clearance, and a protein binding >85% is considered to be a high value)

From HOYUMPA et al 1978

Group I drugs have a high presystemic elimination, and if there is a significant degree of portal-systemic shunting then there may dramatic changes in the availability of these drugs. Changes in protein binding have little effect on the clearance of these drugs.

Group II drugs are independent of liver blood flow and the major determinant of their elimination should be a change in the intrinsic clearance.

Group III drugs have a high protein binding and if this is high enough then the hepatic clearance becomes proportional to the degree of drug binding.

4.2.8 Portal-systemic shunts

In chronic liver disease a proportion of the blood in the portal vein does not come into contact with the hepatocytes but instead is shunted directly into the systemic circulation. This shunting occurs both extrahepatically through oesophageal varices

and intrahepatically as a result of the disturbed liver architecture. In alcoholic liver disease the degree of shunting varies between 60 - 80 % of the total liver blood flow (GROSZMANN et al 1972). This shunting has important pharmacokinetic consequences particularly for drugs with a high hepatic extraction ratio.

It is possible to calculate the degree of shunting which occurs in liver disease. The "intact hypothesis theory" assumes that the true hepatic extraction [E(true)] is normal in liver disease. The hepatic extraction has now to be expressed as:-

$$E(actual) = E(true).fm \tag{15}$$

where fm is the proportion of the portal blood flowing through the functioning hepatic tissue (WOOD et al 1978).

From equation (8)

$$cl(h) = Q.E = Q.fm.E(true) \tag{16}$$

But neither fm or E(true) can be directly measured. Therefore substituting the intrinsic the equation becomes

$$cl(h) = Q.E = \frac{fm.Q.cl(int^*)}{Q + cl(int^*)} \tag{17}$$

then

$$fm = \frac{cl(h)}{cl(int^*)} + \frac{cl(h)}{Q} \tag{18}$$

This equation now allows the calculation of the apparent intrahepatic shunt, but in order to do this hepatic vein catheterisation is required to calculate the liver blood flow. If it assumed that fm will be the same for two different drugs A

and B then

$$\frac{cl(h)A}{cl(int^*)A} + \frac{cl(h)A}{Q} = \frac{cl(h)B}{cl(int^*)B} + \frac{cl(h)B}{Q} \qquad (19)$$

and rearranging gives a value for Q

$$Q = \frac{cl(h)A - cl(h)B}{\left[\frac{cl(h)B}{cl(int^*)B} - \frac{cl(h)A}{cl(int^*)A}\right]} \qquad (20)$$

this value of Q can then be substituted into equation (16) and a value for fm obtained (MCLEAN et al 1979). The value of such calculations has yet to be established.

4.2.9 Route of administration

It is important to consider the route of drug administration when using drugs as tests of liver function. The oral route usually provides a more sensitive test. Orally administered are affected proportionately more by changes in hepatic extraction than a drug given intravenously. So that a reduction of hepatic extraction from 90 to 80% will decrease the intravenous clearance by 10% but the oral clearance by 100% (GILMORE & HOFMANN 1980).

4.2.10 Breath tests

There are two major problems with the measurement of these pharmacokinetic parameters. Firstly there is a need for frequent blood sampling in order to define accurate kinetic parameters and secondly there may be technical difficulties in measuring the very low concentrations of the drugs which occur in the plasma. Breath tests have been developed in an attempt to overcome these

problems. The basis of these tests is that a test drug is labelled with a small dose of radioactivity, usually in the form of a 14C atom which is placed in the drug at the site where metabolism occurs. Following the initial metabolism of the drug the 14C forms 14Co2 which is then measured in the exhaled breath.

There are two limitations to this approach. Firstly the kinetic parameter which is measured is the plasma disappearance rate which is dependent on both the clearance and the volume of distribution. Secondly the metabolism of the drug is not necessarily the rate limiting step in the appearance of the radioactivity in the breath.

4.2.11 Conventional and distributed models

Various theoretical models have been used to describe the hepatic handling of drugs. In the conventional model the hepatocytes are all "lumped" together within the liver (FIGURE 4.1) and the liver is considered as a "well stirred" bag of hepatocytes. This model predicts that after an instantaneous injection of a drug into compartment P, the plasma concentration will decline as defined by the sum of two exponentials whose slopes and intercepts are simple functions of the rate constant for hepatic uptake (k1) and the rate constant for the return of material from the hepatocytes to the plasma (k2). The drug is then irreversible removed from the liver cells (k3) (RICHARDS et al 1959). This model assumes that the plasma volume is a well stirred compartment and that all the hepatocytes are perfused with the same concentration of drug rather than the range of concentrations found down a sinusoid.

The "parallel tube" model assumes that the liver is composed of a number of parallel tubes with the enzymes evenly distibuted. As the perfusing fluid travels down the tubes so the drug is extracted and the concentration of the drug in the fluid declines (FIGURE 4.2) (FORKER & LUXTON 1978). In this model a small central compartment P receives the bolus of drug. The volume of this compartment is Vp and it represents the volume into which the drug is instantaneously mixed. A compartment R contains a portion of the plasma volume, exchange occurs between P and R at a rate H which is equivalent to the cardiac output minus the hepatic plama flow (F). The splanchnic part of the model contains a parrallel array of sinusoids with a mixing compartment C and a simple delay represented by compartment D. The sinusoidal array consists of a number (m) of identical units (FIGURE 4.3).

Mathematical analysis of these models suggests that the "lumped" model systematically underestimates the rate constants for hepatic uptake and reflux in to the plasma. These errors are most marked in the initial extraction phase. The estimates of the excretion rate constant and the steady state plasma clearance were accurate to within 3% (FORKER & LUXTON 1978). A full appreciation of the two basic models is outwith the scope of this thesis but the can be found in a review by PANG and ROWLAND 1977.

FIGURE 4.1 THE CONVENTIONAL OR "LUMPED" MODEL OF HEPATIC PHARMACOKINETICS

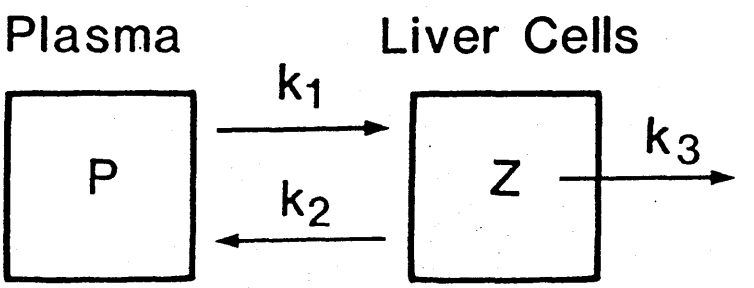


FIGURE 4.2 THE DISTRIBUTED MODEL OF HEPATIC PHARMACOKINETICS

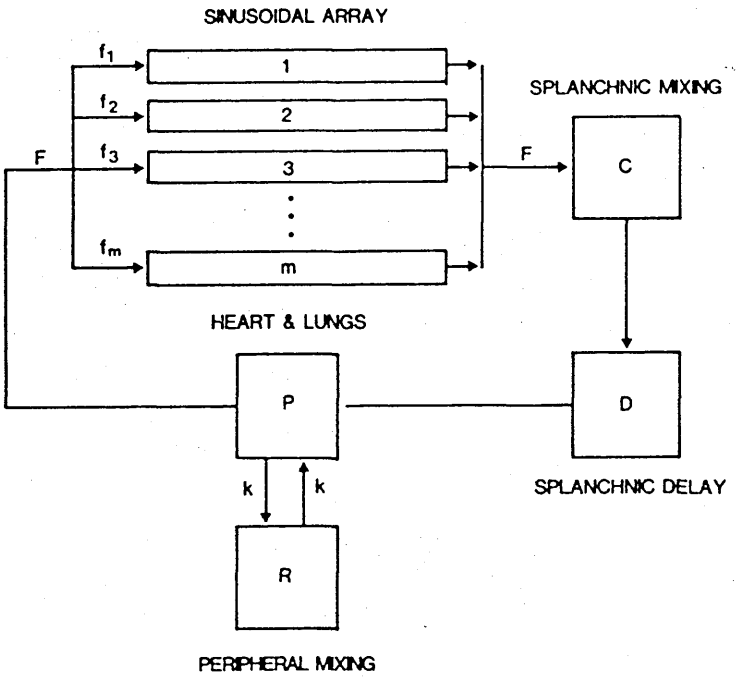
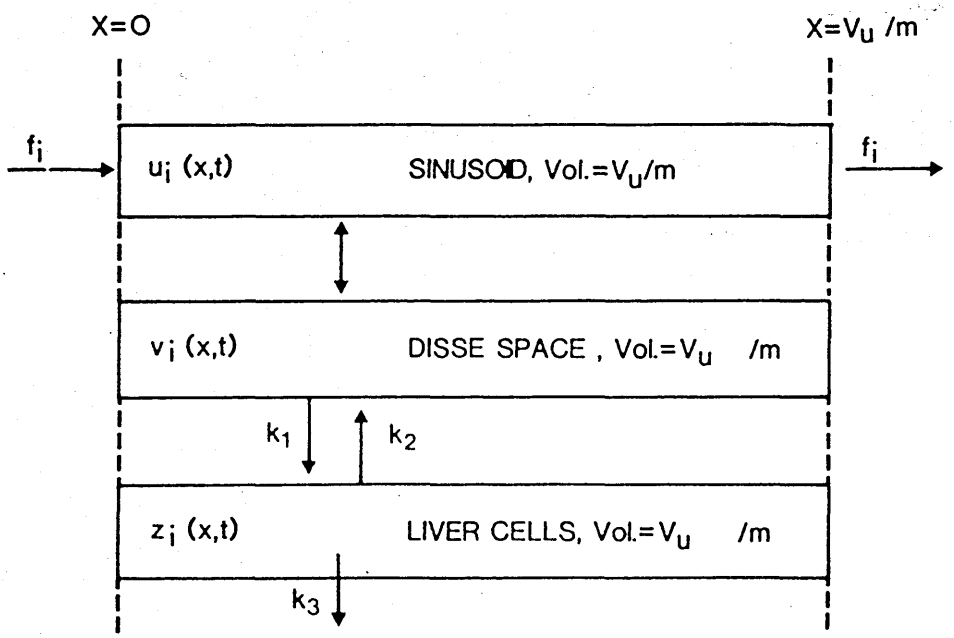


FIGURE 4.3 SINUSOIDAL UNIT OF THE DISTRIBUTED MODEL



4.3 THE INFLUENCE OF LIVER DISEASE ON THE MECHANISMS OF DRUG ELIMINATION

There are three major mechanisms by which liver disease may result in an alteration in the elimination of drugs and each of these mechanisms could theoretically be expected to be particularly relevant to a particular group of drugs. The mechanisms are :-

1. Liver blood flow. There are three factors which it is important to consider in relationship to the liver blood flow.
   a) Total organ flow. This is primarily dependent on the cardiac output and intrahepatic resistance.
   b) Intrahepatic shunts. These are of two types, the large 'anatomical shunts' which allow the passage of 15 micron spheres and red blood cells, and the functional shunts which are vessels perfusion nonfunctioning hepatic tissue (GROSS & PERRIER 1975).
   c) Extrahepatic shunts. These are the major shunts which mainly occur round the oesophagus, retro-peritoneal tissues, umbilicus and scars.

   As previously described alterations in the hepatic blood flow by any of these mechanisms should particularly affect drugs given orally which have a large presystemic elimination.
2. Activity of the microsomal enzymes. A reduction in microsomal enzyme activity may result from a reduced number of viable hepatocytes and possible a reduced functional capacity of the remaining hepatocytes. This mechanism

particularly affects the clearance of drugs with a low hepatic extraction ratio.

3. Plasma Protein. Generally the levels of plasma proteins are reduced in liver disease. Because there are reduced numbers of binding sites in the plasma this will have the effect of increasing the free concentration of the drugs which are highly protein bound. The free drug has a greater degree of access to the elimination mechanisms. So that the major effect of a reduction in plasma proteins will be to increase the plasma clearance of drugs which are highly and restrictively bound to the serum proteins.

Two major theories of the alteration of drug elimination in cirrhosis have arisen. The first termed the "sick cell" theory suggests that the alterations are due to reduced functional activity of the microsomal enzymes within the hepatocytes (BRANCH and SHAND 1976). The second is the "intact hepatocyte" theory which states that the alterations in drug elimination are due to some areas of the liver with normal perfusion and normally functioning enzymes and some areas with large portal-systemic shunts (WOOD et al 1979(b)).

Recent experimental work has cast doubt on the validity of these theoretical considerations. In cirrhotic patients there is an inconsistent alteration in the total liver blood flow but on average there is a modest reduction of 15% (BRANCH & SHAND 1976). This is much less than the changes in clearance which occur in cirrhosis for many of the highly extracted drugs (Appendix 2). It would appear that the critical factors producing the reduction in

clearance is a reduction in the hepatic extraction (HUET and VILLENEUVE 1983). There is however a reasonably good correlation between the clearance of high and low extraction ratio drugs in liver disease (BRANCH & SHAND 1976). From equation (9) for a drug like antipyrine with a low hepatic extraction a twofold reduction in the intrinsic clearance will result in a halving of the total clearance.

ie $$\text{total cl} = \frac{Q.\ \text{int cl}}{Q + \text{int cl}}$$

$$\text{total cl} = \frac{1500.50}{1500 + 50} = 48 \text{ ml/min}$$

with a reduction of the intrinsic clearance of 50%

$$\text{total cl} = \frac{1500.25}{1500 + 25} = 25 \text{ ml/min}$$

Whereas for a drug like indocyanine green with a high extraction ratio a similar reduction in the intrinsic clearance will only reduce the total clearance by 25%.

ie $$\text{total cl} = \frac{1500.3000}{1500 + 3000} = 1000 \text{ ml/min}$$

with a reduction of intrinsic clearance of 50%

$$\text{total cl} = \frac{1500.1500}{1500 + 1500} = 750 \text{ ml/min}$$

This is surprising result because it suggests that the extraction mechanism for drugs with a high hepatic extraction ratio is more sensitive to the effects of liver disease than the mechanism low extraction ratio drugs. This may be so but an alternative explanation has been suggested based on the presence of functional intrahepatic shunts. From equation (13) any change

in the true hepatic extraction ratio produces a smaller than expected change if the actual hepatic extaction ratio because of the presence of shunting. This shunting will have a greater effect on drugs with a high hepatic extraction ratio.

ie low extraction ratio drug

E(actual) = .1 * 100 (if the shunt is 100ml/min)

= 10 ml/min

and for a high extraction ratio drug

E(actual) = .7 * 100

= 70 ml/min

Thus the greater effect of shunting offsets the smaller effect of changes in the hepatic extraction ratio resulting in a good correlation between the clearances of high and low extraction drugs.

4.4 THE EFFECT OF LIVER DISEASE ON THE DISPOSITION OF DRUGS

Appendix 2 contains a list of drugs on which data exists regarding their disposition in various types of liver disease. The list includes a calculation of the percentage difference in the parameters from normal subjects. As expected it can be seen from this list that the elimination of most drugs is impaired to some extent in most forms of liver disease.

There is no standard measure of the severity of liver disease and there is a tendency in the literature to describe the severity of liver disease in histological terms which is clearly invalid. It assumes that patients with cirrhotic liver disease

have a very much poorer prognosis than patients with non-cirrhotic liver disease. However, these generalisations are not valid in clinical practice because many patients with acute hepatitis or alcoholic hepatitis have a much poorer prognosis than patients with inactive cirrhosis. It is therefore not possible to make firm conclusions as to the relative suitability of the various drugs by direct comparison of the results in this list. The list is intended to serve as a data base of the current knowledge of the effects of liver disease on drug metabolism in man.

4.5 THE USE OF DRUGS AS INDICATORS OF HEPATIC DISEASE

There are several drugs which have been evaluated as tests of liver function. Antipyrine and indocyanine green are two of the most extensively studied compounds in this context and their use is reviewed in the appropriate chapters. The other drugs which have been used are reviewed below.

4.5.1 Amylobarbitone

Amylobarbitone has been used as a probe of drug oxidation in man. It elimination depends almost exclusively on hepatic hydroxylation with less than 1% of the administered dose being unchanged in the urine. It is 50-60% protein bound and the salivary concentrations of the drug correlate well with the plasma concentration. The clearance does not correlate well with the clearance of antipyrine suggesting that there may be at least two drug hydroxylating systems in the liver (INABA et al 1976).

4.5.2 Aminopyrine

Dimethylaminoantipyrine (aminopyrine), is rapidly absorbed, evenly distributed in the body water and metabolised by N-demethylation in the liver. A 14C aminopyrine breath test has therefore suggested as an appropriate method for the non-invasive assessment of hepatic demethylation capacity (HEPNER et al 1974). However, there are problems with this technique. Firstly, the rate limiting step of this method remains unclear (PLATZER et al 1978). Secondly, there are various different methods of expressing the results, a 2 hour cumulative excretion (HEPNER & VESSEL 1975; GALIZZI et al 1978(a)) has been used but requires an assumption of the endogenous production of CO_2. Others use repeated measurements to derive a constant for the elimination of 14 CO_2 (BIRCHER et al 1977; SCHOELLER et al 1982). Finally, a modified 2 hour breath test calculated from the area under the breath specific activity curve has been used and found to be more sensitive in detecting enzyme induction by glutethemide than the standard tests (HENRY et al 1979).

Qualitatively, the initial studies suggested that the elimination of aminopyrine was most impaired in parenchymal liver disease rather than cholestasis (HEPNER et al 1977(a)). This allows the test to distinguish between primary biliary cirrhosis and chronic active heptatitis (BURNSTEIN and GALAMBOS 1981). There is a good correlation with serum albumin, BSP clearance (HEPNER & VESELL 1975) the galactose elimination capacity (BIRCHER et al 1973), fasting bile acids, bilirubin, and AST (MORELLI et al 1981). However, the correlation with antipyrine

clearance is poor, and aminopyrine proved to be more sensitive in the detection of minimal liver disease (HEPNER & VESELL 1975). A good correlation has been found between the plasma disapearance rate for the breath test and for direct plasma measurements (BIRCHER et al 1976, HEPNER & VESELL 1976). The breath test responds to the administration of enzyme inducers in normal controls (HEPNER & VESELL 1974) and in patients with cirrhosis (PIKEN & HEPNER 1979). Aminopyrine breath tests have been used to demonstrate intrahepatic enzyme defects in porphyria (OSTROWSKI et al 1983), and as a sensitive indicator of hepatic dysfunction in patients undergoing jejunoileal bypass for obesity (BAKER et al 1983).

When used as a quantitative liver function test there is a good correlation with clinical gradings of the severity of liver disease including the Childs classification (MORELLI et al 1981). The test has prognostic value in alcoholic hepatitis (SCHNEIDER et al 1980) and in patients with liver disease undergoing surgery (GILL et al 1983). In conjunction with thyroid function tests and prothrombin time the aminopyrine breath test is of some value in separating survivors from non-survivors with mixed liver disease (HEPNER & CHOPRA 1979). In a small group of cirrhotic patients the aminopyrine breath test was a poorer predictor of survival than the serum albumin (HENRY et al 1985).

Aminopyrine has two major advantages over antipyrine, firstly it is a completely non-invasive test, and secondly the small doses of aminopyrine involved are unlikely to produce significant microsomal enzyme induction or inhibition, although

induction of gammaglutamyl transpeptidase has been demonstrated in rats (SATOH et al 1982). It also has two major disadvantages, firstly as a breath test it measures the plasma appearance of 14C and this reflects the plasma disapearance rate of aminopyrine which is a variable dependent both on the elimination of aminopyrine and its volume of distribution. Secondly there is doubt about the mechanism of elimination of aminopyrine with a suggestion that only 50-60% of the administered dose is demethylated in the liver (BIRCHER et al 1977).

4.5.3 Cyclobarbital

Cyclobarbital has been evaluated as a suitable probe drug in liver disease. It had a similar ability to descriminate between patients with normal and abnormal liver function test as the aminopyrine breath test (BREYER-PFAFF et al 1984).

4.5.4 Phenacetin

Phenacetin is a drug with a high hepatic extraction ratio whose metabolism is dependent deethylation by cytochrome P448. Its used as a probe drug in liver disease has been suggested and a breath test designed which allowed the clear separation of cirrhotic patients from patients without liver disease (BREEN et al 1984).

4.5.5 HIDA

Technetium-99m n(2,6-dimethylphenylcarbamoylmethyl) iminodiacetic acid (Tc-HIDA) is a radiopharmaceutical which has been extensively investigated as an agent for biliary imaging.

It is eliminated by the liver through its anionic pathway. It has been used as an indicator of liver function but has the disadvantage that its clearance is competitively inhibited by bilirubin (HARVEY et al 1979).

4.6 PHARMACODYNAMIC RESPONSES

This chapter has considered the ways in which liver disease can alter the mechanisms by which drugs are distributed, metabolised and excreted from the body. It is important to remember the effect that these changes may have on the clinical effect of these drugs. Patients with cirrhosis are particularly sensitive to the sedative effects of morphine (LAIDLAW et al 1969), and chlorpromazine (MAXWELL et al 1972, READ et al 1969), tranylcypromine (MORGAN and REID 1972) and diazepam (BRANCH et al 1976(c)). This sensitivity is most pronounced in patients with hypoalbuminaemia or a past history of portosystemic encephalopathy.

The mechanisms of this sensitivity are unknown but may include :

1. Alterations in the cerebral receptors.
2. Increased penetration of the unbound drug into the central nervous system.
3. An accumulation of toxic substances within the central nervous system with the sedatives acting as an extra insult.

The ideal sedative for patients should have a large therapeutic/toxic ratio, it effect should be rapid and easily

titratable, it should have a low degree of protein binding and it should not cause increased cerebral sensitivity. Oxazepam has many of them but it has not been formulated for parenteral use. Lorazepam is metabolised in a similar fashion but its pharmacodynamic response tends to be slow and prolonged. There remains no ideal sedative for patients with severe liver disease.

4.7 CONCLUSION

In conclusion it is possible to identify a number of features which a drug should possess to make it suitable for use as a probe of liver function.

1. It should be non toxic.
2. It should be eliminated solely by the liver.
3. The hepatic elimination mechanism should be altered in liver disease.
4. The drug should be administered orally and should undergo rapid and complete absorption.
5. The drug should have a high hepatic extraction ratio
6. It should be easy to measure in the plasma.

C H A P T E R 5

ANTIPYRINE METABOLISM IN THE ASSESSMENT OF HEPATIC FUNCTION

5.1 INTRODUCTION

Antipyrine was first synthesised in 1884 in the laboratory of Emil Fisher. Initially it was used as an antipyretic but its analgesic properties were soon discovered. It was a popular pain killer until the 1930's when new more effective analgesics such as asprin became available. It was then marketed in combination with chloral hydrate (WELLDORM) and was again widely prescribed.

In 1949 a method for the measurement of antipyrine in plasma was described (BRODIE et al 1949). The observations that it was rapidly and evenly distributed in the body water with a negligible degree of protein binding led to the use of antipyrine as a measurement of the total body water (SOBERMAN et al 1949).

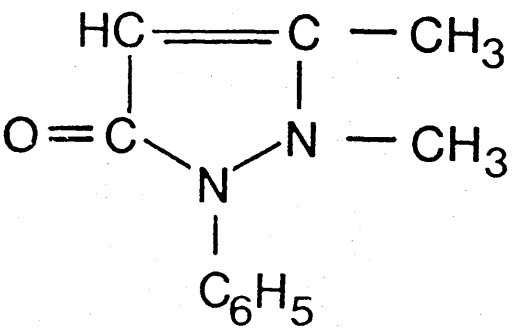
In the 1960's antipyrine was used extensively to investigate the inter-individual variations hepatic drug metabolism and results suggested that these were genetically controlled (VESELL and PAGE 1968). It was also used to measure induction and inhibition of the hepatic monooxygenase enzymes (VESELL and PAGE 1969). The widespread use of antipyrine kinetics as a non-invasive measure of hepatic oxidation was validated by the demonstration of a correlation between antipyrine half life and the cytochrome P-450 content of liver biopsy material taken from patients with liver disease (SOTANIEMI et al 1977a, SOTANIEMI et al 1977b). A close correlation also exists between the antipyrine clearance and the activities of the individual drug metabolising enzymes (VUITTON et al 1981).

In the 1970's antipyrine kinetics was first used to investigate liver disease (BRANCH et al 1973).

Antipyrine has therefore had five major roles in pharmacology :-

1. Therapeutically as Analgesic/Antipyretic.
2. Measurement of total body water.
3. Quantification of interindividual variations in drug metabolism.
4. Measurement of enzyme induction/inhibition.
5. Measurement of liver function.

FIGURE 5.1 THE CHEMICAL STRUCTURE OF ANTIPYRINE



5.2 ANTIPYRINE METABOLISM

5.2.1 Metabolic pathways

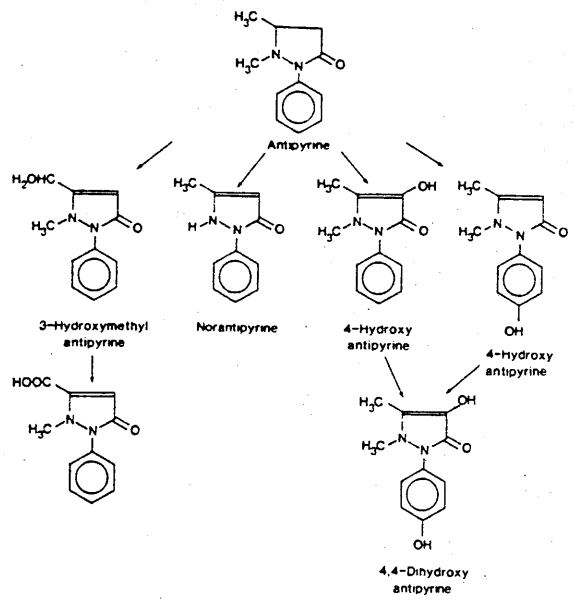
The chemical structure of antipyrine is shown in Figure 5.1. Following the oral administration of antipyrine there is rapid absorption from the gastrointestinal tract and the bio-availability is close to 100%. The drug is evenly distributed in the body water with a negligible degree of protein binding. The hepatic extraction is low at 2% (BRANCH et al 1974) but it is almost completely oxidised by cytochrome P-450 dependent liver microsomal enzymes. Its clearance is therefore relatively independent of liver blood flow. Negligible amounts appearing unchanged in the urine (VESELL 1979(b)) and 65% appears as

oxidised metabolites (DANHOF, VAN ZUILEN et al 1982).

There are at least four major phase 1 metabolites of antipyrine: 4-hydroxy-antipyrine, 3-hydroxymethylantipyrine, norantipyrine and p(4')-hydroxy-antipyrine (BRODIE and AXELROD 1950, YOSHIMURA et al 1968, BATY and PRICE EVANS 1973). It is likely that different enzymes are involved in the production of these different metbolites (DANHOF, et al 1979). These compounds may be further metabolised to 3-carboxy-antipyrine and 4,4 dihydroxy-antipyrine. These metabolites are excreted in the urine as the conjugated glucuronide or sulphated forms. The pathways of antipyrine metabolism are shown in Figure 5.2. The demonstration of a close correlation between the disappearance of antipyrine from the plasma and the appearance of 4-hydroxy-antipyrine in the urine validates the measurement of antipyrine half-life as a measure of antipyrine metabolism (HUFFMAN et al 1974). Antipyrine is also poorly excreted in the bile (ELFSTROM and LINDGREN 1974).

Traditionally its kinetics have been considered to follow a one compartment model (PERRIER and GIBALDI 1974), although there is a biphasic shape to the concentation-time curve suggesting that its kinetics should be evaluated according to a two compartment model. The use of a one compartment model has been justified by a close degree of agreement between the results of data analysed according to the two models (DANHOF, VAN ZUILEN et al 1982). The initial disposition constant and the rates of distribution of antipyrine between the central and peripheral compartments are unaltered in liver disease (GREISEN & ANDREASEN 1976).

FIGURE 5.2 METABOLIC PATHWAYS OF ANTIPYRINE



The initial analysis for antipyrine was by a spectrophotometric assay (BRODIE et al 1949). This method has now been replaced by more sensitive and specific methods based on gas liguid chromatography (PRESCOTT et al 1973, LINDGREN et al 1974), radioimmunoassay (CHANG et al 1976) and high pressure liquid chromatography (DANHOF, De GROOT et al 1979, SHARGEL et al 1979). The methodology for the HPLC method is described in Chapter 7.

The measurement of antipyrine elimination has been simplified by the observation that there if a close correlation between the concentrations in the plasma and saliva (VESELL, PASSANANTI et al 1975(b), WELCH et al 1975, FRASER et al 1976, CHANG et al 1976). Salivary levels of antipyrine are unaffected

by salivary flow rates (VAN BOXTEL et al 1976). Using salivary data the volume of distribution and clearance are slightly elevated compared to data from plasma studies (DANHOF, VAN ZUILEN et al 1982). The use of salivary clearances have validated the use of salivary measurements in in normal subjects and in patients with liver disease (MEFFIN et al 1977, LUOMA and SOTANIEMI 1981). The method can be further simplified by using only a single sample taken at 18 hours after ingestion of antipyrine. A good correlation has been found between this method and multiple plasma sampling (DOSSING et al 1982).

An alternative method of assessing antipyrine metabolism is the measurement of the 4-Hydroxy metabolites in the urine. A good correlation ($r = +0.95$, $P < 0.001$) has been shown between the plasma clearance of antipyrine and the urinary excretion of 4-Hydroxy Phenazone (ANDREASEN & GREISEN 1976).

5.2.3 Antipyrine kinetics in healthy volunteers

Several authors have described normal ranges for the elimination of antipyrine in healthy volunteers (TABLE 5.1) From the result it is clear that there is a very wide inter individual variation in the metabolism of antipyrine.

TABLE 5.1 ANTIPYRINE HALF LIFE IN HEALTHY VOLUNTEERS.

AUTHOR	PLACE	NO	RANGE	MEAN
VESELL & PAGE 1968	PENNSYLVANIA	36	6.9-16.7	10.9
KOLMODIN et al 1969	STOCKHOLM	33	5.2-35.0	13.1
O'MALLEY et al 1971	DUNDEE	61	6.1-23.0	12.0
VESTAL et al 1975	MARYLAND	307	4.8-41.7	13.8

5.2.4 Reproducibility of antipyrine kinetics .

The reproducibility of antipyrine half-lives has been studied in healthy volunteers. The subjects had antipyrine estimations at weekly intervals with a mean variance of 5.1% (VESELL 1979(b)). The reproducibility of antipyrine kinetics in control populations has been demonstrated by other authors (BRANCH et al 1973). In repeated estimations over a periods in excess of a year the half life remains constant (DAVIES et al 1973).

5.3 FACTORS INFLUENCING ANTIPYRINE METABOLISM

The metabolism of antipyrine has been extensively studied in man and a large number of drugs, disease states and patho-physiological states have been identified which influence its metabolism.

5.3.1 Drugs

A list of the percentage changes in antipyrine clearance induced by drugs is included as Appendix One. A large number of drugs exert relatively small changes in the elimination of antipyrine. There are a several drugs which have a major effect in enhancing the elimination of antipyrine (TABLE 5.2). There are only five identified drugs which exert a major inhibiting effect on its elimination (TABLE 5.3). For the purposes of this thesis a major effect on drug metabolism is defined as a mean change in the half life of greater than 30% of the mean baseline.

TABLE 5.2 DRUGS MARKEDLY ENHANCING THE ELIMINATION OF ANTIPYRINE

DRUG	PERCENTAGE CHANGE IN HALF LIFE
Phenytoin	59%
Carbamazepine	55%
Cannabis	55%
Rifampicin	52%
Phenobarbitone	48%
Sulphinpyrazone	42%
Chlorinated Hydrocarbons	41%
Flupenthixol	39%
Spironolactone	38%
Amylobarbitone	36%
Pentobarbitone	35%
Antipyrine	32%
Glutethimide	31%

TABLE 5.3 DRUGS MARKEDLY INHIBITING THE ELIMINATION OF ANTIPYRINE

DRUG	PERCENTAGE CHANGE IN HALF LIFE
Allopurinol	202%
Disulfiram	74%
Combined oral contraceptive	73%
Propranolol	65%
Aminopyrine	60%
Cimetidine	38%

5.3.2 Pathophysiological state

The pathophysiological states in which antipyrine kinetics have been studied are summarised in TABLE 5.4. The changes which occur in the states are generally small.

TABLE 5.4 PATHOPHYSIOLOGICAL STATES AND ANTIPYRINE METABOLISM.

STATE	% CHANGE IN CLEARANCE	AUTHOR
Age (increasing)	52.2	BACH et al 1981
	18.5	VESTAL et al 1975
	Inhibited	O'MALLEY et al 1971
Young men/old men	34.5	GREENBLATT et al 1981
Young women/old women	21.4	GREENBLATT et al 1981
Young men/young women	37.5	GREENBLATT et al 1981
Old men/old women	24.5	GREENBLATT et al 1981
Malnutrition	Inhibited	KRISHNASWAMY et al 1977
	32.8	NARANG et al 1977
Asian Vegetarians	Inhibited	FRASER et al 1977
High carbohydrate/low protein diet	Inhibited	KAPPAS et al 1976
High carbohydrate	18.6	ANDERSON et al 1979
High fat diet	15.7	ANDERSON et al 1979
Low calorie diet	Inhibited	KRISHNASWAMY et al 1984
Anorexia nervosa	19.6	BAKKE et al 1978
Extensive/poor debrisoquine metabolisers	<5	DANHOF et al 1981
White vegeterians	<5	BRODIE et al 1980
Cola nut chewing	<5	VESELL 1979(b)
Exercise	<5	THEILADE et al 1979

STATE	% CHANGE IN CLEARANCE	AUTHOR
Fasting	<5	REIDENBERG et al 1975
High protein	<5	ANDERSON et al 1979
Menstrual cycle	<5	RIESTER et al 1980
Noon/midnight	<5	VESELL,SHIVELY et al 1977
Piperonyl butoxide	<5	CONNEY et al 1982
Summer/winter	<5	PAIGEN et al 1982
Males/female	<5	MUCKLOW et al 1980
Bed rest (3 days)	-12.4	ELFSTROM et al 1978
Sprouts/cabbage diet	-11.3	PANTUCK et al 1978
Charcoal broiled beef	Induced	KAPPAS et al 1978
Low carbohydrate/high protein diet	Induced	KAPPAS et al 1976
High protein diet	Induced	KRISHNASWAMY et al 1984
Ethanol	Induced	VESELL,PAGE et al 1970
Smoking	Induced	WOOD et al 1979(a)
	Induced	HART et al 1976
	-30.1	MUCKLOW et al 1980
Fluid deprivation	-17.2	SWARTZ et al 1974
Exercise	-40.0	SWARTZ et al 1974
Heat	-31.6	SWARTZ et al 1974
Parenteral nutrition	-24.0	PANTUCK et al 1984

5.3.3 Acute liver disease

In acute viral hepatitis the half life of antipyrine can be prolonged by 100% compared to the results on recovery (BURNETT et al 1976). The elimination of antipyrine and galactose indicate correlated with the severity of an attack of acute hepatitis. Patients who died with fulminant liver failure had an almost 100% loss of functioning hepatic cell mass (RAMSOE et al 1980).

5.3.4 Chronic liver disease

The use of antipyrine as a test of liver function was first made popular in 1973 (BRANCH et al 1973). They suggested that the changes in antipyrine kinetics were greater in patients with chronic liver disease than in those with acute reversible liver disease. The antipyrine half life was most prolonged in patients with hypoalbuminaemia and a prolonged prothrombin time suggesting there was a failure of microsomal protein synthesis.

Histology :- There is a correlation between the severity of the histological damage and the antipyrine half life and this was particularly marked in patients with ballooning degeneration of the hepatocytes (FARREL et al 1978).

Encephalopathy :- The antipyrine clearance has been shown to be significantly reduced during episodes of hepatic encephalopathy (4.6 ml/min) compared to measurements when taken there was no clinical evidence of encephalopathy (9.6 ml/min) (ANDREASEN and RANEK 1975). It is suggested that an antipyrine clearance of less than 6 ml/min was usually associated with clinical evidence of encephalopathy.

Severity of liver disease :- The clearance of antipyrine is lower in patients with "incapacitating" liver disease. These "incapacitated" patients had significantly depressed serum albumin but no significant alterations in galactose elimination capacity or the prothrombin time (ANDREASEN et al 1974). The antipyrine half life is prolonged in decompensated chronic liver disease and chronic active hepatitis (FARREL et al 1979). In this study there was a high degree of correlation between the antipyrine half life, prothrombin time, ascites and encephalopathy. Hepatic resection for liver tumours produces a transient reduction in the serum albumin and the clearance of antipyrine (KAIRALUOMA et al 1982).

Enzyme inhibition :- Cimetidine produces no further inhibition of antipyrine metabolism in alcoholic cirrhotics (STAIGER et al 1981). However it is likely that the inhibitory effect of cimetidine was masked by an overall improvement in liver function due to the withdrawal of alcohol. In a similar study the expected inhibition of antipyrine clearance by propranolol was found not to occur in cirrhotics (LARREY et al 1983). This observation may again be due to a concomittant improvement in liver function. However, Propranolol is metabolised within the liver to an active metabolite which inhibits cytochrome P-450 (SCHNECK and PRITCHARD 1981). In cirrhotics the production of this active metabolite may be reduced and therefore the inactivation of cytochrome P-450 may less.

Enzyme induction :- The use of enzyme inducing drugs as

a therapy for patients with liver disease has been explored by observing the effect on standard liver function tests and antipyrine kinetics (RAUTIO et al 1979). Antipyrine has also been used to observe the enzyme inducing effects of spironolactone (MIGUET et al 1980) and glutethimide (FARRELL et al 1979) in liver disease.

Fatty liver :- Non insulin dependent diabetics with fatty livers show a modest reduction in the clearance of antipyrine (PIRTTIAHO et al 1984).

Cholestasis :- The clearance of antipyrine is significantly reduced in patients with intrahepatic cholestasis but not in extrahepatic cholestasis (MIGUET et al 1981).

Screening for liver disease :- Antipyrine kinetics have been used as a screening test for liver disease in a group of workers exposed to various industrial solvents. The induction of antipyrine metabolism was found to be a more sensitive indicator of abnormal liver histology than standard liver function tests (SOTANIEMI et al 1982).

Polycystic liver :- In a family with polycystic liver disease the antipyrine half life was significantly longer in the affected members compared to those with normal livers (LUOMA et al 1980).

Liver volume :- There is a good correlation between liver volume, measured ultrasonically or isotopically, and the clearance of antipyrine has been demonstrated in normal controls

(PIRTTIAHO et al 1978), patients on anticonvulsants (PIRTTIAHO et al 1982) and patients with liver disease (HOMEIDA et al 1979). These results suggest that changes in antipyrine kinetics may reflect changes in hepatic mass but further studies show that in the elderly (BACH et al 1981) and in patients on antiepileptic therapy (ROBERTS et al 1976) there may also be changes in metabolising capacity per unit of hepatic mass. Correction of the antipyrine clearance for the liver volume only marginally improves the seperation of normal subjects from those with cirrhosis (TEUNISSEN et al 1984).

Metabolite production :- The effect of liver disease on antipyrine clearance is complex. In general the production of norantipyrine is reduced more than the rates of formation of hydroxyantipyrine and hydyoxymethylantipyrine (TEUNISSEN et al 1984).

5.3.5 Other disease states

Numerous disease states other than liver disease have been shown to influence the clearance of antipyrine, the effect of these states is summarised in TABLE 5.5. The extent of some of the changes in antipyrine kinetics are marked. For example the antipyrine clearance was reduced 46% in children while they were febrile (FORSYTH et al 1982).

TABLE 5.5 DISEASE STATES AND ANTIPYRINE KINETICS.

Disease state	Clearance	Reference
Etiocholanolone Fever	Inhibited	ELIN et al 1975
Pyrexia	Inhibited	FORSYTH et al 1982
Hypothyroidism	Inhibited	CROOKS et al 1973 EICHELBAUM et al 1974 VESELL,SHAPIRO et al 1974 SAENGER et al 1976
Lead poisoning	Inhibited	MEREDITH et al 1977
Idiopathic hypoalbuminaemia	Nil	PIROLI et al 1981
Uraemia	Induced	MADDOCKS et al 1975
	No Change	HARMAN et al 1977
Osteomalacea	Induced	FRASER et al 1976
Hyperthyroidism	Induced	CROOKS et al 1973 EICHELAUM et al 1974 VESELL,SHAPIRO et al 1974 SAENGER et al 1976

5.4 ANTIPYRINE METABOLISM IN THE PREDICTION OF ALTERED DRUG METABOLISM.

Antipyrine has been used in several studies to predict the metabolism of other drugs. In a small group of cirrhotic patients antipyrine kinetics had some predictive value in determining the livers capacity to metabolise lorcainide (KLOTZ et al 1979) but the correlation just failed to reach statistical significance. Antipyrine kinetics have been used to predict age related changes in the metabolism of benzodiazepines, a correlation was found between antipyrine clearance and those

benzodiazepines which undergo hepatic oxidation (diazepam, prazepam, clorazepam and flurazepam) but not with those which are conjugated (lorazepam, oxazepam and temazepam) (GREENBLATT et al 1981). In another study a significant correlation was found between the clearances of oxazepam and antipyrine (KELLERMAN et al 1979). However the clearance of triazoloam, an hepatically oxidised benzodiazepine, correlated poorly with the clearance of antipyrine (GREENBLATT et al 1983).

The clearance of antipyrine has also been significantly correlated with the clearance of lignocaine (PERRUCA et al 1980), phenylbutazone (DAVIES and THORGEIRSSON 1971a), and oxyphenylbutazone (DAVIES and THORGEIRSSON 1971b).

5.5 CORRELATION OF ANTIPYRINE KINETICS AND STANDARD LIVER FUNCTION TESTS

Most studies show a significant correlation between the serum albumin and prothrombin time and the elimination of antipyrine. Some studies show a weak relationship with the serum bilirubin as well (Table 5.6)

TABLE 5.6 CORRELATION OF ANTIPYRINE KINETICS WITH STANDARD LIVER FUNCTION TESTS.

	n	ALB.	P.T.	BILI	ALK. PHOS	SGOT	SGPT
BRANCH el al 1973	38	***	***	NS	NS	NS	NS
ANDREASEN et al 1974	13	***	***	NA	NA	NA	NA
BURNETT et al 1976	6	NS	NS	NS	NA	NS	NA
FORREST et al 1977	17	**	**	NS	NS	NA	NS
FARRELL et al 1978	62	*	***	*	NA	NA	NS
KRAUSZ et al 1980	25	NS	NS	NS	NS	NS	NS
TAKASHI et al 1981	69	*	*	*	NS	NS	NS

*** $p<0.001$
** $p<0.01$
* $p<0.05$
NS $p>0.05$
NA not available

CHAPTER 6

INDOCYANINE GREEN IN THE ASSESSMENT OF HEPATIC FUNCTION

6.1 INTRODUCTION

Indocyanine green (ICG) was originally synthesised for use as a dye. It has tricarbocyanine structure (Figure 6.1) with a characteristic absorption spectrum at 800nm. During the 1950's it was extensively used in dye dilution studies to measure cardiac output (FOX et al 1957). In the early 1960's its use as a non-invasive measurement of liver blood flow was described (CAESAR et al 1961, LEEVY et al 1962). A good correlation exists between liver blood flow measured by a bolus injection of indocyanine green and direct measurement by electro-magnetic flow meters (NXUMALO et al 1978). The use of ICG clearance as a liver function test was first suggested in the early 1960's (CHERRICK et al 1960).

The use of a drug with a high hepatic extraction ratio is not a new concept in hepatology. For many years the retention of Bromosulphthalein (BSP) has been used as a sensitive indication of hepatic dysfunction. It can be expected that ICG should produce similar results but it has several important advantages compared to BSP :

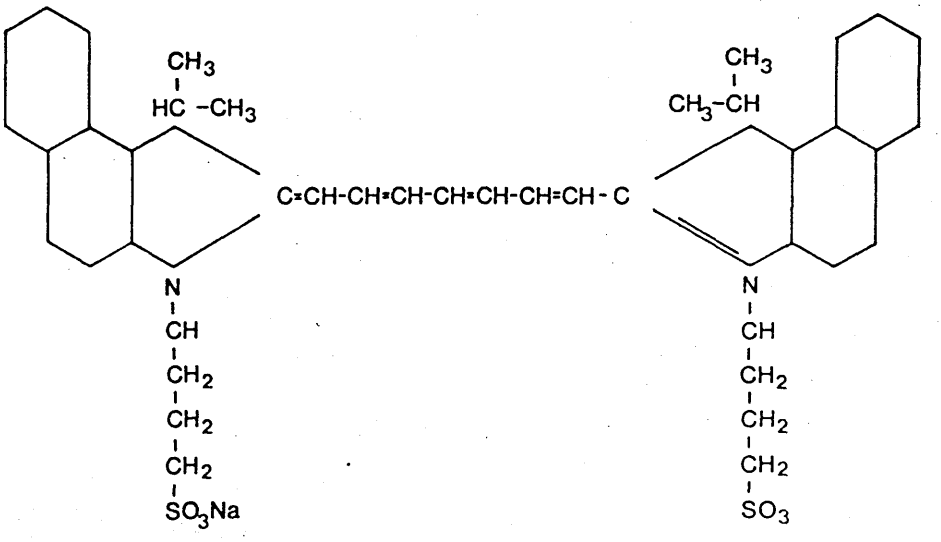
1. Reduced toxicity: One of the reasons that BSP has not been more extensively use is the occurence of occasional anaphylactic reaction. These are less common with ICG (FRICK et al 1979).

2. No hepatic metabolism: ICG is excreted unaltered by the liver, so that its elimination reflects the its rate of delivery to the liver and the liver's ability to extract it from the blood.

3. No enterohepatic circulation: There is evidence for an enterohepatic circulation of BSP, but this has not been found with ICG.

4. No extrahepatic extraction: There is some extrahepatic degradation and elimination of BSP which does not occur with ICG.

FIGURE 6.1 THE CHEMICAL STRUCTURE OF INDOCYANINE GREEN



6.2 INDOCYANINE GREEN DISPOSITION

Following intravenous administration ICG is rapidly bound to albumin (95 %) with some binding to serum globulins (KAMISAKA et al 1974). It is not excreted by the kidney and there is negligible uptake in the peripheral tissues (CHERRICK et al 1960). It is extracted from the blood by the liver but does not undergo biotransformation within the liver (WHEELER et al 1958, RAPAPORT et al 1959, CHERRICK et al 1960). It is excreted in the bile and there is no enterohepatic circulation (HUNTON et al 1960). The use of a constant infusion of ICG at two or three different doses allows the storage capacity of ICG within the liver to be calculated (BRODY & LEICHTER 1979).

The hepatic extraction of ICG can be saturated and at doses of 5mg/kg the plasma disappearance reflects first order kinetics and allows the use of Michaelis-Menton analysis to calculate the maximal rate of removal (Vmax) from the plasma (PAUMGARTNER et al 1970) by the equation:

$$R = \frac{Vmax * (ICG)}{Km + (ICG)}$$

Where R = the disappearance rate of ICG

(ICG) = the dose of ICG

Km = the Michaelis-Menton constant

The estimation of indocyanine green clearance has been simplified by the use of a dichromatic ear piece densitometer for the plasma detection (HOWARD et al 1965). Estimation of the half life and the percentage disappearance rate per minute by this technique shows a close correlation with those determined by

direct plasma measurements (LEEVY et al 1967).

6.3. FACTORS INFLUENCING INDOCYANINE GREEN KINETICS.

6.3.1 Drugs

The elimination of ICG has been shown to be enhanced by phenobarbitone (GOGL et al 1971), which reduced the elimination half life by 64% compared to normal subjects. Similar results were found in a group of patients taking other enzyme inducing drugs including opiates and anticonvulsants (MELIKIAN et al 1972). Further studies failed to find any change in indocyanine green clearance with anticonvulsants (HEPNER et al 1977(b)), phenobarbitone (ROBERTS et al 1979), rifampicin (BREIMER et al 1977) or glutethimide (JACKSON et al 1978). It was postulated that this enhanced elimination may be the result of either increased synthesis of hepatic carrier proteins or increased bile flow, both of these have been demonstrated in animals following drug administration (REYES et al 1971, CONKLIN and WAGNER 1971).

The effect of enzyme inhibition on ICG clearances has also been studied. Single doses of cimetidine reduce the clearance of ICG (FEELY et al 1981), although this is disputed (NELSON et al 1985) and it does not occur with chronic administration (DANESHMEND 1984). Ranitidine has no effect on ICG clearance (MASHFORD et al 1983) or its hepatic extraction (DUNK et al 1983). Propranolol and labetalol produce significant reductions in ICG clearance (DANESHMEND et al 1981) presumably as a result of reduced liver blood flow. Alpha blockade with

Phenoxybenzamine produced no consistent effect on ICG clearance (DANESHMEND 1981 et al). Nifedepine produces an increase in ICG clearance but glyceryltrinitrate reduces it (FEELY 1984).

6.3.2. Pathophysiological states

Genetic: A selective genetic defect in the clearance of ICG is described (OKUDA et al 1976, OHKUBO et al 1981, NAMIHISA et al 1981). It is suggested that there are two separate disorders, one inherited as an autosomal recessive and the other as an autosomal dominant trait (OHKUBO et al 1981). The patients with this defect have a normal or near normal BSP retention.

Smoking: There is no effect of moderate cigarette smoking on ICG clearance (WOOD et al 1979).

Age: The clearance of ICG consistently falls with age (WOOD et al 1979).

Fasting: The effect of calorie restriction on ICG kinetics has been studied in man and in rats (OHKUBO et al 1978). There is an increase in the elimination of ICG in the fasting state and it is suggested that this is the result of

enhanced biliary excretion rather than improved hepatic uptake. This in contrast to the reduced elimination of bilirubin (BARRET 1971) and bromosulphthalein (BRADLEY et al 1969) seen in the fasted state. There is no change in ICG clearance following the intragastric administration of 500ml milk (DANESHMEND et al 1981). Other workers have shown a small increase in ICG clearance following the ingestion of 200 and 400 gram carbohydrate meals (SVENSSON et al 1984).

Pyloric stenosis: An unconjugated hyperbilirubinaemia can complicate pyloric stenosis in infants and has been termed the icteropyloric syndrome. The mechanism of this syndrome is unknown. The clearance of ICG is reduced in children with pyloric stenosis who are not jaundiced but returns to normal levels following surgery to correct the pyloric stenosis (ROTH et al 1981). These results indicate either a reduced liver blood flow or a reduced extraction of ICG in pyloric stenosis. The latter is more likely and may be a result of fasting. this syndrome is not seen in adults with gastric outlet obstruction.

Multisystem injury: The plasma disappearance rate (PDR) of ICG is significantly lower in non-survivors with critical injuries. No patient with a PDR of < 6%/min survived (POLLACK et al 1979). This finding has been confirmed using

the ICG clearance (ICG clearance non-survivors = 4.8ml/min; survivors = 11.1ml/min) (KHOLOUSSY et al 1984). Following major injury the elimination of ICG is reduced and becomes biphasic. The second slower phase of elimination becomes most marked about four days after the injury, at this time the liver blood flow has returned to normal but there is evidence of a marked reduction in the hepatic extraction of ICG (GOTTLIEB et al 1984). The second slower phase of elimination is thought to be due to the removal of the dye across the cannilicular membrane, although it may be due to a failure of intrahepatocyte transport or localisation of the dye within the hepatocyte.

Posture: The erect posture and exercise significantly reduce the clearance of ICG (DANESHMEND et al 1981).

6.3.3. Acute liver disease.

The clearance of ICG is reduced in acute viral hepatitis without any change in the volume of distribution (WILLIAMS et al 1976).

6.3.4. Chronic liver disease.

Gilbert's Syndrome: Studies in Gilbert's syndrome show that some patients have abnormal excretion patterns of ICG. These studies suggest that there is two sub-populations of Gilbert's Syndrome who have abnormalities in the hepatic

transport of organic ions other than bilirubin. There are similarities in Gilbert's Syndrome between the excretion of BSP and ICG suggesting that these two drugs have a common hepatic uptake mechanism (MARTIN et al 1976).

Rotor's syndrome: There is a marked reduction in the clearance of ICG, bromosulphthalein and unconjugated bilirubin in patients with Rotor's syndrome (KAWASAKI et al 1979).

Other liver-disease: ICG has been found to be a sensitive test in the detection of liver disease. This sensitivity may be enhanced by increasing the dose from 0.5mg/kg to 5mg/kg (LEEVY et al 1967). ICG clearance is particularly reduced in patients with surgical portocaval shunts, hypo-albuminaemia (BRANCH et al 1976 (b)), alcoholic cirrhosis and primary biliary cirrhosis (GILMORE et al 1982). The estimation of Vmax has been suggested as a measurement of the functional reserve of the human liver (MOODY et al 1974). Improvements in the Vmax have correlated with improvements in the hepatic histology (BRODY & LEICHTER 1979). But in chronic active hepatitis no consistent improvement in Vmax is found during treatment with azathioprine (RIKKERS & SHERLOCK 1975). In patients undergoing partial hepatectomies for hepatocellular carcinoma a good correlation has been found between the extent of the hepatectomy and the ICG retention at 15 minutes relative to the patients' outcome (OKAMOTO et al

1984).

In chronic liver disease there is a poor correlation between the estimated liver blood flow measured by ICG and that estimated by I131 labelled albumin. The discrepancy arose because of the reduced hepatic extraction of ICG in chronic liver disease (COHN et al 1972). In a group of cirrhotics ICG clearance was found not to be limited by liver blood flow but by changes in the intrinsic hepatic clearance (HUET & VILLENEUVE 1983).

Using discriminant functional analysis ICG clearance has been found to be one of the most useful differential diagnostic tests of liver disease (ITOSHIMA et al 1983).

6.4 INDOCYANINE GREEN KINETICS IN THE PREDICTION OF ALTERED DRUG METABOLISM.

The clearance of ICG does not predict the clearance of propranolol, and the simultaneous administration of propranolol produces an increase in the hepatic extraction of ICG (GRAINGER et al 1983(a)). In acute viral hepatitis there is no correlation between the clearance of lignocaine and any of the standard liver function test or any parameter of ICG disposition (WILLIAMS et al 1976). In patients with congestive cardiac failure and in patient controls there is a good correlation between ICG clearance and Lignocaine clearance (ZITO and REID 1978, HUET & LELORIER 1980) although this is disputed (BAX et al 1980). A good correlation has been demonstrated between estimations of liver blood flow using ICG and Diethyl-Ida. In a group of patients with liver

disease the hepatic extraction of Diethyl-Ida was approximately twice that of ICG suggesting that in these patients with severe liver disease an estimation of liver blood flow by Diethyl-Ida may be more appropriate than that with ICG (MUNOZ et al 1982). The clearance of ICG correlates poorly with the clearances of Diazepam, aminopyrine and antipyrine (HEPNER et al 1977(b)).

6.5 OTHER USES OF INDOCYANINE GREEN IN HEPATOLOGY

The kinetics of ICG and colloidal gold isotope scans have been used as non-invasive monitors of portal hypertension. A significant negative correlation has been demonstrated between the elimination constant of ICG and the portohepatic gradient ($r = -0.612 : p < 0.005$) (MILLETTE et al 1973). In a similar study, however, there was no relationship between the severity of portal hypertension as measured by the corrected hepatic vein pressure neither ICG or Lignocaine clearance (HUET & VILLENEUVE 1983).

The relationship between abnormalities in hepatic colloid scans and liver blood flow has been investigated using ICG (HORISAWA et al 1976). In this study it was suggested that the abnormalities in colloid scans resulted from intrahepatic shunting of blood rather than from a reduction in total liver blood flow.

Recently the intravenous injection of ICG has been combined with peritoneoscopy. This technique allows the demonstration of the distribution of hepatocytes and has also been used to investigate the effect of liver disease on regional liver blood flow (ITO et al 1983; SATO et al 1983).

6.6 CORRELATION WITH STANDARD LIVER FUNCTION TESTS

The ICG clearance has been correlated with serum albumin ($r = -0.63 : p < 0.001$), serum bilirubin ($r = 0.63 : p < 0.001$), and prothrombin time ($r = 0.59 : p < 0.001$). No correlation was found with AST, serum globulin, alkaline phosphatase, age or weight (BRANCH et al 1976).

ICG clearance correlates with serum antipyrine clearance ($r = 0.94 : p < 0.001$) (BRANCH et al 1976).

C H A P T E R 7

METHODOLOGY

In this chapter the basic methodology that was used is described. Where a protocol was used in only one study it is described in the appropriate chapter.

7.1 CLINICAL ASSESSMENT

7.1.1 Diagnosis

The patients with liver disease were admitted either for diagnostic assessment of liver dysfunction or for the investigation and treatment of the complications of liver disease. The aetiology of liver disease has been diagnosed on conventional grounds, based on the clinical history, biochemical liver function tests, specific diagnostic tests and histology.

7.1.2 Clinical Features

The patients were assessed clinically and the size of the liver and spleen recorded in centimetres below the costal margin. The presence or absence of ascites and portosystemic encephalopathy was documented. Patients were graded for portal hypertension (PHT) as follows; a score of 0 = No PHT, 1 = Varices present, 2 = Previous bleeding from varices, 3 = Surgical portocaval shunt.

The serum alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase, gamma glutamyl transpeptidase (GGT) activities and bilirubin and albumin concentrates were measured using standard autoanalyser techniques (Technicon). The clinical and biochemical information were combined to grade the patients using Pugh's modification (PUGH et al 1973) of Child's

classification of the severity of liver disease (See Chapter 3 for details).

7.1.3 Histology

A liver biopsy was performed on 85 patients who had a clinical indication for this technique. The biopsy was performed in the standard intercostal fashion using either a Menghini or Tru-cut needle. The liver sections were stained with the following stains:- haematoxylin and eosin, periodic acid Schiff (PAS) before and after diastase, Masson's Trichrome, Van Giesson, Gordon and Sweets reticulum, Perl's Prussian blue for iron and Shikata's orcein. They were examined by an experienced hepatic histopathologist (Professor R.N.M. MacSween) without reference to the patient's clinical details. The biopsies were graded according to the scheme described by Farrell in 1978 for the following characteristics:

1) Architecture: Graded as:- normal,
dissarray,
active cirrhosis,
or inactive cirrhosis.

2) Necrosis: Graded as:- absent,
focal,
diffuse,
piecemeal,
or confluent.

3) Degree of hepatocellular abnormality: (Graded 1-4 according to the percentage of morphologically abnormal hepatocytes.)

Grade 1 = less than 25% abnormal
Grade 2 = 25-50%
Grade 3 = 50-70%
Grade 4 = > 75%.

4) The presence of specific histological features such as fatty change, parenchymal iron and ballooning degeneration of hepatocytes was also recorded.

7.2 ANTIPYRINE

7.2.1 Protocol

Following an overnight fast 600mg of antipyrine were administered orally at 9.00am and 10ml blood samples collected immediately prior to ingestion over 0,3,5,8,12,24 and 32 hours later. Samples were placed in lithium heparin tubes which were spun in a centrifuge at 2500 revolutions/min for 3 to 5 minutes and the plasma was extracted and stored at minus 20 degree centigrade.

7.2.2 Analytical methods

Antipyrine analysis was performed using a modification (MacPHEE et al 1984) of a high pressure liquid chromatography method (SHARGEL et al 1979). Standard solutions containing 20,15,10,5, and 2 microlitres/ml of antipyrine in methanol were produced. Twelve standard solutions were included in each analytical run. These were three 20's, two 15's, three 10's, two 5's, and two 2's. An internal standard was made using 10 mg of antipyrine in 100ml of methanol.

The test samples were prepared by pipetting one ml of the plasma into each test tube, 100 ul of the internal standard, 250 ml of 0.5 sodium hydroxide and 5 mls of dichloromethane was added to all tubes. The tubes were then centrifuged at 2500 revolutions per minute for 5 to 10 minutes. The supernatant was

removed and placed in a 30 degree centigrade water bath, blown dry and stored at minus 20 degrees centigrade until analysis. Before analysis the samples were reconstituted with 200-400 ul of methanol. The standard samples were used to produce a standard curve. The test samples were then analysed with a further standard included as every sixth sample.

The samples were injected onto a Waters C18V Bondabak column. Antipyrine was detected using a Cecil variable wave length ultraviolet detector. A typical HPLC tracing is shown in Fig. 7.1.

7.2.3 Reproducibility

The laboratory error for the HPLC method was assessed by repeating the analysis on 5 standard solutions. The coefficient of variation varied from 4.1% for the 20ng/ml samples to 8.2% for the 2ng/ml samples (Table 7.1).

The clinical reproducibility of antipyrine kinetics was assessed in fifteen patients with liver disease. Samples were taken on two separate occasions within 2 months with the patients remaining in a stable clinical condition. The mean variance was 7.3% for the half life, 11.7% for volume of distribution and 3.6% for the plasma clearance (Table 7.2).

Figure 7.1 A TYPICAL HIGH PRESSURE LIQUID CHROMATOGRAPHY TRACE SHOWING A PEAK FOR ANTIPYRINE AND THE ANTIPYRINE INTERNAL STANDARD.

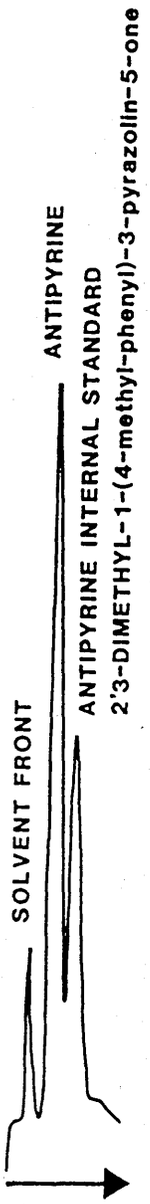


TABLE 7.1

MEAN, STANDARD DEVIATION AND COEFFICIENT OF VARIATION OF REPEATED HIGH PRESSURE LIQUID CHROMATOGRAPHY ANALYSIS OF STANDARD ANTIPYRINE SOLUTIONS VARYING FROM 2-20mg/ml.

Standard concentration	20mg/ml	15mg/ml	10mg/ml	5mg/ml	2mg/ml
1	19.5	13.7	9.0	5.7	2.0
2	19.0	14.3	9.7	4.5	2.3
3	20.8	15.9	11.0	4.8	2.2
4	19.8	15.3	10.3	5.5	1.7
5	18.9	15.7	9.4	5.5	1.9
6	21.0	16.3	10.4	4.7	2.0
7	21.0	15.7	10.6	4.8	2.1
8	20.7	15.2	10.0	4.9	1.9
9	20.3	15.7	10.4	5.0	2.0
10	20.8	14.2	10.7	5.4	1.9
Mean	20.18	15.2	10.15	5.1	2.0
Standard Deviation	0.82	0.85	0.62	0.41	0.17
Standard Error	0.26	0.27	0.20	0.13	0.05
Coefficient of Variance	4.1%	5.6%	6.1%	8.1%	8.2%

TABLE 7.2 REPRODUCIBILITY OF ANTIPYRINE KINETICS IN 15 PATIENTS WITH LIVER DISEASE

	SET 1			SET 2			VARIANCE		
NO.	HALF LIFE (hrs)	VOLUME OF DISTRI BUTION (l)	CLEARANCE (ml/min)	HALF LIFE (hrs)	VOLUME OF DISTRI BUTION (l)	CLEARANCE (ml/min)	HALF LIFE (%)	VOLUME OF DISTRI BUTION (%)	CLEARANCE (%)
1	15.6	27.1	20.1	15.7	27.6	20.3	0.7	1.8	1.5
2	5.7	26.2	53.1	5.6	24.5	50.5	1.8	6.4	4.9
3	12.7	36.5	33.3	12.5	34.7	32.2	1.6	5.2	3.3
4	24.2	17.8	8.5	26.8	17.7	7.6	0.6	7.6	10.6
5	26.4	35.3	15.5	23.4	34.8	17.2	2.0	1.4	9.9
6	29.8	45.7	17.7	29.0	41.5	16.5	3.0	6.8	6.8
7	35.4	48.1	15.7	32.3	44.8	16.0	8.7	16.0	1.9
8	21.4	28.9	15.3	20.5	11.9	16.7	4.2	58.9	6.0
9	20.6	26.3	14.7	21.4	28.4	15.3	3.9	7.4	3.9
10	21.1	35.7	19.5	24.8	42.3	19.7	14.9	18.5	0.1
11	48.4	35.2	8.4	46.0	34.6	8.7	5.0	1.7	3.4
12	25.0	33.4	15.5	23.4	31.7	15.6	6.4	5.2	0.6
13	46.5	45.8	11.4	46.6	46.6	11.5	1.1	1.7	1.0
14	15.6	33.0	24.5	10.3	21.9	24.5	34.0	33.6	0.0
15	10.0	31.6	36.4	10.3	30.7	34.5	3.0	2.9	0.3
				MEAN VARIANCE			7.9	11.7	3.6
				STANDARD DEVIATION			8.5	15.6	3.5
				VARIANCE OF VARIANCES			71.8	244.7	97.0

7.3 INDOCYANINE GREEN

7.3.1 Protocol

Indocyanine green was given as an intravenous bolus of 0.5mg/kg body weight. The patients were fasted overnight, remained recumbent for 30 minutes prior to the injection and throughout the test. Venous blood samples were taken from the contralateral arm through an indwelling catheter at 3 minute intervals to 21 minutes. The samples were centrifuged and the plasma extracted Indocyanine green was assayed spectrophotometrically (CAESAR et al 1961).

7.3.2 Analytical Methods

All specimens were analysed photometrically using a Pye Unicam SP8-200uv/vis spectrophotometer. In an aliquot of plasma blank a known dye concentration of approximately 5ng per litre was prepared from the vial of dye administered to the patient. For each patient plasma specimens and standards were read against the patient's plasma blank.

7.3.3 Reproducibility

The reproducibility of indocyanine green kinetics was assessed in 19 patients with chronic liver disease. Two sets of samples were taken within a 2 month period while the patients were clinically stable. The mean variance was 8.1% for the half life, 12.6% for the volume of distribution, 10.7% for the plasma clearance and 13.4% for the whole blood clearance (Table 7.3).

TABLE 7.3 REPRODUCIBILITY OF INDOCYANINE GREEN KINETICS IN 19 PATIENTS WITH CHRONIC LIVER DISEASE

NO	HALF LIFE (min)	VOLUME OF DISTRIBUTION (l)	PLASMA CLEARANCE (ml/min)	WHOLE BLOOD CLEARANCE (ml/min)	HALF LIFE (min)	VOLUME OF DISTRIBUTION (l)	PLASMA CLEARANCE (ml/min)	WHOLE BLOOD CLEARANCE (ml/min)	HALF LIFE (min)	VOLUME OF DISTRIBUTION (l)	PLASMA CLEARANCE (ml/min)	WHOLE BLOOD CLEARANCE (ml/min)
1	7.1	1.4	134.5	226.5	7.2	2.7	259.7	436.7	1.1	49.4	12.9	48.1
2	19.4	3.87	135.8	212.3	12.6	3.5	190.7	295.6	35.7	9.8	10.2	28.3
3	13.9	5.01	249.4	481.9	14.1	4.0	196.4	365.8	1.4	20.6	21.2	20.8
4	14.1	4.1	201.7	373.6	13.7	4.2	213.2	387.7	3.1	2.6	5.6	3.6
5	8.3	5.4	447.4	780.8	5.7	3.0	366.7	288.7	31.2	43.7	18.1	1.0
6	9.4	3.8	277.3	390.5	8.2	3.1	263.7	399.6	12.5	16.5	5.3	2.3
7	8.2	3.1	263.8	399.7	8.6	4.0	322.5	532.7	4.3	21.8	19.3	25.0
8	5.1	3.8	519.0	887.0	6.1	3.7	419.5	670.6	16.5	2.1	20.8	24.5
9	5.8	5.6	697.0	1203.0	5.6	5.6	697.7	1202.0	0.7	0.0	0.1	0.1
10	12.6	5.0	275.6	488.6	10.7	4.8	313.3	535.6	15.0	3.9	12.0	16.3
11	22.4	6.7	209.0	231.2	24.6	5.1	142.4	237.0	9.1	24.9	47.1	28.4
12	21.2	6.2	201.0	327.9	18.9	4.9	193.1	330.1	11.0	20.5	4.0	0.6
13	8.5	5.2	427.4	633.1	8.5	5.2	424.9	910.0	0.1	0.0	0.7	30.4
14	38.5	4.3	77.7	131.7	36.8	4.4	82.7	142.6	3.2	2.1	6.1	7.7
15	10.5	2.9	189.9	316.6	10.4	2.9	191.0	312.3	1.0	0.0	0.0	1.3
16	14.3	3.9	191.0	282.8	14.4	3.4	164.3	254.7	0.7	12.8	14.1	10.2
17	11.8	4.4	259.2	370.3	11.7	4.3	253.6	367.0	0.9	2.3	2.3	0.8
18	11.1	5.5	343.9	529.1	11.5	5.7	342.7	523.3	3.5	3.1	0.3	1.1
19	3.9	3.1	546.6	881.7	3.9	3.2	561.5	913.0	2.6	3.1	2.8	3.5
						MEAN VARIANCE			8.1	12.6	10.7	13.4
						STANDARD DEVIATION			10.4	14.6	11.4	14.1
						VARIANCE OF VARIANCE			107.2	214.7	130.7	198.4

7.4. MEPTAZINOL

7.4.1 Protocol

See chapter 13

7.4.2 Analytical Methods

The plasma samples were stored in glass tubes at -20 degrees Centigrade prior to analysis.

Preparation of Standard Solutions

Standard solutions were prepared using meptazinol hydrochloride (Batch no. 3/E/11773), 10mg were added to 100ml of methanol (MEOH) and mixed with a rotor for 15 minutes. One ml of this solution was added to a further 100ml of MeOH and mixed for 15 minutes. This working standard solution contains 100ug of meptazinol hydrochloride in 100ml MeOH.

Twenty milligrams of an internal standard (WY 32128A: M-(1- Cyclopropylmethyl-3-Ethylhexahydro-1H-Azepin-3-YL Phenol) was mixed for 15 minutes with 100ml MeOH and one ml of this solution mixed with 100ml of MeOH for a further 15 minutes. The internal standard contained 200ug in 100ml MeOH.

A Buffer solution was prepared using 8.4grams of sodium bicarbonate in 100ml of water with the Ph adjusted to 9.7 with strong sodium hydroxide.

Preparation of samples

One ml of the unknown plasma was added to glass screw top test tubes. For the blanks and standard samples 1ml of pooled plasma was used. A range of standard solutions was produced containing 5,10,20,50,100,150 and 200ng of meptazinol hydrochloride.

To all the tubes except the blanks, 100ml (200ng) of the internal standard was added and the samples mixed. 200ml of the 1M NaHCo3 Buffer was added to all tubes and the samples were mixed. 5ml of Dichloromethane was added to each tube and they were immediately vortex mixed for 3 seconds. All the samples were mixed for a further 15 minutes in a flat mixer.

The samples were then spun at 2,500 rpm for 10 minutes. The top layer was pipetted off and the samples placed in a water bath at 50 degrees Centigrade and dried with an air blower. The dried samples were stores at -80 degrees Centigrade.

Chromatography

The samples were reconstituted using MEOH prior to high pressure liquid chromatography. The reconstituted extracts (100nl) were injected using a WISP (Model 710B, Waters Associates Ltd., Hertfordshire) onto a 5 micron analytical column. This column was packed using Shandon column packer. The column was of 5mm internal diameter and 25cms in length. This column was used in conjunction with a pre-column of the

same material and same size. A reciprocating HPLC pump (Gilson) was used to elute the column and the eluent composition was 50% acetenitryl and 50% amodium acetate solution (0.5% W/V) at a flow rate of 1.8ml/min (pressure approximately 2000 psi).

A fluourescent spectrometer (Model 3000, Perkin Elmer, Beaconsfield, Bucks) assess an accentation wave length of 282 nanometers and internal standard by means of their native fluourescence. Both monochromators were set with 10 nanometer slit widths. Data handling was carried out by a computing integrator (Shimadzu C-Rib) operating at the peak area mode. A calibration curve was prepared from samples of drug free plasma to which meptazinol various concentrations was added. The peak areas were integrated and after calculating the peak area ratio (meptazinol - internal standard) the integrator computed the best fit line through the calibration points. The plasma concentrations of meptazinol were then calculated from this line. A typical tracing is shown in Fig. 7.2.

7.4.3 Reproducibility

The laboratory error of this method was investigated by analysing 10 identical samples and 5 different concentrations. The results of this analysis are shown in Table 7.4. The limited detection of meptazinol was 10ng/ml.

Figure 7.2 A TYPICAL HIGH PRESSURE LIQUID CHROMATOGRAPHY TRACE SHOWING PEAKS FOR MEPTAZINOL AND MEPTAZINOL INTERNAL STANDARD

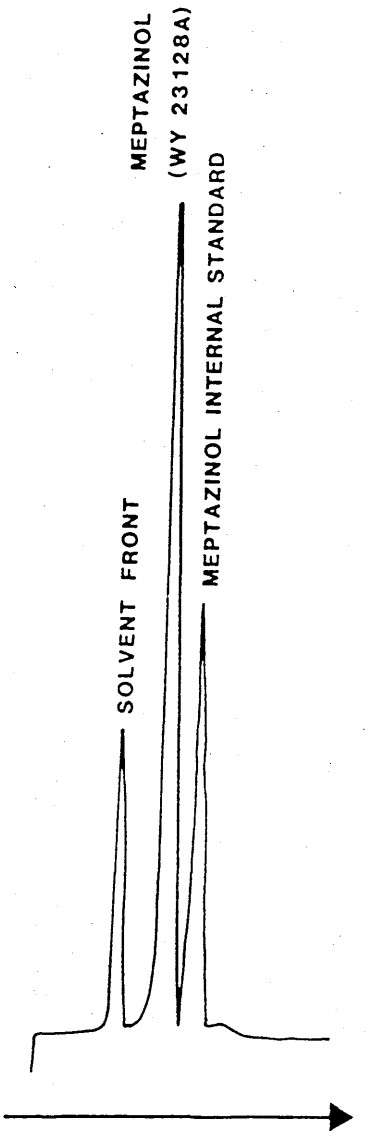


TABLE 7.4 MEANS, STANDARD DEVIATION, STANDARD ERROR AND COEFFICIENT OF VARIATION OF MEPTAZINOL MEASUREMENTS AT 5 DIFFERENT CONCENTRATIONS.

	100ng corrected to first whole no.	75ng corrected to first whole no.	50ng corrected to first whole no.	20ng correct to first dec.place	10ng corrected to first dec.place
1.	110	80	50	18.0	8.4
2.	100	73	56	20.9	9.7
3.	99	70	55	19.3	12.0
4.	93	78	50	18.9	10.4
5.	100	73	51	21.3	10.0
6.	100	75	47	17.0	9.8
7.	95	73	49	20.8	10.7
8.	96	76	53	20.0	8.9
9.	95	79	54	21.5	9.8
10.	103	74	48	20.4	10.5
Mean	99.1	75.1	51.3	19.8	10.0
Standard Deviation	4.9	3.1	3.0	1.5	1.0
Standard Error	1.6	1.0	1.0	0.5	0.3
Coefficient Variation	5.0%	4.6%	5.9%	7.5%	9.9%

7.5 MIDAZOLAM

7.5.1 Protocol

See chapter 12

7.5.2 Analytical Methods

Plasma midazolam concentrations were determined using a gas chromatography method (HEINZMANN and VAN ALTEN 1981). This method has a sensitivity of 5ng/ml and a 6 point calibration curve was included in each sample batch along with quality assurance samples. This analysis was performed by Dr. Dixon at the Royal Bath Hospital, Harrogate.

7.6 PHARMACOKINETIC ANALYSIS

For antipyrine and indocyanine green the pharmacokinetic constant of elimination (k) was calculated by the method of least square regression analysis assuming a one compartment model. The apparent volume of distribution (Vd) was calculated from the formula -

$$Vd = Dose/CO$$

where CO = the estimated concentration of the drug at time zero, extrapolated in a log-linear scale.

The apparent plasma clearance was calculated from the relationship -

$$Cl = Vd * K$$

For indocyanine green the plasma clearance was corrected by the haematocrit to give the whole blood clearance.

Area under the concentration/time curve was calculated by the trapezoidal rule.

This analysis was performed on an Apple IIE microcomputer and the programs used for antipyrine and indocyanine green are listed in Appendix 4.

The pharmacokinetic analysis of the midazolam and intravenous meptazinol data was performed using an iterative non linear least squares regression program (included in the VASP software package made available by Dr. A.W. Kelman, Department of Nuclear Medicine and Materia Medica, Stobhill Hospital, Glasgow) on a NODECREST V70 series digital computer. The data was fitted using one and two compartment models.

The function for the one compartment model was :

$$Y = Co \times e^{-Ke\ t}$$

where $Ke = Cl/vd$

The two compartment model was fitted to a biexponential model using the function

$$Y = Ae^{-Alpha.t} + Be^{-Beta.t}$$

where A and B were expressed using the parameters Cl, V1, K12, K21.

where Cl = clearance

K12 = rate constant for the central to peripheral compartment

K21 = the rate constant for the peripheral to central compartment

V1 = the volume of the central compartment

The two models were compared using the F distribution where:

$$F = \frac{SSQ(R) - SSQ(F)}{df(R) - df(F)} \Big/ \frac{SSQ(F)}{df(F)}$$

where SSQ(R) = Residual sum of squares for one compartment model

SSQ(F) = Residual sum of squares for two compartment model

df(R) = Degrees of freedom for one compartment model

df(F) = Degrees of freedom for two compartment model

The one compartment model was selected unless the significance of the F statistic was < 0.05.

7.7 PHARMACODYNAMIC ASSESSMENT

In the midazolam and meptazinol projects assessments were made of the degree of sedation and nausea induced by the drugs.

Psychomotor function was assessed using a Leeds Psychomotor tester. This measures the critical flicker fusion threshold (CFFT) and the choice reaction time (CRT). (HINDMARCH 1980). The CFFT is measured by asking the subject to observe 4 small red lights (Fig. 7.3). The frequency at which these lights flicker is then increased or decreased and the subject indicates the frequency at which the lights fuse or start to flicker by pressing a button. A mean of six readings are taken. The CRT measures the time the subject takes to move his finger from one button to another at a given signal (Fig. 7.4). The subject is presented with a choice of six buttons to which he must move his finger, each being indicated by a red light. The CRT is split into the CRT1 or recognition time which is the time taken from the indicator light being switched on to the subject lifting his finger from the base point. The total reaction time, or CRT2, is

the total time from the indicator light being illuminated to the subject moving his finger to the appropriate button. For each CRT reading a mean of 30 responses were taken. During the 24 hours prior to the administration of the drugs the subjects had a minimum of three practice runs on the Leeds tester followed by a further 3 runs to establish a base line response. For the analysis the difference between the mean CRT/CFFT results and the patient's baseline results were calculated and the mean of these differences for each time point compared between the control and disease groups.

Simple visual analogue scales of sedation and degree of nausea were also used. These were 10cm lines marked as follows:

Wide awake ----------Very sleepy

Not nauseated----------Feeling very sick

The subjects were asked to record their feelings at each time point in these scales.

FIGURE 7.3 CRITICAL FLICKER FUSION THRESHOLD

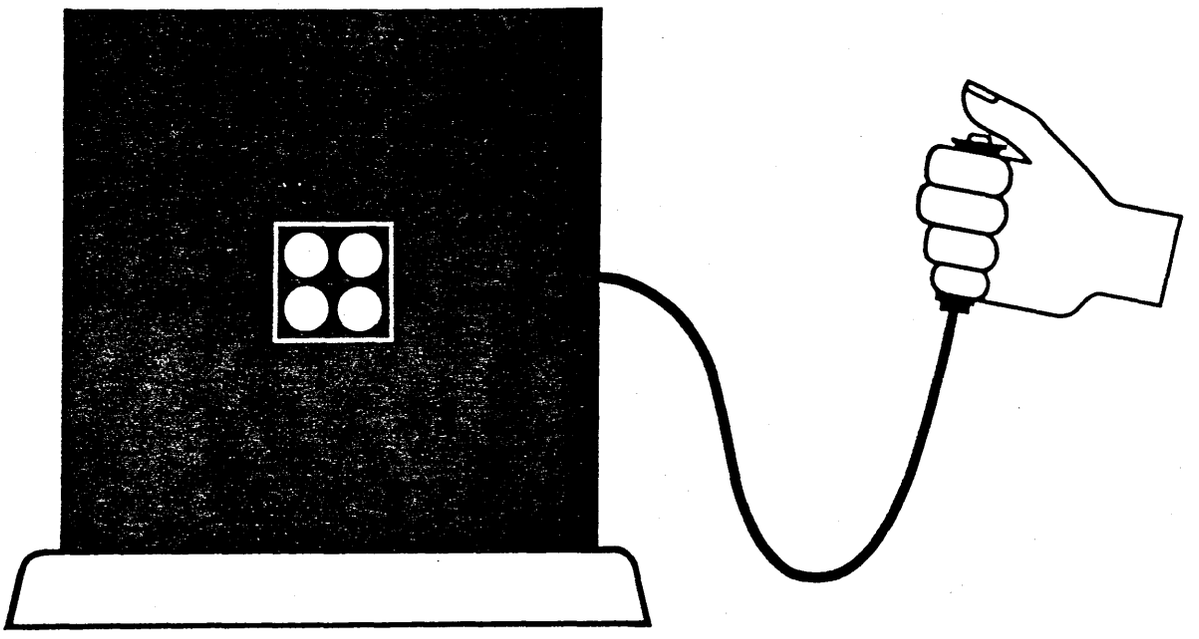
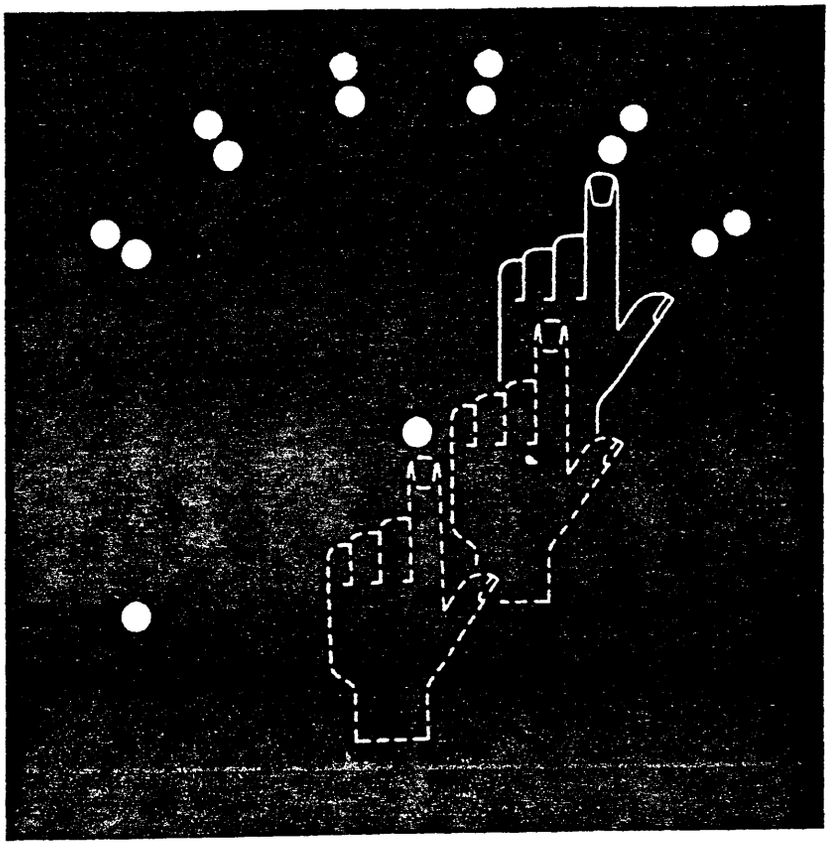


FIGURE 7.4 CHOICE REACTION TIME



7.8 STATISTICAL METHODS

7.8.1 Standard Statistics

Standard parametric and non parametric statistical techniques have been used for comparing the various groups in this thesis. Where appropriate, Paired Wilcoxon, Mann Whitney U-tests and Kruskal Wallis analysis of variance, Student's t-test and parametric analysis of variance have been used. The specific tests used are indicated in the text. Non parametric correlation was performed using the Spearman Ranking procedure. The following microcomputer programs were used in the analysis:

a) MINITAB - (Minitab Incorporated, 215 Pond Laboratory, University Park, PA 16802). This program was modified for use on an Apricot microcomputer by the department of computing at Glasgow University and was supplied by them with a sub-license.

b) STATSTREAM. A program originally devised at the School of Biological Sciences, University of East Anglia, Norwich NR4 7TJ. The program is written for an Apple II microcomputer and is distributed through Elsevier - Biosoft, 68 Hills Road, Cambridge CB2 1LA.

c) BIODATA HANDLING FOR MICROCOMPUTERS. This program was written by R.B. Barker of the Department of Clinical Pharmacology, Bristol University and is also distributed by Elsevier-Biosoft.

7.8.2 Proportional Hazards Regression

The simultaneous influence of a number of variables on the survival of the patients have been investigated using Cox's Proportional Hazard model (COX 1972). This type of analysis has been designed to take into consideration two characteristics of survival data. Firstly, the data usually contains incomplete observations. If a number of patients are followed for a period of time, a proportion are likely to survive to the time of analysis. The complete survival information is not available on on these patients. Nevertheless, the information that they survived for a certain period of time can be used in the analysis. Secondly the distribution of survival times mean that standard multiple linear regression is not an appropriate statistical test for the analysis of such data. Proportional hazards regression does not assume a specific distribution of the data.

In the Cox's proportional hazard model the hazard or risk of death (H) at time t for a patient with variables Z1 to Zp is expressed by -

$$H(t) = Ho \ (B_1 \ Z_1 + \ldots\ldots Bp \ Zp) \ t > 0$$

where Ho is the underlying hazard and Bl-------Bp are regressional coefficients of variables Z1 to Zp. If regressional coefficient Bl is positive high values of the corresponding variable Z1 indicate a high hazard or worse progression and vice versa if Bl is negative. If Bl is zero the corresponding variable Z1 has no influence in survival.

CHAPTER 8

ANTIPYRINE METABOLISM IN PORPHYRIA IN RELAPSE AND REMISSION

8.1 SUMMARY

Antipyrine kinetics following a single oral dose were obtained in porphyric patients in attack and in remission and in controls. The clearance of antipyrine was significantly lower during an acute porphyric attack (median: 0.34 ml/min^{-1} kg^{-1}; range: 0.1 - 0.71, $P < 0.05$) than in patients in remission (median 0.53 $ml/min^{-1}kg^{-1}$, range: 0.28 - 0.87) or controls (median: 0.52 ml/min^{-1} kg^{-1}; range: 0.32 - 0.93). There was a significant negative correlation between weight-adjusted antipyrine clearance and the urinary excretion of the porphyrin precursors, delta-aminolaevulinic acid ($r = -0.86$, $p< 0.001$) and porphobilinogen ($r = -0.82$, $p<0.002$). These data suggest that the more severe the porphyric attack, the greater the impairment of hepatic monooxygenase activity.

8.2 INTRODUCTION

The acute hepatic porphyrias are a group of rare conditions in which there are hereditary abnormalities in the biosynthesis of haem (GOLDBERG et al, 1983) (Figure 8.1). Patients can present with acute abdominal pain, autonomic dysfunction and neuropsychiatric disturbance (BRODIE and GOLDBERG 1980). During an acute attack an excess of the porphyrin precursors delta-aminolaevulinic acid (ALA) and porphobilinogen (PBG) is found in the urine. This abnormality persists when the acute attack remits although usually to a lesser degree. In all patients, hepatic haem synthesis is diminished due to reduced activity of one enzyme in the pathway specific for each type of porphyria. Consequently, the initial and rate-limiting enzyme, ALA-synthase (ALA-S), is derepressed by negative feedback. Elevated activity of this enzyme can be measured in circulating leucocytes (BRODIE et al, 1977b) and provides an important extra index for the identification of latent cases (McCOLL et al, 1982).

The majority of haem synthesised in the liver is utilised for the formation of the haemoprotein cytochrome P450 which forms the terminal component of the hepatic mixed function oxidase enzyme system (GOLDBERG et al, 1983).

The purpose of this study was to assess monooxygenase activity, as reflected by antipyrine metabolism, in patients with acute porphyria in attack and in remission, and to attempt to correlate this activity with the extent of the biochemical defect in haem biosynthesis.

8.3 PATIENTS AND METHODS

The study was carried out in 16 patients (14 female, 2 male) with hereditary hepatic porphyria. Fourteen had acute intermittent porphyria (AIP) and 2 variegate porphyria (VP). The diagnosis had previously been made by demonstrating increased porphyrin and precursor excretion together with reduced activity of the appropriate enzyme in circulating blood cells and elevation of leucocyte ALA-S activity. Eight patients (7 AIP, 1 VP) had typical symptoms of an acute attack (Group 1) and a further 8 (7 AIP, 1 VP) were clinically in remission (Group 2). No patient was receiving any drug known to affect antipyrine metabolism. Eight non-medicated patients investigated for irritable bowel syndrome served as controls (Group 3). All patients had normal standard biochemical liver function tests. Females predominated in each group with 8 in Group 1 and 7 each in the other 2 groups. One patient in Group 1 smoked fewer than 10 cigarettes per day. No patient in the other two groups smoked tobacco. The median age of the patients in the three groups was as follows: Group 1: 32 years (range 18-47), Group 2: 38 years (range 17-54), Group 3: 45 years (range 30-50). The patients with acute porphyria in attack were lighter than those in the other two groups but this difference was not statistically significant. [Group 1: median 55.8kg (range 43-71); Group 2: median 66kg (range 52-74); Group 3: median 68.7kg (range 55-79)].

Antipyrine kinetics were determined using the Protocol in Chapter 7. Prior to the administration of the antipyrine dose,

30ml of blood were withdrawn for immediate assay of leucocyte ALA-S activity and a 24 hour collection of urine for porphyrin and precursor measurement was commenced.

Leucocyte ALA-S activity (BRODIE et al, 1977b) and urinary ALA, PBG and total porphyrin content (MOORE 1983) were obtained using standard techniques.

Results are quoted as medians and ranges. The statistical analysis used Mann Whitney U tests and correlations were obtained by the Spearman ranking procedure.

8.4 RESULTS

Leucocyte ALA-S activity and porphyrin precursor excretion in the porphyric patients together with the kinetics of antipyrine for all 3 groups are shown in Table 8.1. The porphyrics in attack had significantly higher leucocyte ALA-S activity and increased urinary ALA, PBG and total porphyrin excretion compared with those in remission (all $p<0.05$). The weight-adjusted clearance of antipyrine was lower in these patients (median 0.34ml/min^{-1} kg^{-1}; range 0.1-0.71; $p<0.05$, Figure 8.2) than in those in remission (median 0.53ml/min^{-1} kg^{-1}; range 0.28-0.87) and than in controls (median 0.52ml.min^{-1} kg^{-1}; range 0.32-0.93). The volume of antipyrine distribution was reduced in both porphyric groups (attack: median 22.5L; range 10.1-42.4; remission: median 23.2L; range 17.2-41.3; controls: median 37.3L; range 24.6-50.0, $p<0.05$). There were significant negative correlations between the antipyrine clearance (ml/min^{-1} kg^{-1}) and the urinary excretion of ALA ($r = -0.86$, $p<0.001$) and PBG ($r = -0.82$, $p<0.002$) but not with total porphyrins ($r = -0.45$) or the activity of leucocyte ALA-S ($r = -0.45$).

8.5 DISCUSSION

This study confirms that acute attacks of porphyria are associated with temporary impairment of hepatic oxidation of antipyrine (ANDERSON et al 1977). Altered hepatic metabolism has also been reported for Salicylamide (SONG et al 1974), and aminopyrine (OSTROWSKI et al 1983) but not for phenylbutazone (ANDERSON et al 1976) or indocyanine green (STEIN et al 1970). The reduction in antipyrine volume of distribution in all the porphyric patients was unexpected and remains unexplained. It may reflect a diminution in muscle bulk consequent upon the motor neuropathy.

In the acute hepatic porphyrias there are various enzyme defects in the haem biosynthetic pathway which result in a relative deficiency of hepatic haem and an accumulation of circulating haem precursors. The majority of haem synthesised in the liver is incorporated into cytochrome P450 which forms the terminal component of the mixed function oxidase enzyme system (GOLDBERG et al, 1983). Antipyrine is almost completely metabolised in the liver by oxidative processes and the different rates of production of its metabolites reflect the activities of the enzymes producing them (BOOBIS et al 1981). Reduced elimination of antipyrine in patients with porphyria could be a consequence either of reduced cytochrome P450 necessary for its metabolism or from a functional inhibition of monooxygenase activity by circulating ALA or PBG. The significant negative correlation between the extent of porphyrin precursor excretion and the elimination of antipyrine can support either possibility. The correlation between leucocyte ALA-S activity and antipyrine

clearance did not reach statistical significance. However, the patient numbers were small and the activity of ALA-S in leucocytes may not reflect that present in hepatic tissue.

The close correlation between the amount of both porphyrin precursors excreted in the urine and the antipyrine clearance suggests that the more severe the porphyric attack the greater is the impairment of hepatic monooxygenase activity.

TABLE 8.1 HAEM BIOSYNTHETIC ENZYME ACTIVITIES, URINARY PORPHYRIN AND PRECURSOR EXCRETION AND ANTIPYRINE KINETICS IN PORPHYRICS IN ATTACK AND IN REMISSION TOGETHER WITH ANTIPYRINE KINETICS IN CONTROLS

	LEUCOCYTE	<----------URINARY---------->			<----------ANTIPYRINE---------->		
	ALA-S (umol h^{-1} mg protein^{-1})	ALA (umol/ 24h)	PBG (umol/ 24h)	TOTAL PORPHYRINS (ug/24h)	HALF LIFE (hrs)	VOLUME OF DISTRIBUTION (l)	CLEARANCE (ml/min)
Attack (n = 8)	3327[a] (746-7812)	128[a] (71-418)	280[a] (62-651)	670[a] (329-5006)	15.1[b] (7.7-34.9)	25.5[c] (10.1-42.2)	20.4[b] (5.9-42.5)
Remission (n = 8)	747 (419-2542)	19 (8-166)	10 (0-260)	95 (26-291)	8.1 (4.6-15.5)	23.2[c] (17.2-41.3)	36.0 (15.7-43.0)
Control (n = 8)	[50-300]	[0-40]	[0-16]	[0-300]	11.0 (8.7-14.1)	37.3 (24.6-50)	39.5 (24.3-54.7)

Figures are medians (ranges) with normal ranges in square brackets [ ]

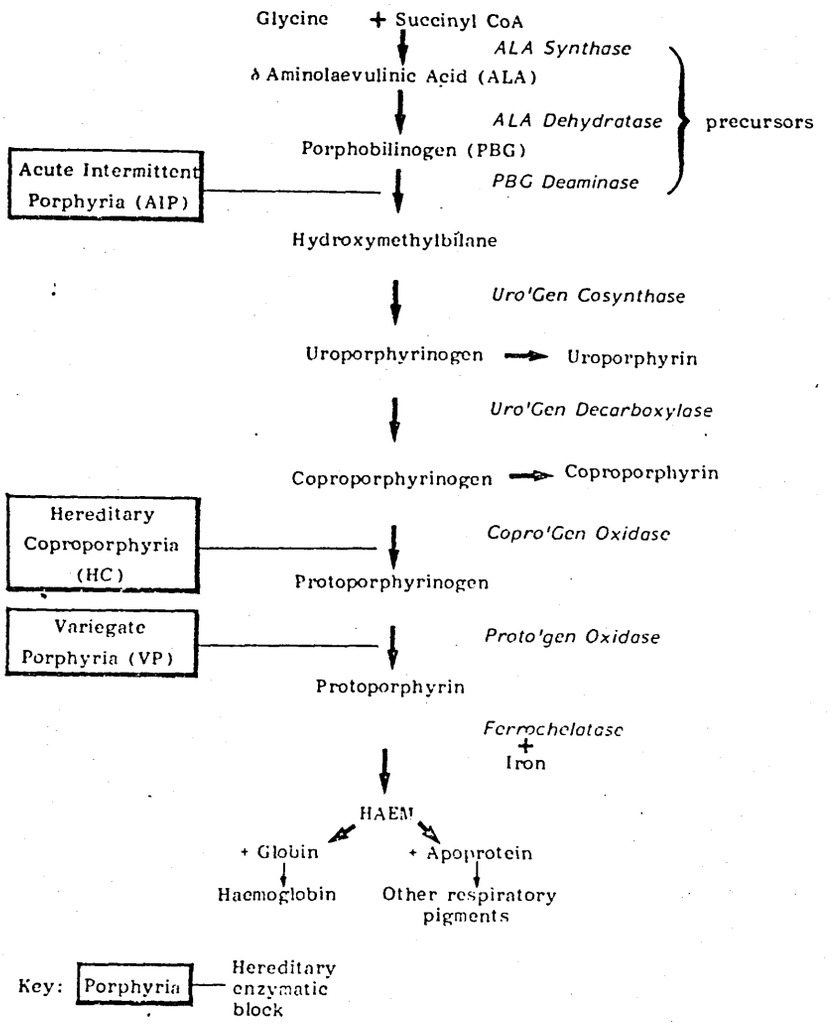
Statistical analysis by Mann-Whitney U test

a $p<0.05$ between attack vs remission
b $p<0.05$ between attack vs remission and controls
c $p<0.05$ between attack and remission vs controls

ALA = delta-aminolaevulinic acid PBG = porphobilinogen

FIGURE 8.1

HAEM BIOSYNTHETIC PATHWAYS



CHAPTER 9

HEPATIC METABOLIC FUNCTION IN PATIENTS RECEIVING LONG TERM METHOTREXATE THERAPY: COMPARISON WITH TOPICALLY TREATED PSORIATICS, PATIENT CONTROLS AND CIRRHOTICS

9.1 SUMMARY

Standard biochemical liver function tests and the clearances of antipyrine and indocyanine green have been compared in psoriatic patients taking methotrexate, psoriatic patients on topical treatment, patient controls and patients with hepatic cirrhosis. The methotrexate-treated patients showed significant elevations in alkaline phosphatase ($p<0.025$) and gamma glutamyl transpeptidase activities ($p<0.05$) compared to topically treated psoriatics and patient controls. The clearance of antipyrine was reduced in the methotrexate treated group but not significantly ($0.1 > p > 0.05$). In contradistinction, the weight-adjusted clearance of indocyanine green was significantly impaired in the methotrexate group in comparison with the topically treated psoriatics ($p < 0.01$).

The clearance of both antipyrine and indocyanine green were markedly lowered in the cirrhotics ($p < 0.001$ against all other groups). These data suggest that the serial measurement of alkaline phosphatase and indocyanine green clearance may provide a non-invasive indicator of the development and progression of methotrexate-related liver injury.

9.2 INTRODUCTION

Methotrexate has been employed in the treatment of severe psoriasis for more than 25 years (EDMUNDSON & GUY 1958). The systemic use of this drug has been associated with hepatic fibrosis (DAHL et al 1971; ZACHERIAE et al 1975) and cirrhosis (COE and BULL 1968; ZACHERIAE et al 1980). An increased mortality due to the hepatic complications has been reported (BAILIN et al 1975). The identification of patients developing progressive liver injury has not been possible with standard biochemical liver function tests (ROENIGK et al 1971) or technetium 99 sulphur colloid liver scans (GERONEMUS et al 1982). The current policy is to recommend liver biopsy after each gram of methotrexate administered (ROENIGK et al 1982). This requires hospital admission and is associated with a small but significant morbidity and mortality (CALLEN & HANNO 1980; CRESWELL & BURROWS 1980). In addition, a single biopsy may be unrepresentative of the overall liver architecture and gives no indication of the functional capacity of the liver.

Dynamic liver function tests are safe, inexpensive and can be performed on outpatients. These tests reflect aspects of the liver's metabolic function. The aim of this study was to investigate the clearances of antipyrine and indocyanine green in the assessment of hepatic function in patients with psoriasis receiving long term methotrexate therapy.

9.3 PATIENTS

Four groups of patients have been studied. The first group consisted of 11 patients (8 male, 3 female) on long term

methotrexate therapy. The mean age of the group was 55.5 ± 7.8 years. The patients had been receiving regular weekly or fortnightly intravenous doses (5-15mg) of methotrexate for 1-16 years, the mean total dose being 2168mg (range 620-3200mg). The second group consisted of 14 psoriatic patients (6 male, 8 female) who had never received methotrexate. The third group was made up of 15 patients without psoriasis or liver disease who were regarded as patient controls. No patient in any of these three groups was known to abuse ethanol. The fourth group contained 15 non-dermatological patients with histologically proven hepatic cirrhosis. None of the patients in any of the groups was receiving drugs known to affect hepatic metabolic function or liver blood flow. The mean age of groups 2,3 and 4 did not differ significantly from that of the methotrexate treated group (group 2 = 56.3 ± 3.5 years; group 3 = 54.1 ± 7.1 years; group 4 = 54.0 ± 5.6 years). All the cirrhotic patients and the patients receiving methotrexate had percutaneous liver biopsies performed for routine histological evaluation.

The study was performed with the approval of the local Ethical Committee and written informed consent was obtained from all patients prior to inclusion in the study.

9.4 METHODS

See chapter 7.2 for antipyrine method.

See chapter 7.3 for indocyanine green method.

The data are expressed as means ± the standard error of the mean unless otherwise stated. Statistical analyses were performed using Student's t-test with a one way analysis of variance. Correlation coefficients were obtained by the Spearman ranking procedure.

9.5 RESULTS

Serum alkaline phosphatase ($p < 0.025$) and gamma glutamyl transpeptidase ($p < 0.05$) activities were significantly elevated in the methotrexate treated patients compared to the topically treated psoriatics and the patient controls (Table 1). There were no other significant differences in the standard biochemical tests of liver function between these three groups. As expected all the standard biochemical liver function tests were disturbed in the group with cirrhosis compared to the healthy controls ($p < 0.001$).

Antipyrine and indocyanine green kinetic data for all four groups are shown in Table 2. There was a small fall in the antipyrine clearance (ml/min) in the methotrexate treated group compared to the healthy controls but this was only significant at the 10% level. Similarly when adjusted for body weight, antipyrine clearance (ml/min/kg) was not significantly different between the psoriatic groups and the patient controls (Fig. 1).

The indocyanine green plasma clearance was also reduced in the treated patients (576 ± 163 ml/min) compared to the psoriatic

control group (695 ± 170 ml/min) and the healthy controls (726.8 ± 252 ml/min), these differences being significant at the 10% and 5% levels respectively. When the clearances were corrected for body weight these differences reached 5% and 1% significance levels (Fig. 2).

In the patients with proven hepatic cirrhosis there was a substantial reduction in the antipyrine and indocyanine green clearances ($p < 0.001$) compared to the other three groups.

There was no significant correlation between the total dose of methotrexate received and the weight adjusted antipyrine ($r = 0.03$) and indocyanine green ($r = 0.35$) clearances or the alkaline phosphatase activity ($r = 0.08$). Histological evaluation of the liver biopsies in the methotrexate treated patients showed that only one patient had developed hepatic fibrosis. This patient had elevated alkaline phosphatase and gamma glutamyl transpeptidase activities (231 iu/l and 46 iu/l respectively) on antipyrine clearance of 0.34 ml/min/kg and indocyanine green clearance of 6.26 ml/min/kg (Fig. 2).

9.6 DISCUSSION

The standard biochemical tests of liver function are not regarded as reliable screening tests for liver disease in patients taking methotrexate (ROENIGK et al 1971). However, DAHL and his colleagues (1971) showed that a raised alkaline phosphatase activity was associated with the subsequent development of hepatic fibrosis. Alkaline phosphatase of hepatic origin is indicative of an obstruction to biliary flow.

In this circumstance the concentration of alkaline phosphatase in the hepatocyte increases and then overspills into the circulation (PRICE & SAMMONS 1976). We have demonstrated a significant elevation in alkaline phosphatase among psoriatics taking methotrexate. In only two patients was it elevated outwith the control range, and one of these patients had histological evidence of hepatic fibrosis. The methotrexate treated patients also had a significantly elevated gamma glutamyl transpeptidase activity. The activity of this enzyme is also increased in conditions which produce an obstruction to biliary flow (LUM & GAMBINO 1972) but this is less specific as its activity is also increased by ethanol excess (ROSALKI 1975).

The clearances of antipyrine and indocyanine green were well preserved in the methotrexate treated patients compared to the florid deterioration in metabolic function observed in the cirrhotic patients. However, in comparison to the control population there is a tendency to a reduction in both clearances which reaches statistical significance for the indocyanine plasma clearance. This reduction in clearance may be due to a fall in liver blood flow (CAESAR et al 1961) or a reduction in the intrinsic uptake of the dye by the hepatocyte (HUET & VILLENEUVE 1983). In the methotrexate treated patients who otherwise appear to have well maintained hepatic metabolic function it is likely that the reduction in indocyanine green clearance is a reflection of reduced liver blood flow resulting from a distortion of the liver architecture. The clearance of

bromosulphthalein (BSP) another highly hepatically extracted substance, has been shown to be impaired in patients with methotrexate induced liver injury (WEINSTEIN et al 1970), but no correlation was found between the degree of retention of BSP and the histological severity of the liver damage (DAHL et al 1971).

Despite these metabolic changes suggesting that the hepatic architecture is disturbed, examination of hepatic histology revealed only one patient with demonstrable hepatic fibrosis on light microscopy. The prevelance of methotrexate associated liver injury is low in this small series with only 1/9 patients affected. In previous studies 33-39% of patients had hepatic fibrosis or cirrhosis (DAHL et al 1971; ZACHERIAE et al 1975; WEINSTEIN et al 1970). We believe that this may be a reflection of the policy of giving doses of methotrexate intravenously at weekly or fortnightly intervals (ALMEYDA et al 1972; WARIN et al 1975).

In this preliminary study the alkaline phosphatase activity was elevated and the indocyanine plasma clearance significantly lowered in a small group of psoriatics receiving systemic methotrexate. This combination of changes may be related to a fine distortion of the liver architecture which is not apparent on light microscopy of a single liver biopsy core. The serial measurement of serum alkaline phosphatase activity and indocyanine green clearance may provide a non-invasive method of assessing the development and progression of methotrexate associated liver injury. These tests may obviate the need for routine annual liver biopsies by identifying those patients with deteriorating liver function. Further studies

are needed to confirm these findings.

ACKNOWLEDGEMENT

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TABLE 9.1 STANDARD BIOCHEMICAL LIVER FUNCTION TESTS IN ALL PATIENT GROUPS (mean ±SEM)

			Bilirubin umol/l	Alanine transferase (SGOT) iu/l	Aspartate transferase (SGPT) iu/l	Gamma Glutamyl transpeptidase iu/l	Alkaline phosphatase iu/l	Albumin g/l
	Normal Range		(3-22 umol/l)	(12-42 umol/l)	(8-55 umol/l)	(3-30 iu/l)	(21-170 iu/l)	(35-53 g/l)
Methotrexate group	11	Mean	9.0	26.6	36.5	44.2^{2}*	125.5^{2}**	42
		SEM	1.5	1.9	5.8	9.6	17.3	1.3
Psoriatic controls	14	Mean	9.2	23.6	28.7	34.0	89.9	41.6
		SEM	1.7	2.1	4.6	5.9	7.9	0.9
Patient controls	15	Mean	9.9	25.9	28.2	26.0	81.1	41.8
		SEM	1.1	2.4	3.8	5.4	6.0	0.7
Cirrhosis	15	Mean	54.4^{1}***	96.9^{1}***	75.9^{1}***	151.8^{1}***	194.3^{1}***	31.5^{1}***
		SEM	10.0	17.3	12.6	51.0	22.2	2.2

Statistics by student's t-test and one way analysis of variance

^{1} = versus the other three groups

^{2} = versus patient controls and psoriatic controls

* = $p < 0.05$

** = $p < 0.025$

*** = $p < 0.001$

TABLE 9.2 ANTIPYRINE AND INDOCYANINE GREEN KINETICS IN ALL PATIENT GROUPS (mean ± SEM)

			Antipyrine Half Life (hours)	Antipyrine Volume of Distribution (l)	Antipyrine Plasma Clearance (ml/min)	Indocyanine Green Half Life (mins)	Indocyanine Green Volume of Distribution (l)	Indocyanine Green Plasma Clearance (ml/min)
Methotrexate group	11	Mean	13.8	33.9	37.4	3.9	3.1^{2*}	576.0^{2*}
		SEM	1.7	2.8	4.0	0.3	0.3	51.4
Psoriatic controls	14	Mean	12.9	43.7	39.5	3.8	3.8	695.1
		SEM	1.0	4.2	3.9	0.2	0.2	47.1
Patient controls	15	Mean	11.2	34.5	42.2	3.8	3.9	726.8
		SEM	0.7	2.5	3.3	0.1	0.2	61.6
Cirrhosis	15	Mean	25.9^{1***}	39.0	23.9^{1***}	14.4^{1***}	4.1^{3**}	253.5^{1***}
		SEM	1.9	1.6	2.2	1.1	0.2	19.1

Statistics by Student's t-test and one way analysis of variance

*p < 0.05

**p < 0.025

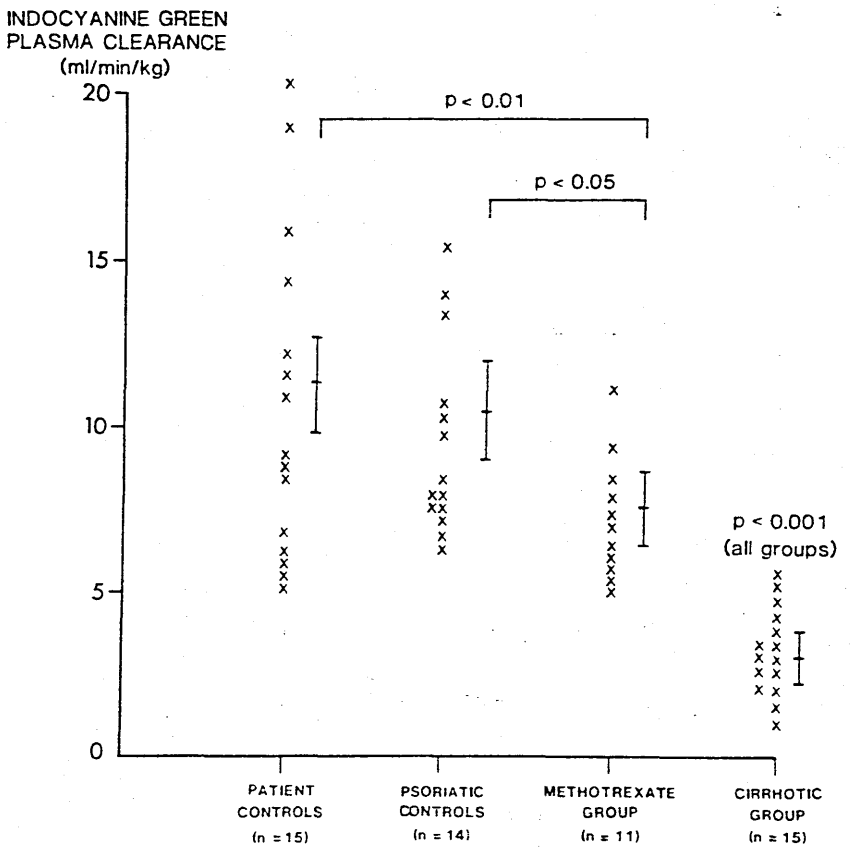
***p < 0.001

[1] = versus the other three groups

[2] = versus patient controls

[3] = versus psoriatic controls

FIGURE 9.2 : INDOCYANINE GREEN CLEARANCE (ML/MIN/KG) IN ALL PATIENT GROUPS. Bars represent mean ± SEM. Statistics were obtained using one way analysis of variance.



C H A P T E R 10

ANTIPYRINE AND INDOCYANINE GREEN KINETICS IN THE PREDICTION OF THE NATURAL HISTORY OF LIVER DISEASE.

10.1 SUMMARY

Data are presented in this chapter demonstrating the relative value of standard liver function tests, antipyrine and indocyanine green elimination in the assessment of the natural history of chronic liver disease. One hundred and sixteen patients with chronic liver disease were studied.

When the patients were divided by diagnostic groups there were similar changes in the standard liver function tests and kinetic parameters in all the groups. The only exception was that patients with primary biliary cirrhosis had a marked reduction in the volume of distribution of antipyrine (controls = 36.3 $\pm$ 13.7 l; PBC = 25.4 $\pm$ 7.3 l : $p<0.005$). This suggests that these patients have a reduced total body water, which may be a consequence of the hyperlipidaemia seen in this condition.

The patients were divided into those with and without the major complications of liver disease - Encephalopathy, ascites and portal hypertension. A reduction in antipyrine clearance of 2,16 and 14% respectively was found in the patients with these complications. The reductions in indocyanine green clearance were much greater at 44,48 and 37% respectively. The antipyrine clearance was reduced by 26% in patients with biopsy proven active cirrhosis compared to a reduction of 50% in the indocyanine green clearance. The non-survivors had a 3% reduction in antipyrine clearance, and a 75% reduction in indocyanine green clearance.

When these data were analysised by multiple regression and Cox's proportional hazard model, the most powerful of the kinetic parameters was the indocyanine green half-life. When

this was included with the patients age in the model all the other biochemical, histological and kinetic data became redundant.

These data show that indocyanine green elimination provides important information regarding the severity of liver disease. The greater magnitude of change seen with indocyanine green compared to antipyrine suggests that an important determinant of the complications and survival in liver disease is the functional liver blood flow rather than the hepatic metabolic capacity.

10.2 INTRODUCTION

The aim of this study was to explore the value of antipyrine and indocyanine green kinetic data in the evaluation of patients admitted to hospital with chronic liver disease. The kinetic data from these drugs were compared to the clinical features of liver disease, biochemical and histological data. The patients with liver disease were divided by diagnostic group, hepatic complications, and into survivors and non-survivors.

10.3 PATIENTS AND METHODS

One hundred and sixteen patients with liver disease were studied. Histological diagnoses were alcohol-related liver disease [ALD](65), primary biliary cirrhosis [PBC] (25), chronic active hepatitis [CAH](12), cryptogenic cirrhosis (6), acute viral hepatitis (3), haemochromatosis (2), primary sclerosing cholangitis (2) and idiopathic portal hypertension (1). The last five diagnostic categories have been combined as "liver disease - other causes". A group of 40 patients with no clinical or biochemical evidence of liver disease was included as controls. These patients were all admitted to hospital for investigation of non-hepatological gastrointestinal symptoms. The majority had either peptic ulceration or severe constipation of non-organic origin.

The methods of data collection, correction, and transfer are described in Appendix 4.

The raw data obtained in this study was gathered as Appendix

3. It is organised in three separate reports. The first report contains the basic clinical and biochemical data on the patients. The second includes the antipyrine and histological data, and the third lists the indocyanine green data.

The follow-up on the patients was taken from entry into the study to the last observation (either death or censoring). Cox multiple regression model was used for censored survival data (Cox 1972). Before inclusion in the Cox analysis, the distributions of the continuous variables were checked for normality and if necessary logarithmic or reciprocal transformations were made. In a skewed distribution any outlying results exert a disproportionate effect on multiple regressional analysis. However a normal distribution is not an absolute pre-requisite for this type of analysis, and the most appropriate transformation can be determined by repeated testing with the regressional analysis. In the regressional analysis variables which were significant at the 5% level were introduced into the model and they were discarded from the model if their significance failed to attain the 10% level.

The study had the approval of the local ethical committee and all patients gave written informed consent.

10.4 RESULTS

10.4.1 Results of Comparison Between Disease Groups

The age and sex data (Table 10.1) show a typical distribution for a large population of patients with liver disease. There was a significant predominance of females in the PBC (96%) and CAH (75%) groups and there was a slightly more

males in the alcoholic (69%) and mixed liver disease groups (64%). The groups were well matched for age except for the PBC group, who were on average 10 years older that the other patients.

The prevalance of the three major complications of liver disease are shown in Table 10.2. The distribution of these complications was not significantly different in any group. However there was a tendency towards a lower prevalance of encephalopathy and ascites in the PBC group suggesting that this group had less severe liver disease.

The results of the standard biochemical tests of liver function are summarised in Tables 10.3a and 10.3b. As expected most of these were significantly abnormal compared to controls in all the patient groups.

The antipyrine kinetic data are summarised in Table 10.4. There were significant deviations from the control results in all patient groups. Generally the pattern of abnormalities was similar in each patient group with a reduction in the plasma clearance and a prolongation in the half life, with no altertion in the volume of distribution The only deviation from this pattern occurred in the PBC group, where there was a significant reduction in the volume of distribution (Controls = 36.3 $\pm$ 13.7 l; PBC group = 25.4 $\pm$ 7.3 l; $P < 0.005$). This offset the reduction in the clearance so that there was not a significant alteration in the half life.

The indocyanine green kinetics are summarised in Table 10.5. The general pattern is similar to that seen with antipyrine but

the overall differences were greater.

10.4.2 Encephalopathy

There was a clinical history of encephalopathy in 32 (27%) of the patients with liver disease. The results of standard biochemical liver function tests, antipyrine and indocyanine green kinetic data for patients with and without encephalopathy are summarised in Tables 10.6, 10.7 and 10.8. The serum albumin was significantly reduced in the encephalopathic group (Encephalopathy = 29.8 $\pm$ 6.8 g/l: No Encephalopathy = 36.5 $\pm$ 6.7 g/l, $P < 0.005$). The serum bilirubin was higher in the encephalopathic patients (Encephalopathy = 94.8 $\pm$ 113.9mmol/l; No encephalopathy = 25.4 $\pm$ 24.2mmol/l; $P < 0.001$). There was no significant alteration in the other standard liver function tests including aspartate transaminase, alanine transaminase and the gamma glutamyl transpeptidase (Table 10.6).

The antipyrine kinetics show a curious pattern with a marked increase in the volume of distribution in the encephalopathic patients (Encephalopathy group = 39.8 $\pm$ 17.3 L: No encephalopathy = 30.2 $\pm$ 8.9 L; $P < 0.001$). There was a concomitant small increase in the elimination half life but no alteration in the plasma clearance (Table 10.7).

The indocyanine green kinetic data also show a small increase in the volume of distribution in the encephalopathic patients. However, for this drug there is a marked reduction in the clearance (Encephalopathy group = 231.2 $\pm$ 240.2ml/min; No encephalopathy = 406.2 $\pm$ 214.7ml/min, $P < 0.001$). Consequently

the elimination half life is markedly prolonged in the encephalopathic group (Encephalopathic group = 21.6 ± 13.0min; No encephalopathy = 8.9 ± 9.2 ml/min; $P < 0.001$) (Table 10.8).

10.4.3 Ascites

There was clinical evidence of ascites in 40 (34%) of the liver disease patients studied. The results of the standard biochemical liver function tests, antipyrine and indocyanine green kinetic data are shown in Tables 10.9, 10.10 and 10.11.

The standard biochemical tests showed significant elevations of the serum bilirubin and a significant reduction in the serum albumin (Table 10.9).

The antipyrine kinetic data showed a small but significant increase in the volume of distribution (Ascites = 37.0 ± 16.5 L; No ascites = 30.8 ± 9.4 L; $P < 0.05$). There was a small but insignificant reduction in the plasma clearance. However, the combination of these two changes resulted in a major prolongation of the elimination half life (Ascites = 31.1 ± 22.2 hrs; No ascites = 16.5 ± 8.6 hrs; < 0.001) (Table 10.10).

The indocyanine green kinetic data shows marked differences in all the parameters studied with a significant increase in the volume of distribution and half life with a reduction clearance (Ascites = 227.3 ± 211.1 L; no ascites = 435.9 ± 212.9 L: $p<0.001$) (Table 10.11).

10.4.4 Portal Hypertension

In the liver disease group there were 2 patients (2%) with surgical portocaval shunts, 19 (17%) who had previous bleeding

from oesophageal varices and 16 (14%) who had oesophageal varices on routine barium swallow. These 37 patients (33%) were combined to form a portal hypertension group.

There were only small changes in the standard biochemical liver function tests between the two groups (Table 10.12). Similarly there were no significant alterations in the kinetics of antipyrine (Table 10.13). However, the indocyanine green kinetics were significantly altered (Table 10.14) in the portal hypertension group with a significant increase in the half life and volume of distribution with a reduction in the plasma clearance (Portal hypertension = 254.1 $\pm$ 131.5ml/min; no portal hypertension 407.9 $\pm$ 256.2ml/min: $p<0.005$). Although these changes were significant they were less marked than those seen in the encephalopathy and ascitic group.

10.4.5 Histological Classification

On the basis of the findings on histological examination of the liver biopsies the patients were divided into four groups. There were 33 patients who had evidence of an active cirrhosis. These patients had histological evidence of both cirrhosis and an active hepatitis with most of these patients having an alcoholic aetiology. Five patients had an inactive cirrhosis and in 35 patients the liver histology showed evidence of liver disease which had not progressed to cirrhosis. In a further 32 patients liver biopsy was not performed either because it was judged to be too hazardous or because it was not clinically indicated.

The results of the standard biochemical liver function tests

are shown in Table 10.15. The patients without biopsy evidence of cirrhosis had significantly elevated levels of gamma glutamyl transpeptidase. This probably reflects the disproportionate number of patients with primary biliary cirrhosis in this group. The serum albumin was also significantly higher indicating better metabolic function in the non cirrhotic group compared to the cirrhotic patients.

Similar patterns are seen for antipyrine and indocyanine green (Tables 10.16 and 10.17). The clearance of both drugs is significantly reduced in the active cirrhotic group compared to the non cirrhotic group. Small increases occurred in the volume of distribution of both drugs, together with a marked prolongation of the half life. Once again the changes were greater for indocyanine green than antipyrine.

10.4.6 Comparison Between Survival Groups

During the study 29 patients died with liver disease, the details of the diagnosis, age, sex, follow up and cause of death are shown in Table 10.17. The majority of these deaths were as a direct result of one of the complications of liver disease. However, three patients died of disseminated non hepatic malignancy, two of which were bronchogenic carcinomas and one cervical carcinoma.

The results of the standard biochemical tests for the non-survivors and survivors is shown in in Table 10.18. Comparison between the survivors and non-survivors shows that the serum albumin is signficiantly low (Survivors = 36.9 $\pm$ 6.9g/l; Non-survivors 28.8 $\pm$ 6.5g/l; $P<0.001$), and serum bilirubin elevated

(Survivors = 28.4 ± 49.4umol/l : Non-survivors = 86.7 ± 95.5 umol/l : P<0.001) in non-survivors. The non-survivors also showed higher serum globulins concentrations together with higher aspartate transaminase and gamma glutamyl transpeptidase activities. The alanine transaminase and alkaline phosphatase activities did not differ significantly between survivors and non-survivors.

The results of antipyrine kinetic in the survivors and non-survivors are shown in Table 10.19. There were significant differences between the patients with liver disease and the control group for both the half-life and the clearance. Only the differences in the half-lives were signficantly different between survivors and non-survivors. (Survivors = 19.3 ± 15.3hrs: Non-survivors = 28.3 ± 17.9hrs : P<0.05) (Figure 10.1).

The kinetic data for indocyanine green in survivors and non-survivors are summarised in table 10.20. There are highly signficant alterations in all the kinetic parameters between the survivors and non-survivors. (Figure 10.2).

10.4.7 Multiple Regression Analysis

Analysis 1: The first analysis was designed to assess the prognostic value of the antipyrine and indocyanine green kinetic data. The multiple regression analysis program was started with the patients age. The program was then offered all the antipyrine and indocyanine green kinetic parameters and their logarithmic transformations. The result of the

initial step of the regressional analysis is shown in Table 10.22. Any variable with a Chi-square > 4 and a P value < 0.05 has additional prognostic value. The most useful antipyrine parameter was the half-life (Chi-square = 9.69) and the strength of this variable was improved by log transformation (Chi-square = 11.57). None of the other antipyrine data had prognostic value.

Several of the ICG parameters were of prognostic importance and the most powerful of the was the log of the half-life (Chi-square = 38.61). This variable was added to the age because it was the most powerful prognostic variable offered and the program is rerun. The results of the analysis are shown in Table 10.22 At this stage of the analysis none of the Chi-square or P values for inclusion in the model were significant.

Analysis 2: This analysis repeated Analysis 1 using the square root and reciprocal of the ICG half-life. The results of this analysis are shown in Table 10.23. The most powerful mathematical transformation of the ICG half-life was its reciprocal (Chi-square = 45.02; P<0.001)

Analysis 3: The following variables were used in this analysis:- Age, albumin, log bilirubin concentration, Log AST activity, Log GGT activity, prothrombin time, presence of portal hypertension, sex, presence of ascites, presence of encephalopathy, Childs Classification, reciprocal of ICG

half-life and reciprocal of antipyrine half-life.

Results of this initial step of this analysis are shown in Table 10.24. The serum bilirubin is the only standard liver function test which significantly contributed to the analysis and in the next four steps the program eliminates ALT, Prothrombin time, AST and GGT (Table 10.25). At this stage the program accepted the reciprocal of the ICG half-life with the result that the serum bilirubin became redundant and was removed. The final result of the second analysis is shown in Table 10.26. There were now only three significant variables age, serum albumin concentration and the reciprocal of ICG half-life. Of these, the serum albumin was exerting only a very weak influence (Chi-square = 2.75; P=0.097).

Analysis 4: This analysis repeated analysis 2 using all the same variables but on this occasion not allowing the redundant variables to be discarded. Again the program was started with age and the standard biochemical liver function tests and these variables are forced to stay in the analysis. Only the presence of ascites and the reciprocal of ICG half-life exceeded the limits for inclusion (Table 10.27) but when the ICG t1/2 was included then the significance of ascites was lost (Chi-Squared = 0.99, p = 0.319).

10.5 CONCLUSION

This is the first large study which compares kinetic data

for the elimination of low and high hepatic extraction ratio drugs using multiple regressional analysis. It confirms previous work showing that liver disease is associated with impairment of the excretion of antipyrine (BRANCH et al 1973 and 1976(b); ANDREASEN 1974, 1975, 1976(a); FARRELL et al 1978; KRAUS et al 1980) and indocyanine green (BRANCH et al 1976(b); GILMORE et al 1982).

For the different diagnostic groups the pattern of abnormality in the kinetic data generally shows a reduced clearance of both drugs with little change in the volume of distribution, so that there is a concomitant increase in the elimination half life. The only exceptions were the 23 patients with primary biliary cirrhosis where there was a marked reduction in the volume of distribution of antipyrine. This change in distribution was not seen with indocyanine green. This does not reflect the severity of the disease in the PBC group as they appeared to have relatively mild liver disease, judged from the standard liver function tests and the incidence of complications. However, one of the features of primary biliary cirrhosis is a marked increase in the total serum lipids particularly the phospholipids and total cholesterol (SHERLOCK 1975). These changes are not seen to the same degree in other forms of liver disease. Measurement of the distribution of antipyrine is a standard method for determining total body water (SOBERMAN et al 1949) and so the changes seen in primary biliary cirrhosis may reflect a reduction in the total body water content, consequent upon an increase in total body lipid content. A previous study of antipyrine metabolism in patients undergoing dietary

manipulation, showed that following a high saturated fat diet there was a rise in the serum cholesterol and a fall in the volume of distribution of antipyrine (ANDERSON et al 1979).

The differences in indocyanine green clearance tended to be greater than the differences in antipyrine clearance in all the groups. In the encephalopathic patients there was a 45% reduction in ICG clearance and a 2% reduction in AP clearance, similarly for the ascitic group (54% vs 16%) and for the portal hypertension group (39% vs 14%). Indocyanine green is extracted and excreted by the liver without biochemical transformation. It has a high hepatic extraction ratio so that its rate of elimination is primarily dependent on the functional liver blood flow. For antipyrine the rate of elimination is primarily dependent on hepatic metabolism. If the primary factor determining the occurence of a complication of liver disease was the hepatic metabolic capacity then the clearance of antipyrine should be a more sensitive indicator of complicated liver disease than indocyanine green. The observation that indocyanine green appears to be a better indication of liver dysfunction suggests that the functional liver blood flow is more important than hepatic metabolic capacity in determining the occurence of complications. In chronic liver disease there is a reduction in functional liver blood flow because of the porto-systemic shunting of blood through extra and intrahepatic connections (POPPER et al 1952).

This concept is further supported by the observation that concentrations of cytochrome P-450, and activities of aminopyrine demethylation, P-nitrosonisole demekthylation and NADPH-

cytochrome C reductase in liver biopsies show little alteration in mild liver disease (MAY et al 1974) and are only reduced in the presence of very severe disease (SCHOENE et al 1972). The relative importance of ICG elimination as a test of liver function is further emphasised by the 57% reduction in non-survivors with liver disease compared to a reduction of 44% in antipyrine clearance and 22% in serum albumin. The only factor which showed a greater percentage change in the non-survivors was the serum bilirubin which was elevated by 96%.

The Cox Proportional hazard analysis suggests that ICG elimination has prognostic importance independent of any other factor measured with the exception of age. The analysis also reveals that the strongest ICG parameter is the half life. Previous studies of the use of drugs as probes of liver dysfunction have tended to concentrate on the measurement of the clearance of the drug as it is a purer measurement of organ function. The half life is dependent on the clearance and the volume of distribution. Both of these factors are altered in liver disease so that the half life may be a more suitable measurement of the severity of liver disease.

These data suggest the relative importance of indocyanine green elimination as a measurement of the severity of liver disease. They suggest that an important factor in determining the deterioration of function that occurs in liver disease is the mismatching of functional hepatocytes with blood flow as a result of intra and extrahepatic portosystemic shunting.

TABLE 10.1 DETAILS OF AGE AND SEX IN CONTROL SUBJECTS AND PATIENTS WITH LIVER DISEASE

		AGE (yrs)			SEX	
	n	Mean	SD	SEM	Female (%)	Male (%)
CONTROL	40	54.1	13.4	2.1	18 (46)	21 (54)
LIVER DISEASE	116	53.9	12.0	1.1	59 (51)	57 (49)
PRIMARY BILIARY CIRRHOSIS	25	61.3++	9.3	1.9	24 (96)	1*(4)
CHRONIC ACTIVE HEPATITIS	12	53.6	13.7	3.9	9 (75)	3 (25)
ALCOHOLIC LIVER DISEASE	65	51.6	11.4	1.4	21 (31)	44 (69)
OTHER LIVER DISEASE	14	51.8	13.3	3.6	5 (36)	9 (64)

Statistics by Chi-squared test Comparison with Control Group

* = $p < 0.05$

Statistics by analysis of variance Comparison with Control Group

++ = $p < 0.001$

TABLE 10.2 DETAILS OF THE MAJOR COMPLICATIONS OF LIVER DISEASE IN EACH DIAGNOSIS GROUPS

	LIVER DISEASE	PRIMARY BILIARY CIRRHOSIS	CHRONIC ACTIVE HEPATITIS	ALCOHOLIC LIVER DISEASE	OTHER LIVER DISEASE
	n (%)	n (%)	n (%)	n (%)	n (%)
ENCEPHALOPATHY					
Absent	84 (73)	23 (92)	9 (75)	42 (65)	10 (71)
Present	32 (27)	2 (8)	3 (25)	23 (35)	4 (29)
ASCITES					
Absent	76 (66)	22 (88)	8 (67)	36 (55)	10 (71)
Present	40 (34)	3 (12)	4 (33)	29 (45)	4 (29)
PORTAL HYPERTENSION					
No Varices	76 (67)	18 (72)	10 (84)	42 (65)	9 (64)
Varices	16 (14)	6 (24)	1 (8.5)	9 (14)	0 (0)
Previous Variceal Bleeding	19 (17)	1 (4)	0 (0)	14 (21)	4 (29)
Portocaval Shunt	2 (2)	0 (0)	1 (8.5)	0 (0)	1 (7)

No significant differences by Chi-Squared Test

TABLE 10.3a STANDARD BIOCHEMICAL (AST, ALT, GGT, ALBUMIN) TESTS IN CONTROL SUBJECTS AND PATIENTS WITH LIVER DISEASE (Statistical analysis to Control Group)

	ASPARTATE AMINOTRANSFERASE (IU/L)				ALANINE AMINOTRANSFERASE (IU/L)			
	n	mean	SD	SEM	n	mean	SD	SEM
CONTROL	37	26.6	9.6	1.6	38	29.5	13.2	2.0
LIVER DISEASE	115	97.6	114.0	10.9	116	85.9	105.0	10
PRIMARY BILIARY CIRRHOSIS	25	82.3**	36.3	7.3	25	97.7***	61.3	12.3
CHRONIC ACTIVE HEPATITIS	12	160.4**	276.0	79.6	12	119.3***	177.0	51.0
ALCOHOLIC LIVER DISEASE	65	89.9**	76.5	9.5	65	64.3***	70.5	8.7
OTHER LIVER DISEASE	13	108.0**	119.0	33.0	12	136.3***	182.0	48.7

	GAMMA GLUTAMYL TRANSPEPTIDASE (IU/L)				ALBUMIN (g/L)			
	n	mean	SD	SEM	n	mean	SD	SEM
CONTROL	38	30.3	21.2	3.4	38	42.2	7.0	1.1
LIVER DISEASE	114	328.8	491.0	47.2	116	34.6	7.5	1.1
PRIMARY BILIARY CIRRHOSIS	25	493.4**	576.0	115.1	25	36.9**	5.5	1.1
CHRONIC ACTIVE HEPATITIS	11	163.6**	204.0	61.6	12	32.8**	9.1	2.6
ALCOHOLIC LIVER DISEASE	64	334.0***	521.0	65.0	65	33.7**	7.8	1.1
OTHER LIVER DISEASE	14	90.4**	57.1	15.3	14	36.7**	6.6	1.8

Statistics by analysis of variance * = $P < 0.05$ ** = $P < 0.005$ *** = $P < 0.001$

TABLE 10.3b STANDARD BIOCHEMICAL TESTS (ALKALINE PHOSPHATASE, GLOBULIN, CREATININE, BILIRUBIN) IN CONTROL SUBJECTS AND SUBJECTS WITH LIVER DISEASE (Statistical analysis with control group)

	ALKALINE PHOSPHATASE (IU/L)				GLOBULIN (G/L)			
	n	mean	SD	SEM	n	mean	SD	SEM
CONTROL	39	86.9	28.5	4.6	28	26.1	4.7	0.9
LIVER DISEASE	116	264.4**	284.0	26.5	115	35.0	12.1	1.1
PRIMARY BILIARY CIRRHOSIS	25	621.7**	49.0	83.8	25	34.5***	9.6	1.4
CHRONIC ACTIVE HEPATITIS	12	194.7**	104.0	30.1	12	39.1***	21.0	6.0
ALCOHOLIC LIVER DISEASE	65	164.1**	107.0	13.3	64	35.9***	11.2	1.4
OTHER LIVER DISEASE	14	151.8**	106.0	28.3	14	28.1	7.3	1.9

	CREATININE (mmol/l)				BILIRUBIN (umol/l)			
	n	mean	SD	SEM	n	mean	SD	SEM
CONTROL	32	85.3	20.4	3.6	39	16.1	50	0.8
LIVER DISEASE	110	86.9	24.1	2.3	116	44.5***	70.0	0.5
PRIMARY BILIARY CIRRHOSIS	25	83.7	22.5	4.5	25	31.3***	41.1	8.2
CHRONIC ACTIVE HEPATITIS	12	88.3	27.1	7.8	12	20.1*	25.0	7.2
ALCOHOLIC LIVER DISEASE	61	88.2	23.3	3.0	65	57.5***	87.2	10.8
OTHER LIVER DISEASE	12	85.8	30.5	8.8	14	19.5**	15.6	4.2

Statistics by analysis of variance * = $P < 0.05$ ** = $P < 0.005$ *** = $P < 0.001$

TABLE 10.4 ANTIPYRINE DATA IN CONTROL SUBJECTS AND IN PATIENTS WITH LIVER DISEASE

		CONTROL	LIVER DISEASE	PRIMARY BILIARY CIRHOSIS	CHRONIC ACTIVE HEPATITIS	ALCOHOLIC LIVER DISEASE	OTHER LIVER DISEASE
	n	37	104	23	12	56	13
HALF LIFE (hrs)	Mean	11.8	21.7***	13.7	23.6***	25.1***	19.4**
	SD	3.5	16.1	6.9	18.5	18.4	13.2
	SEM	0.6	1.6	1.4	5.3	2.5	3.8
VOLUME OF DISTRIBUTION (l)	Mean	36.3	33.0	25.4**	31.3	36.1	34.5
	SD	13.7	12.7	7.3	11.2	13.9	10.8
	SEM	2.4	1.2	1.5	3.2	1.9	3.1
VOLUME OF DISTRIBUTION (l/kg)	Mean	0.57	0.52	0.43	0.55	0.55	0.51
	SD	0.20	0.19	0.13	0.24	0.19	0.15
	SEM	0.03	0.02	0.03	0.07	0.03	0.04
PLASMA CLEARANCE (ml/min)	Mean	37.2	24.1***	24.8**	22.1**	24.2***	24.3**
	SD	15.1	14.2	10.8	13.7	16.1	12.9
	SEM	2.5	1.4	2.3	3.9	2.1	3.7
PLASMA CLEARANCE (ml/min/kg)	Mean	0.59	0.38***	0.43*	0.38*	0.36***	0.38**
	SD	0.25	0.22	0.21	0.25	0.23	0.21
	SEM	0.04	0.02	0.05	0.07	0.03	0.06

Statistics by analysis of variance and multiple T-test Comparison with Control Group

* = P<0.05
** = P<0.005
*** = P<0.001

TABLE 10.5 INDOCYANINE GREEN DATA IN CONTROL SUBJECTS AND PATIENTS WITH LIVER DISEASE

		CONTROL	LIVER DISEASE	PBC	CAH	ALD	OTHER
	n	32	102	20	11	61	10
HALF LIFE (min)	Mean	3.7	12.4	6.5***	10.7***	15.4**	7.9**
	SD	0.7	11.7	3.7	6.8	13.7	7.2
	SEM	0.13	0.2	0.8	2.1	1.8	2.3
VOLUME OF DISTRIBUTION (l)	Mean	3.8	3.8	3.2	3.1	4.1	4.0
	SD	1.1	1.5	1.1	1.3	1.6	1.4
	SEM	0.2	0.2	0.2	0.4	0.2	0.4
VOLUME OF DISTRIBUTION (l/kg)	Mean	0.06	0.06	0.06	0.05	0.06	0.06
	SD	0.02	0.02	0.03	0.02	0.02	0.02
	SEM	0.002	0.004	0.008	0.006	0.003	0.006
PLASMA CLEARANCE (ml/min)	Mean	714.4	358.2	405.2***	276.3***	328.0***	538.4*
	SD	230.0	234.0	184.0	141.0	222.0	371.0
	SEM	23.4	41.1	48.9	47.2	28.5	115.9
PLASMA CLEARANCE (ml/min/kg)	Mean	11.3	5.5	6.8***	4.7***	4.7***	8.4
	SD	4.6	3.7	3.0	3.1	3.3	5.9
	SEM	0.4	0.82	0.7	0.9	0.42	1.8
WHOLE BLOOD CLEARANCE (ml/min)	Mean	1255.1	592.9	678.0***	463.1***	545.4***	855.4**
	SD	386.0	410.0	362.0	253.0	397.0	601.0
	SEM	41.1	68.9	80.4	76.7	50.9	187.8
WHOLE BLOOD CLEARANCE (ml/min/kg)	Mean	19.6	9.2	11.0***	7.9***	8.1***	13.2*
	SD	7.1	6.3	5.4	5.3	5.9	9.6
	SEM	0.6	1.3	1.2	1.6	0.8	3.0

Statistics by analysis of variance * $P < 0.05$ ** $P < 0.005$ *** $P < 0.001$

TABLE 10.6 MEAN, STANDARD DEVIATION (SD) AND STANDARD ERROR OF THE MEAN (SEM) OF STANDARD BIOCHEMICAL FUNCTION TESTS IN PATIENTS WITH LIVER DISEASE WITH AND WITHOUT ENCEPHALOPATHY

		BILIRUBIN (mmol/l)	ASPARTATE AMINOTRANSFERASE (iu/l)	ALANINE AMINOTRANSFERASE (iu/l)	GAMMA GLUTAMYL TRANSPEPTIDASE (iu/l)	ALBUMIN (g/l)
NO	MEAN	25.3	99.4	96.3	343.1	36.5
ENCEPHALOPATHY	SD	24.2	127.5	118.1	474.1	6.7
(n = 84)	SEM	2.6	13.9	12.9	51.7	1.2
	MEAN	94.8***	92.9	58.5	286.6	29.8***
ENCEPHALOPATHY	SD	113.9	63.3	48.9	543.4	6.8
(n = 32)	SEM	20.1	11.4	8.6	99.2	1.2

Statistics by Analysis of Variance

* $P < 0.05$
** $P < 0.005$
*** $P < 0.001$

TABLE 10.7 MEAN, STANDARD DEVIATION (SD), AND STANDARD OF THE MEAN (SEM) OF ANTIPYRINE KINETIC DATA IN LIVER DISEASE PATIENTS WITH AND WITHOUT ENCEPHALOPATHY

		HALF LIFE (hrs)	VOLUME OF DISTRIBUTION (l)	VOLUME OF DISTRIBUTION (l/kg)	CLEARANCE (ml/min)	CLEARANCE (ml/min/kg)
NO	MEAN	19.5	30.2	0.47	24.2	0.39
ENCEPHALOPATHY	SD	16.0	8.9	0.13	12.6	0.21
(n = 74)	SEM	1.9	1.0	0.02	1.5	0.02
	MEAN	26.9*	39.8***	0.64***	23.8	0.37
ENCEPHALOPATHY	SD	16.4	17.3	0.25	17.8	0.27
(n = 30)	SEM	3.0	3.1	0.05	3.3	0.05

Statistics by Analysis of Variance

* $P < 0.05$
** $P < 0.005$
*** $P < 0.001$

TABLE 10.8 MEAN, STANDARD DEVIATION (SD) AND STANDARD OF THE MEAN (SEM) OF INDOCYANINE GREEN KINETIC DATA IN LIVER DISEASE PATIENTS WITH AND WITHOUT ENCEPHALOPATHY

		HALF LIFE (min)	VOLUME OF DISTRIBUTION (l)	VOLUME OF DISTRIBUTION (l/kg)	PLASMA CLEARANCE (ml/min)	PLASMA CLEARANCE (ml/min/kg)	WHOLE BLOOD CLEARANCE (ml/min)	WHOLE BLOOD CLEARANCE (ml/min/kg)
NO	MEAN	8.9	3.6	0.06	406.2	6.3	676.4	10.5
ENCEPHALOPATHY	SD	9.2	1.3	0.02	214.7	3.5	391.9	6.0
(n = 74)	SEM	1.1	0.15	0.002	24.9	0.41	45.5	0.7
	MEAN	21.6***	4.4*	0.07*	231.2***	3.5***	372.0***	5.6***
ENCEPHALOPATHY	SD	13.0	1.8	0.19	240.3	3.7	379.5	5.9
(n = 30)	SEM	2.5	0.34	0.004	45.4	0.70	71.7	1.1

Statistics by Analysis of Variance

* $P < 0.05$
** $P < 0.005$
*** $P < 0.001$

TABLE 10.9 MEAN, STANDARD DEVIATION (SD) AND STANDARD ERROR OF THE MEAN (SEM) OF STANDARD BIOCHEMICAL LIVER FUNCTION TESTS IN LIVER DISEASE PATIENTS WITH AND WITHOUT ASCITES

		BILIRUBIN (mmol/l)	ASPARTATE TRANSAMINASE (iu/l)	ALANINE TRANSAMINASE (iu/l)	GAMMA GLUTAMYL TRANSPEPTIDASE (iu/l)	ALBUMIN (g/l)
NO	MEAN	22.1	96.7	97.9	372.7	37.6
ASCITES	SD	21.1	78.5	121.1	492.9	5.7
(n = 76)	SEM	2.4	14.5	13.9	56.9	0.7
	MEAN	86.9***	99.5	62.9	242.7	28.9***
ASCITES	SD	103.8	84.4	58.4	483.4	7.1
(n = 40)	SEM	16.4	13.5	9.2	77.4	1.1

Statistics by Analysis of Variance

* $P < 0.05$
** $P < 0.005$
*** $P < 0.001$

TABLE 10.10 MEAN, STANDARD DEVIATION (SD) AND STANDARD ERROR OF THE MEAN (SEM) OF ANTIPYRINE KINETIC DATA IN LIVER PATIENTS WITH AND WITHOUT ASCITES.

		HALF LIFE (hrs)	VOLUME OF DISTRIBUTION (l)	VOLUME OF DISTRIBUTION (l/kg)	CLEARANCE (ml/min)	CLEARANCE (ml/min/kg)
NO	MEAN	16.5	30.8	0.49	25.5	0.41
ASCITES	SD	8.6	9.4	0.14	12.1	0.20
(n = 67)	SEM	1.1	1.1	0.02	1.5	0.02
	MEAN	31.1***	37.0*	0.58*	21.5	0.32
ASCITES	SD	22.2	16.5	0.24	17.4	0.26
(n = 37)	SEM	3.6	2.7	0.04	2.9	0.04

Statistics by Analysis of Variance

* $P < 0.05$
** $P < 0.005$
*** $P < 0.001$

TABLE 10.11 MEAN, STANDARD DEVIATION (SD) AND STANDARD ERROR OF THE MEAN (SEM) OF INDOCYANINE GREEN KINETIC DATA IN LIVER PATIENTS WITH AND WITHOUT ASCITES

		HALF LIFE (min)	VOLUME OF DISTRIBUTION (l)	VOLUME OF DISTRIBUTION (l/kg)	PLASMA CLEARANCE (ml/min)	PLASMA CLEARANCE (ml/min/kg)	WHOLE BLOOD CLEARANCE (ml/min)	WHOLE BLOOD CLEARANCE (ml/min/kg)
NO	MEAN	7.4	3.4	0.05	435.9	6.7	788.8	11.4
ASCITES	SD	8.9	1.2	0.02	212.9	3.5	389.3	6.0
(n = 64)	SEM	1.1	0.16	0.002	26.6	0.4	48.7	0.75
	MEAN	20.9***	4.5***	0.07***	227.3***	3.4***	363.8***	5.5***
ASCITES	SD	11.2	1.6	0.02	211.2	3.2	339.2	5.1
(n = 38)	SEM	1.8	0.3	0.003	34.3	0.5	55.0	0.83

Statistics by Analysis of Variance

* $P < 0.05$
** $P < 0.005$
*** $P < 0.001$

TABLE 10.12 MEAN, STANDARD DEVIATION (SD) AND STANDARD ERROR OF THE MEAN (SEM) OF STANDARD BIOCHEMICAL LIVER FUNCTION TESTS IN LIVER DISEASE PATIENTS WITH AND WITHOUT PORTAL HYPERTENSION

		BILIRUBIN (mmol/l)	ASPARTATE TRANSAMINASE (iu/l)	ALANINE TRANSAMINASE (iu/l)	GAMMA GLUTAMYL TRANSPEPTIDASE (iu/l)	ALBUMIN (g/l)
NO PORTAL	MEAN	41.4	105.8	99.5	386.3	35.6
HYPERTENSION	SD	78.2	127.3	117.3	567.2	7.9
(n = 79)	SEM	8.8	14.3	91.7	63.8	0.9
PORTAL	MEAN	51.0	79.6	56.7*	197.0	32.4*
HYPERTENSION	SD	48.5	73.8	63.8	197.7	6.0
(n = 37)	SEM	8.0	12.2	10.5	33.4	1.0

Statistics by Analysis of Variance

* $P < 0.05$
** $P < 0.005$
*** $P < 0.001$

TABLE 10.13 MEAN, STANDARD DEVIATION (SD) AND STANDARD ERROR OF THE MEAN (SEM) OF ANTIPYRINE KINETIC DATA IN LIVER DISEASE PATIENTS WITH AND WITHOUT PORTAL HYPERTENSION

		HALF LIFE (hrs)	VOLUME OF DISTRIBUTION (l)	VOLUME OF DISTRIBUTION (l/kg)	CLEARANCE (ml/min)	CLEARANCE (ml/min/kg)
NO PORTAL	MEAN	21.6	32.6	0.52	25.2	0.34
HYPERTENSION	SD	18.6	13.0	0.18	14.9	0.23
(n = 72)	SEM	2.2	1.5	0.02	1.8	0.03
PORTAL	MEAN	21.9	33.8	0.51	21.6	0.34
HYPERTENSION	SD	10.1	12.1	0.20	12.4	0.21
(n = 32)	SEM	1.8	2.1	0.04	2.2	0.04

Statistics by Analysis of Variance

* $P < 0.05$
** $P < 0.005$
*** $P < 0.001$

TABLE 10.14 MEAN, STANDARD DEVIATION (SD) AND STANDARD ERROR OF THE MEAN (SEM) OF INDOCYANINE GREEN KINETIC DATA IN LIVER DISEASE PATIENTS WITH AND WITHOUT PORTAL HYPERTENSION

		HALF LIFE (min)	VOLUME OF DISTRIBUTION (l)	VOLUME OF DISTRIBUTION (l/kg)	PLASMA CLEARANCE (ml/min)	PLASMA CLEARANCE (ml/min/kg)	WHOLE BLOOD CLEARANCE (ml/min)	WHOLE BLOOD CLEARANCE (ml/min/kg)
NO PORTAL	MEAN	10.5	3.6	0.6	407.9	6.3	679.2	10.6
HYPERTENSION	SD	11.0	1.4	0.02	256.2	4.1	436.4	6.8
(n = 69)	SEM	1.3	0.2	0.002	30.8	0.50	52.5	0.82
PORTAL	MEAN	16.4*	4.3*	0.7	254.1**	3.9**	412.2**	6.2***
HYPERTENSION	SD	12.5	1.6	0.02	131.5	2.0	275.9	3.2
(n = 33)	SEM	2.2	0.3	0.004	22.9	0.35	48.0	0.7

Statistics by Analysis of Variance

* $P < 0.05$
** $P < 0.005$
*** $P < 0.001$

TABLE 10.15 MEAN, STANDARD DEVIATION (SD) AND STANDARD ERROR OF THE MEAN (SEM) OF STANDARD BIOCHEMICAL LIVER FUNCTION TESTS IN PATIENTS WITH LIVER DISEASE DIVIDED BY MAJOR HISTOLOGICAL FINDINGS

		BILIRUBIN (mmol/l)	ASPARTATE TRANSAMINASE (iu/l)	ALANINE TRANSAMINASE (iu/l)	GAMMA GLUTAMYL TRANSPEPTIDASE (iu/l)	ALBUMIN (g/l)
ACTIVE CIRRHOSIS (n = 40)	MEAN	54.7	125.5	88.5	197.1	31.4
	SD	90.7	173.0	118.0	208.0	7.2
	SEM	14.4	27.5	14.0	33.0	1.1
INACTIVE CIRRHOSIS (n = 5)	MEAN	39.4	42.6	25.6	90.8	29.8
	SD	25.3	113.0	9.4	82.2	9.1
	SEM	11.5	52.4	4.3	37.4	4.1
NO CIRRHOSIS (n = 40)	MEAN	28.7	92.2	95.3	600.7 1-** 4-**	38.1 1-*** 2-***
	SD	40.9	56.6	75.6	714.0	5.2
	SEM	18.6	9.0	12.0	113.3	0.8
NO BIOPSY (n = 32)	MEAN	50.9	77.2	78.7	171.7	35.2
	SD	72.1	69.4	125.0	194.0	8.1
	SEM	12.6	12.2	21.9	34.0	1.4

Statistics by Analysis of Variance

1 = vs Active Cirrhosis
2 = vs Inactive Cirrhosis
3 = vs Non Cirrhotic
4 = vs No Biopsy

* = $P < 0.05$
** = $P < 0.005$
*** = $P < 0.001$

TABLE 10.16 MEAN, STANDARD DEVIATION (SD) AND STANDARD ERROR OF THE MEAN (SEM) OF ANTIPYRINE KINETIC DATA IN PATIENTS WITH LIVER DISEASE DIVIDED INTO HISTOLOGICAL FINDINGS

		HALF LIFE (hrs)		VOLUME OF DISTRIBUTION (l)	CLEARANCE (ml/min)	
ACTIVE CIRRHOSIS (n = 33)	MEAN	26.7		36.3	20.5	
	SD	16.5		14.7	14.1	
	SEM	2.9		2.6	2.5	
INACTIVE CIRRHOSIS (n = 5)	MEAN	30.7		22.6	13.0	
	SD	15.8		10.2	13.4	
	SEM	7.2		4.6	6.2	
NO CIRRHOSIS (n = 35)	MEAN	15.6	1-*** 2-**	31.6	27.8	1-* 2-**
	SD	9.1		10.4	12.4	
	SEM	1.5		1.8	2.1	
NO BIOPSY (n = 32)	MEAN	21.7		31.9	26.6	
	SD	21.4		12.1	15.5	
	SEM	3.8		2.1	2.7	

Statistics by Analysis of Variance

1 = vs Active Cirrhosis
2 = vs Inactive Cirrhosis
3 = vs Non Cirrhotic
4 = vs No Biopsy

* = $P < 0.05$
** = $P < 0.005$
*** = $P < 0.001$

TABLE 10.17 MEAN, STANDARD DEVIATION (SD) AND STANDARD ERROR OF THE MEAN (SEM) OF INDOCYANINE GREEN KINETIC DATA IN PATIENTS WITH LIVER DISEASE DIVIDED INTO MAJOR HISTOLOGICAL FINDINGS

		HALF LIFE (mins)		VOLUME OF DISTRIBUTION (l)		PLASMA CLEARANCE (ml/min)		WHOLE BLOOD CLEARANCE (ml/min)	
ACTIVE CIRRHOSIS (n = 33)	MEAN	17.3		4.0		230.0		373.6	
	SD	11.3		1.3		174.0		293.0	
	SEM	2.0		0.2		30.5		51.4	
INACTIVE CIRRHOSIS (n = 5)	MEAN	25.9		3.8		155.4		235.1	
	SD	25.4		1.3		92.0		137.0	
	SEM	11.5		0.6		41.8		62.3	
NO CIRRHOSIS (n = 35)	MEAN	6.9	1-*** 2-***	3.4	1-*	454.0	1-*** 2-**	750.6	1-*** 2-**
	SD	6.9		1.1		191.0		357.0	
	SEM	1.2		0.2		32.4		60.5	
NO BIOPSY (n = 32)	MEAN	11.3	1-* 2-* 3-*	4.2	3-*	423.4	1-**	708.9	1-*** 2-*
	SD	10.1		1.9		276.0		474.0	
	SEM	1.8		0.3		48.4		83.2	

Statistics by Analysis of Variance
1 = vs Active Cirrhosis
2 = vs Inactive Cirrhosis
3 = vs Non Cirrhotic
4 = vs No Biopsy

* = $p < 0.05$
** = $P < 0.005$
*** = $P < 0.001$

TABLE 10.18 CAUSE OF DEATH IN 29 PATIENTS DYING WITH LIVER DISEASE

NO.	DIAGNOSIS	AGE	SEX	FOLLOW UP (months)	CAUSE OF DEATH
1	PBC	67	F	36	Variceal Bleed
3	PBC	59	F	8	Hepatorenal Failure
130	PBC	67	M	20	Hepatorenal Failure
2	CAH	74	F	15	Encephalopathy
32	CAH	39	F	17	Encephalopathy
111	CAH	58	M	4	Liver Failure
150	CAH	63	F	1	Liver Failure
191	CAH	45	F	14	Carcinoma of Cervix
6	ALD	50	F	32	Liver Failure
10	ALD	58	M	20	Myocardial Infarct
16	ALD	65	F	32	Septicaemia
24	ALD	58	F	35	Bronchogenic Carcinoma
25	ALD	62	M	24	Variceal Bleed
53	ALD	66	F	27	Bronchogenic Carcinoma
63	ALD	68	M	4	Liver Failure
76	ALD	62	F	1	Liver Failure
94	ALD	61	M	4	Variceal Bleed
127	ALD	50	M	4	Liver Failure
139	ALD	56	M	4	Hepatocellular Carcinoma
144	ALD	61	M	1	Liver Failure
152	ALD	61	M	3	Liver Failure
159	ALD	68	M	10	Hepatorenal Failure
205	ALD	67	M	16	Liver Failure
210	ALD	48	F	3	Liver Failure
233	ALD	40	M	1	Hepatorenal Failure
5	IPH	58	M	28	Hepatorenal Failure/Portal vein thrombosis
14	CC	64	F	14	Cardiac Failure
26	CC	64	F	14	Liver Failure
86	CC	76	M	12	Hepatorenal Failure

PBC = PRIMARY BILIARY CIRRHOSIS
CAH = CHRONIC ACTIVE HEPATITIS
ALD = ALCOHOLIC LIVER DISEASE
IPH = IDIO PORTAL HYPERTENSION
CC = CRYPTOGENIC CIRRHOSIS

TABLE 10.19 STANDARD BIOCHEMISTRY DATA IN SURVIVORS WITH LIVER DISEASE (n = 75) AND PATIENTS DYING WITH LIVER DISEASE (n = 27)

	SURVIVORS			NON SURVIVORS		
	Mean	Standard Deviation	Standard Error of the Mean	Mean	Standard Deviation	Standard Error of the Mean
Albumin (g/l)	36.9	6.9	0.8	28.8+++	6.5	1.3
Globulin (g/l)	33.3	9.9	1.1	39.3	15.8	3.0
Creatinine (nmol/l)	84.1	21.4	2.5	93.7+	29.2	5.6
Aspartate Transaminase (iu/l)	82.6	60.0	6.9	136.8	189.0	36.4
Alanine Transaminase (iu/l)	83.4	95.0	11.0	92.3	129.0	24.8
Gamma Glutamyl Transpeptidase (iu/l)	391.3	555.0	63.8	159.5+	169.0	32.5
Alkaline Phosphatase (iu/l)	293.1	323.0	37.1	189.0	113.0	21.7
Bilirubin (umol/l)	28.4	49.4	5.7	86.7+++	95.5	18.0

Statistics by one way analysis of variance and multiple T-tests.

P values Survivors vs Non-Survivors
+ = < 0.05
++ = < 0.01
+++ = < 0.001

TABLE 10.20 ANTIPYRINE KINETIC DATA IN SURVIVORS WITH LIVER DISEASE (n = 76) AND PATIENTS DYING WITH LIVER DISEASE (n = 28)

	SURVIVORS			NON SURVIVORS		
	Mean	Standard Deviation	Standard Error of the mean	Mean	Standard Deviation	Standard Error of the Mean
Half Life (hrs)	19.3	15.3	1.8	28.3+	17.9	3.4
Volume of Distribution (l)	31.9	12.1	1.4	35.8	14.0	2.7
Volume of Distribution (l/kg)	0.5	0.2	0.1	0.6	0.3	0.06
Plasma Clearance (ml/min)	25.5	14.0	1.6	20.2	14.4	2.8
Plasma Clearance (ml/min/kg)	0.4	0.2	0.1	0.3	0.2	0.04

No significant differences in a one way analysis of variance.

P value Survivors versus Non-survivors

+ < 0.05
++ < 0.01
+++ < 0.001

TABLE 10.21

INDOCYANINE GREEN KINETIC DATA IN SURVIVORS WITH LIVER DISEASE (n = 75) AND PATIENTS DYING WITH LIVER DISEASE (n = 27)

	SURVIVORS			NON SURVIVORS		
	Mean	Standard Deviation	Standard Error of the Mean	Mean	Standard Deviation	Standard Error of the Mean
Half Life (min)	8.5	7.5	0.9	23.3+++	14.5	2.8
Volume of Distribution (l)	3.6	1.3	0.1	4.4+++	1.7	0.2
Volume of Distribution (l/kg)	0.07	0.02	0.002	0.07	0.02	0.003
Plasma Clearance (ml/min)	421.5	236.0	27.1	182.2+++	104.0	20.6
Plasma Clearance (ml/min/kg)	6.5	3.8	0.4	2.8+++	1.5	0.29
Whole Blood Clearance (ml/min)	701.9	416.0	47.6	290.0+++	175.0	33.7
Whole Blood Clearance (ml/min/kg)	10.9	6.4	0.7	4.4+++	2.5	0.5

Statistics by one way analysis of variance and multiple T-tests.

P values Survivors versus Non-survivors + < 0.05
++ < 0.01
+++ < 0.001

TABLE 10.22 RESULTS OF THE INITIAL STEP OF SURVIVAL ANALYSIS 1

VARIABLE	CHI-SQUARE TO ENTER	CHI-SQUARE TO REMOVE	P-VALUE
AGE	-	4.26	0.039
Antipyrine Tl/2	9.69	-	0.002
Antipyrine Vd	5.04	-	0.025
Antipyrine Vd/kg	5.64	-	0.018
Antipyrine TB cl	0.84	-	0.360
Antipyrine TB cl/kg	1.27	-	0.261
ICG Tl/2	20.77	-	<0.001
ICG Vd	5.29	-	0.021
ICG Vd/kg	2.72	-	0.010
ICG TB cl	25.79	-	<0.001
ICG TB cl/kg	24.54	-	<0.001
ICG WB cl	26.06	-	<0.001
ICG WB cl/kg	28.41	-	<0.001
LOG Antipyrine Tl/2	11.57	-	<0.001
LOG Antipyrine Vd	5.86	-	0.016
LOG Antipyrine Vd/kg	4.75	-	0.029
LOG Antipyrine TB cl	3.54	-	0.060
LOG Antipyrine TB cl/kg	4.61	-	0.032
LOG ICG Tl/2	41.62	-	<0.001
LOG ICG Vd	5.90	-	0.015
LOG ICG Vd/kg	4.00	-	0.046
LOG ICG TB cl	25.10	-	<0.001
LOG ICG TB cl/kg	21.58	-	<0.001
LOG ICG WB cl	25.96	-	<0.001
LOG ICG WB cl/kg	29.01	-	<0.001

TABLE 10.23 FINAL RESULT OF SURVIVAL ANALYSIS 1

VARIABLE	CHI-SQUARE TO ENTER	CHI-SQUARE TO REMOVE	P-VALUE
AGE	-	13.96	0.0002
ANTIPYRINE Tl/2	0.14	-	0.7090
ANTIPYRINE Vd	0.02	-	0.9004
ANTIPYRINE Vd/kg	0.02	-	0.8930
ANTIPYRINE TB Cl	0.34	-	0.5613
ANTIPYRINE TB Cl/kg	0.32	-	0.5701
ICG Vd	0.26	-	0.6128
ICG Vd/kg	0.69	-	0.4075
ICG TB Cl	0.27	-	0.6058
ICG Cl/kg	0.85	-	0.3566
ICG WB Cl	0.34	-	0.5577
ICG WB Cl/kg	1.23	-	0.2682
LOG ANTIPYRINE Tl/2	0.11	-	0.7357
LOG ANTIPYRINE Vd	0.19	-	0.6601
LOG ANTIPYRINE Vd/kg	0.06	-	0.8045
LOG ANTIPYRINE TB cl	0.23	-	0.6304
LOG ANTIPYRINE TB cl/kg	0.09	-	0.7658
LOG ICG Tl/2	-	41.62	0.0001
LOG ICG Vd	0.10	-	0.7568
LOG ICG Vd/kg	0.28	-	0.5998
LOG ICG TB cl	0.00	-	0.9972
LOG ICG TB cl/kg	0.00	-	0.9881
LOG ICG WB cl	0.02	-	0.8832
LOG ICG WB cl/kg	0.18	-	0.6749

TABLE 10.24 MULTIPLE REGRESSION ANALYSIS OF VARIOUS TRANSFORMATIONS OF INDOCYANINE GREEN HALF LIFE

VARIABLE	CHI-SQUARE TO ENTER	CHI-SQUARE TO REMOVE	P-VALUE
AGE	-	4.43	0.035
ICG T1/2	20.77	-	<0.001
LOG ICG T1/2	38.61	-	<0.001
SQUARE ROOT ICG T1/2	29.84	-	<0.001
RECIPROCAL ICG T1/2	45.02	-	<0.001

TABLE 10.25 INITIAL STEP OF ANALYSIS 3

STEP 1

VARIABLE	CHI-SQUARE TO ENTER	CHI-SQUARE TO REMOVE	P-VALUE
AGE	-	4.09	0.043
ALBUMIN	-	2.31	0.129
LOG BILIRUBIN	-	8.48	0.004
LOG AST	-	1.29	0.256
LOG ALT	-	0.40*	0.525
LOG GGT	-	3.52	0.061
PROTHROMBIN TIME	-	0.80	0.370
SEX	1.53	-	0.216
PORTAL HYPERTENSION	1.22	-	0.269
ASCITES	4.64	-	0.031
ENCEPHALOPATHY	2.00	-	0.158
CHILDS	0.65	-	0.419
RECIPROCAL ICG T1/2	9.73	-	0.002
RECIPROCAL ANTIPYRINE T1/2	0.00	-	0.948

* REMOVED

TABLE 10.26 SUMMARY OF STEPS FOR ANALYSIS 3

STEP	VARIABLE ENTERED	VARIABLE REMOVED	IMPROVEMENT IN CHI-SQUARED	P VALUE
1	-	ALT	0.403	0.525
2	-	PROTHROMBIN TIME	0.714	0.398
3	-	AST	0.540	0.463
4	-	GGT	1.966	0.161
5	RECIPROCAL ICG T1/2		9.702	0.002
6	-	BILIRUBIN	1.405	0.236

TABLE 10.27 RESULTS OF ANALYSIS 3

VARIABLE	COEFFICIENT	STANDARD ERROR	CHI-SQUARE TO REMOVE	P-VALUE
AGE	0.08	0.03	12.17	0.005
ALBUMIN	-0.07	0.04	2.75	0.0974
Reciprocal ICG T1/2	-24.66	7.67	17.05	<0.0001

TABLE 10.28 FINAL RESULTS OF ANALYSIS 4

VARIABLE	CHI-SQUARE TO ENTER	CHI-SQUARE TO REMOVE
AGE]		
ALBUMIN]		
BILIRUBIN (LOG)]		
ALT]	- are in and may not be removed	
AST]		
GGT]		
PROTHROMBIN TIME]		
SEX	2.36	0.125
PORTAL HYPERTENSION	1.88	0.170
ASCITES	5.84	0.016
ENCEPHALOPATHY	1.54	0.215
CHILDS	0.22	0.639
RECIPROCAL OF ICG T1/2	6.38	0.012
RECIPROCAL OF ANTIPYRINE T1/2	0.05	0.822

FIGURE 10.1 ANTIPYRINE HALF-LIFE IN CONTROL SUBJECTS, SURVIVORS AND NON SURVIVORS WITH LIVER DISEASE (means ±I SD)
Statistics by one way analysis of variance.

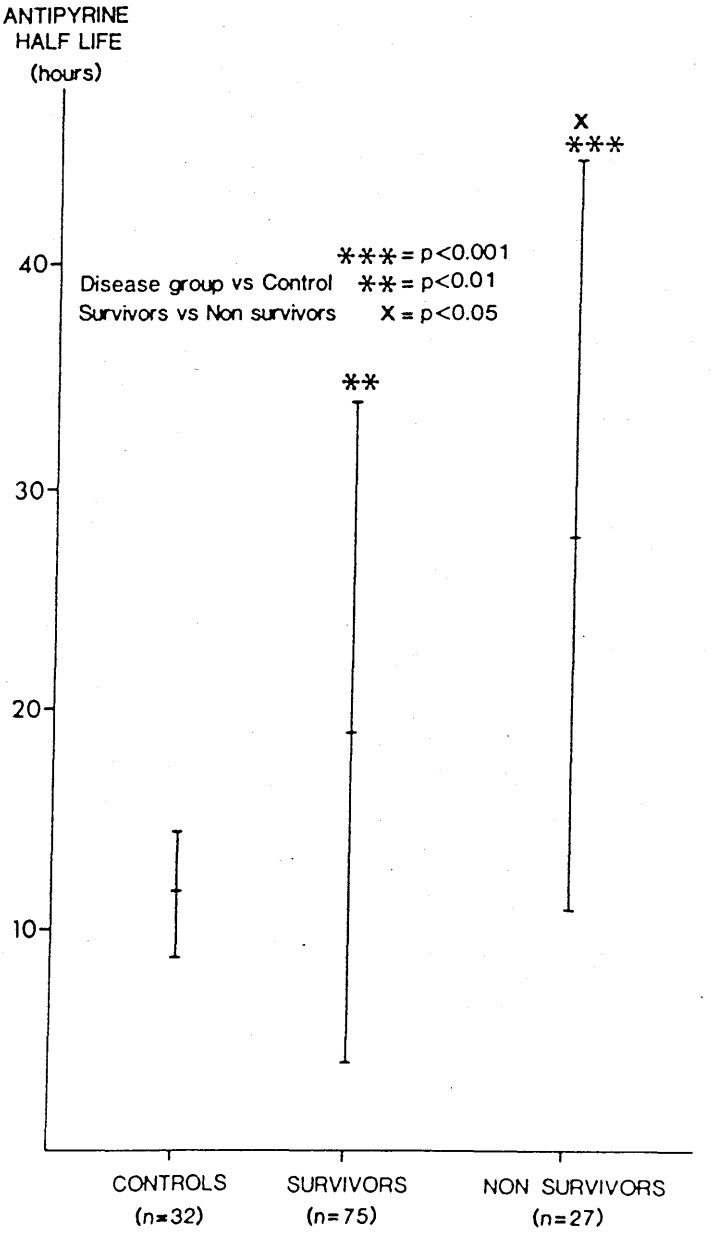


FIGURE 10.2 INDOCYANINE GREEN HALF-LIFE IN CONTROL SUBJECTS, SURVIVORS AND NON-SURVIVORS WITH LIVER DISEASE (means ± I SD). Statistics by one way analysis of variance.

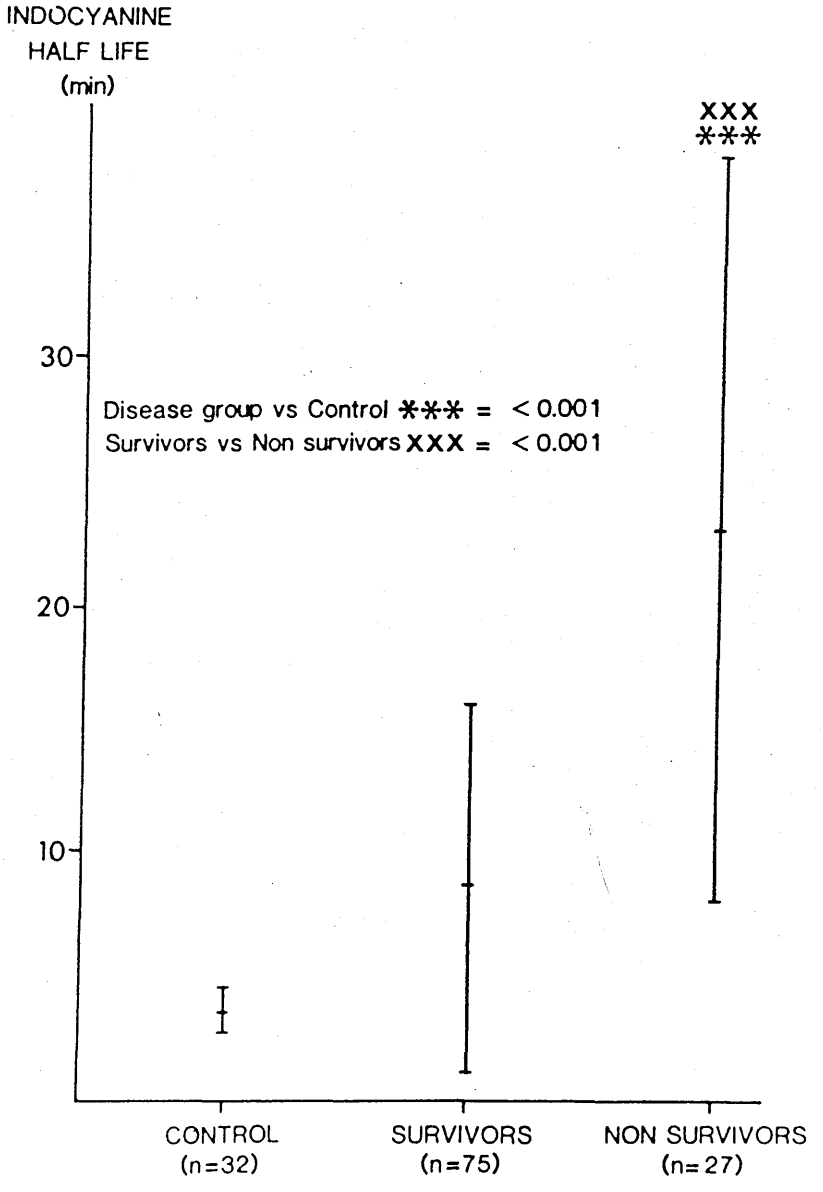


FIGURE 10.3 MATHEMETICAL TRANSFORMATIONS OF INDOCYANINE GREEN HALF-LIFE.

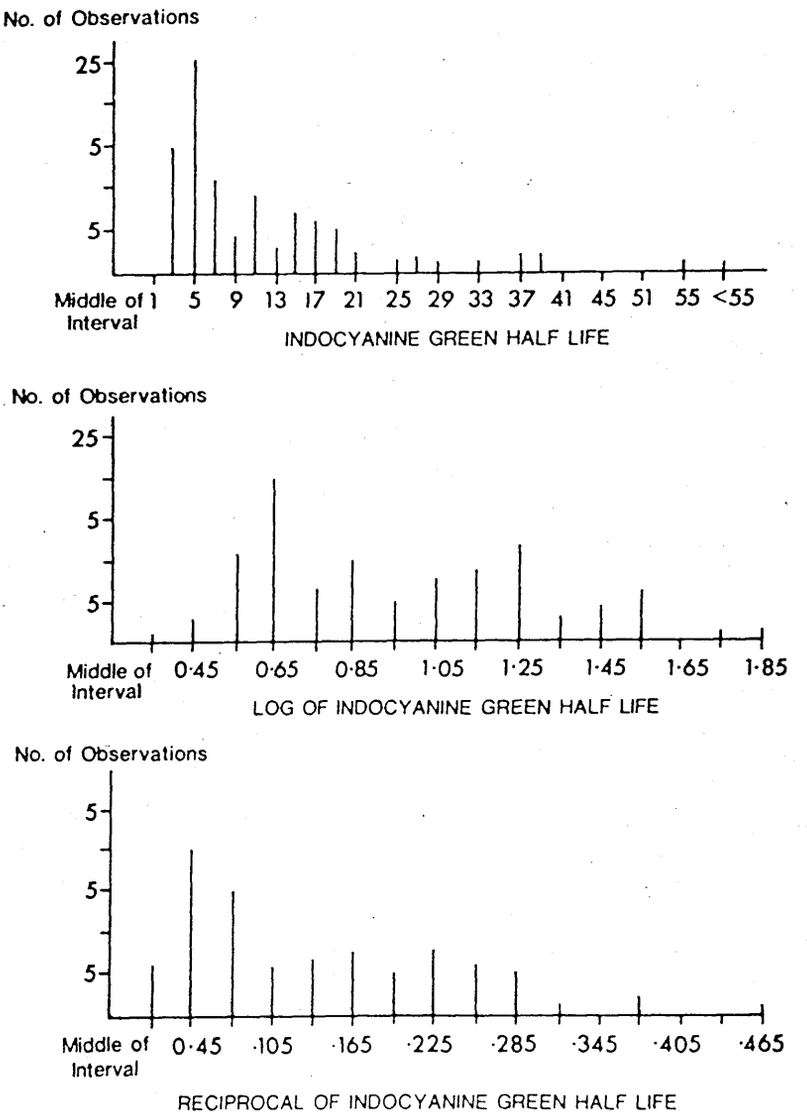
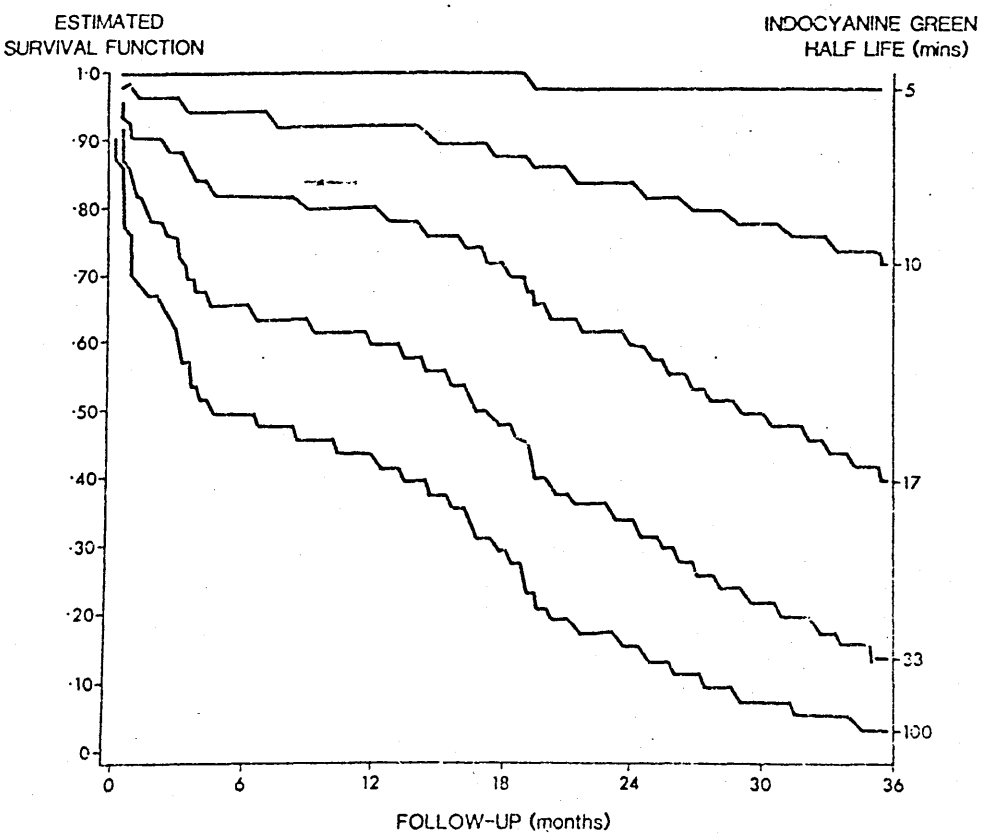


FIGURE 10.4 ESTIMATES OF SURVIVAL FUNCTIONS FOR DIFFERENT VALUES OF INDOCYANINE GREEN HALF-LIFE IN A PATIENT AGED 50.



C H A P T E R 11

BETA-ADRENERGIC BLOCKADE WITH NADOLOL IN PORTAL HYPERTENSION

11.1 SUMMARY

The effect of Nadolol 160mg/day on antipyrine and indocyanine green kinetics and wedged hepatic vein pressure was assessed in 6 patients with hepatic cirrhosis and portal hypertension. There was a significant reduction in wedged hepatic vein pressure during treatment with nadolol (Nadolol = 13.1 $\pm$ 3.6 mmHg: Placebo = 19.9 $\pm$ 5.6 mmHg). There were no significant alterations in the standard liver function tests, antipyrine or indocyanine green kinetics.

These data show that Nadolol produces a fall in portal pressure similar to that of propranolol. Nadolol is excreted by the kidney so that its elimination should be predictable even in patients with severely compromised liver function.

11.2 INTRODUCTION

A mortality of up to 80% is associated with bleeding from oesophageal varices (ORLOFF et al 1967, GRAHAM and SMITH 1981). In the acute management of variceal bleeding drugs have been used to lower the portal pressure. Initially vasopressin (BAUM and NAUSBAUM 1971, CONN et al 1975) was popular, then its synthetic analogue triglycyl vasopressin (Glypressin) (FREEMAN et al 1982) and more recently with somatostatin (THULIN et al 1979, BOSCH et al 1981). These agents have to be administered parenterally and are therefore unsuitable for chronic administration either in the primary prophylaxis of variceal bleeding or in the secondary prevention of rebleeding.

A reduction in portal pressure has been demonstrated with the beta-adrenergic blocking drugs propranolol (HILLON et al 1982, LEBREC et al 1981 and 1982, RECTOR 1986), atenolol (HILLON et al 1982), and metoprolol (WESTABY et al 1985), a selective beta 2 blocker (BIHARI et al 1984), and the alpha receptor blocker prazosin (MILLS et al 1984). These drugs can be administered chronically and the use of these drugs in the secondary prevention of variceal bleeding has been investigated with inconclusive results. In a selected group of patients with portal hypertension a reduction in the incidence of rebleeding in patients treated with propranolol has been shown (LEBREC et al 1981). Similar studies have failed to confirm this finding (BURROUGHS et al 1983, CONN 1982 and 1984).

Propranolol is a lipid soluble drug with a high first pass metabolism with a low systemic availability. In patients with

chronic liver disease there is an increase in its systemic availability (BRANCH et al 1976, PESSAYRE et al 1978), with marked increases in the steady state concentrations (WOOD et al 1978), and an increase in the unbound fraction of the drug, all of which result in an increased pharmacodynamic response (ARTHUR et al 1985). The therapeutic dose of propranolol is therefore difficult to predict in cirrhotic patients and concern has been expressed over the possibility of excessive beta-blockade in these patients (POSNER et al 1982, BURROUGHS et al 1983). Propranolol also produces a marked reduction in liver blood flow (WEISS et al 1978). This reduction in liver blood flow may theoretically reduce liver function in a group of patients with already compromised liver function. There are therefore doubts about the efficacy and suitability of propranolol as a therapeutic agent for the treatment of portal hypertension.

Nadolol is a water soluble non-cardioselective beta-adrenergic blocking drug with a long duration of action (OPIE 1980), which is mainly excreted by the kidney (HEEL et al 1980). The aim of this study is to evaluate the effect of nadolol on portal pressure, hepatic monoxygenase enzyme activity and apparent liver blood flow.

11.3 PATIENTS AND METHODS

Six patients admitted with upper gastrointestinal bleeding from oesophageal varices were studied. The source of blood loss was demonstrated by endoscopy, at which the varices were

injected with ethanolamine oleate. Hepatic cirrhosis was proven histologically and was attributed to alcohol in all 6. Only one patient was female. A double blind placebo controlled crossover study design was used. When the patients had been haemodynamically stable for at least five days with no evidence of blood loss, they were randomly allocated to receive either nadolol 160mg per day or a matching placebo tablet. They continued this medication for 28 days as an outpatient.

Clinical laboratory and haemodynamic measurements were made following the first 28 day treatment period and again after the patient had been crossed over onto the other medication for a further 28 day treatment period. Clinically the patients were assessed for evidence of porto-systemic encephalopathy, ascites and the resting pulse and blood pressure were measured. Laboratory tests included the measurement of haemoglobin, serum urea, creatinine, electrolytes, and standard biochemical liver function tests. The portal pressure was determined by passing a Cournand catheter through the femoral vein into the hepatic vein for the measurement of free and wedged hepatic vein pressure. The difference between these two measurements is termed the porto-hepatic venous pressure gradient and is accepted as an indirect measurement of portal pressure (BOYER et al 1977). Cardiac output was measured by a thermodilution method using a Swan-Ganz catheter passed into the main pulmonary artery (FORRESTER et al 1972). A mean of three measurements was used.

Antipyrine clearance and indocyanine green clearance were measured using the protocols discussed in Chapter 7. During the two months treatment period no further gastrointestinal bleeding

occured, and the patients received no other medication. In one patient no catheterisation data is available because of technical problems with the equipment.

The results are express as means ± the standard deviation. In order to avoid making assumptions about the distributions of the data the groups were analysed using paired Wilcoxon sign rank tests. All patients gave informed written consent and the project was approved by the local ethical committee.

11.4 RESULTS

There was no alteration in the standard biochemical liver function tests (Table 11.1). No patient developed evidence of gastrointestinal blood loss, ascites or portosystemic encephalopathy during the study. There was no significant alteration in the disposition of antipyrine or indocyanine green between the two phases (Table 11.2). There was a significant reduction in the wedged hepatic vein pressure in patients during the nadolol phase compared to the placebo phase (19.9 ± 5.6 mmHg vs 13.1 ± 3.6 mmHg: $P<0.05$). There was a significant reduction in the heart rate and a trend towards a reduced cardiac output during the nadolol phase but this failed to reach statistical significance.

11.5 DISCUSSION

This study demonstrates a reduction in wedged hepatic vein pressure of 34% following one months treatment with nadolol. This reduction is similar to that previously demonstrated with nadolol

GATTA et al 1984), and other non cardioselective beta blockers. It is greater than that seen with the cardioselective beta blockers atenolol (MILLS et al 1984) or metoprolol (WESTABY et al 1984, WESTABY et al 1985).

The portal tract is devoid of beta receptors (RICHARDSON and WITHRINGTON 1981). The major effect of betablockers in portal hypertension is to reduce cardiac output, which results in a reflex constriction of the hepatic artery, as a consequence of the reduction of the inflow to the liver there is a fall in portal pressure. The non cardioselective beta blockers have an additional action by blocking the vasodilator beta 2 receptors in the splanchnic circulation this leading to unopposed alpha stimulation and vasoconstriction and a fall in the blood flow into the portal circulation (LEBREC et al 1982). This additional mode of action may explain the greater reduction in portal pressure with the nonselective beta blockers.

There was no significant alteration in either the disposition of antipyrine or indocyanine green during therapy with nadolol. Similar results have been demonstrated in healthy volunteers (PARKER et al 1984). Propranolol has been shown to inhibit the clearance of antipyrine (GREENBLATT et al 1978) and indocyanine green (PARKER et al 1984). Propranolol has been shown to produce a marked reduction in effective liver blood flow which was not seen with the cardioselective beta blocker metoprolol (WESTABY et al 1984). The reduction of liver blood flow by propranolol has been implicated in the production of portosystemic encephalopathy (TARVER et al 1983).

This study demonstrates that nadolol has a similar effect on portal pressure to other noncardioselective beta blockers. In patients with abnormal liver function nadolol has several theoretical advantages. It is excreted by the kidney so that its elimination should be predictable even in severe liver failure. There is no inhibition of the hepatic monooxygenase enzymes and this reduces the likelihood of major drug interactions. The failure to reduce indocyanine green clearance suggests that total liver blood flow may be relatively unimpaired during nadolol therapy but this requires confirmation by a more direct measurement of liver blood flow. This suggests that nadolol may be a more suitable beta blocking drug for use in patients with severely compromised liver function.

ACKNOWLEDGEMENT

I acknowledge the help and expertise of Dr Ian Findlay and Dr. Henry Dargie in performing the cardiac catheterisations in these patients.

Table 11.1 NADOLOL STUDY - STANDARD BIOCHEMICAL LIVER FUNCTION TESTS

	ALBUMIN (g/l)	BILIRUBIN (mmol/l)	SGOT (iu/l)	SGPT (iu/l)	GGT (iu/l)
PLACEBO					
1.	30	18	114	46	242
2.	32	10	22	14	254
3.	33	32	32	24	57
4.	51	15	50	53	224
5.	42	17	54	42	71
6.	37	15	41	34	113
MEAN	37.5	17.8	52.2	35.5	160.1
SD	7.9	7.5	32.5	14.5	89.9
SEM	3.2	3.0	13.3	5.9	36.7
NADOLOL					
1.	34	24	109	36	807
2.	31	15	21	22	268
3.	34	5	25	70	52
4.	48	21	46	69	275
5.	38	15	58	38	58
6.	36	17	42	38	122
MEAN	36.8	16.2	50.2	45.5	263.7
SD	5.9	6.5	31.9	19.5	283.7
SEM	2.4	2.7	13.0	8.0	115.8
STATISTICS BY PAIRED WILCOXON SIGN RANK TESTS					
P VALUE	NS	NS	NS	NS	NS

Table 11.2 ANTIPYRINE AND INDOCYANINE GREEN DATA FROM 6 PATIENTS ON PLACEBO AND NADOLOL

	ANTIPYRINE			INDOCYANINE GREEN			
TABLE 7.2	HALF LIFE (hrs)	VOLUME OF DISTRIBUTION (l)	CLEARANCE (ml/min)	HALF LIFE (min)	VOLUME OF DISTRIBUTION (l)	PLASMA CLEARANCE (ml/min)	BLOOD CLEARANCE (ml/min)
PLACEBO							
1.	42.5	17.8	4.8	9.4	3.8	277.3	390.5
2.	17.6	30.3	19.9	17.6	3.1	465.3	878.0
3.	16.7	43.3	29.9	33.9	5.5	120.3	183.7
4.	26.7	72.0	31.2	8.5	5.2	427.4	633.1
5.	29.8	45.7	17.7	13.9	5.0	249.4	461.1
6.	6.6	19.1	33.4	5.1	3.8	518.0	887.2
MEAN	23.3	38.0	22.8	14.7	4.4	343.0	572.3
SD	12.5	20.3	10.9	10.4	0.96	151.9	280.3
SEM	5.1	8.3	4.4	4.2	0.39	62.0	114.4
NADOLOL							
1.	20.5	11.9	6.7	8.6	4.0	322.5	533.0
2.	9.8	46.7	54.8	6.8	3.3	342.6	665.2
3.	48.4	35.4	8.4	38.0	4.3	77.7	131.7
4.	31.3	27.3	10.1	6.0	4.7	548.5	915.6
5.	26.4	35.5	15.5	14.1	4.1	201.8	373.6
6.	29.2	20.5	8.1	5.6	5.6	697.7	120.2
MEAN	27.6	29.6	17.3	13.2	4.3	365.2	456.6
SD	12.8	12.3	18.6	12.6	0.77	226.2	311.7
SEM	5.2	5.0	7.6	5.1	0.31	92.4	127.2
P VALUE	NS	NS	NS	NS	NS	NS	NS

Statistics by Mann Whitney U Tests

Table 11.3 CARDIAC CATHETERISATION DATA FROM 5 PATIENTS ON PLACEBO AND NADOLOL THERAPY

	Cardiac Output (l/min)	Pulmonary Artery Pressure mmHg Systolic (mmHg)	Diastolic (mmHg)	Pulmonary Wedged Pressure (mmHg)	Right Ventricle Pressure mmHg Systolic (mmHg)	Diastolic (mmHg)	Wedged Hepatic Vein Pressure (mmHg)	Free Hepatic Vein Pressure (mmHg)	Gradient WHFP-FAVP (mmHg)
PLACEBO									
1.	5.9	23	8	6	22	0	28.0	2.0	88
2.	12.8	24	12	13	20	0	13.0	4.0	90
3.	6.3	18	9	8	20	6	17.5	10.0	86
4.	7.3	18	7	7	20	4	19.0	1.0	76
5.	6.4	27	12	10	28	0	22.0	6.0	72
MEAN	7.7	22.0	9.6	8.8	22.0	2.0	19.9	4.6	82.4
SD	2.9	3.9	2.3	2.8	3.5	2.8	5.6	3.6	7.9
SEM	1.3	1.8	1.0	1.2	1.5	1.3	2.5	1.6	3.5
NADOLOL									
1.	3.9	18	6	9	22	0	19.0	10.0	72
2.	8.8	16	6	6	33	1	14.0	0.0	68
3.	6.0	16	7	6	20	4	10.5	3.0	74
4.	5.8	19	6	6	14	0	10.1	4.6	72
5.	5.0	24	13	12	33	0	12.0	4.0	64
MEAN	5.9	18.6	7.6	7.8	24.4	1.0	13.1	4.5	70.0
SD	1.8	3.3	3.0	2.7	8.4	1.7	3.6	4.6	4.0
SEM	2.8	1.5	1.4	1.2	3.7	0.8	1.6	2.0	1.8
P VALUE	NS	NS	NS	NS	NS	NS	$p < 0.048$	NS	$p<0.05$

Statistics by Paired Wilcoxon Sign Rank Tests

CHAPTER 12

PHARMACOKINETIC AND PHARMACODYNAMIC RESPONSES TO MIDAZOLAM IN PATIENTS WITH HEPATIC CIRRHOSIS AND NORMAL CONTROLS

12.1 SUMMARY

Midazolam kinetics and psychomotor function were studied after an intravenous dose of 0.075 mg/kg body weight in 7 patients with alcoholic cirrhosis and 8 patient controls. Four of the 7 cirrhotics died of complications of their liver disease within 6 months of completion of the study. The clearance of midazolam was significantly impaired in the cirrhotic patients (Cirrhotics = 4.0 $\pm$ 0.4 ml/ml/kg; Controls = 15.5 $\pm$ 4.7 ml/min/kg: $p < 0.003$). These patients also had evidence of greater sedation than the control group for up to 6 hours after the dose was administered ($p<0.05$). The clearance of midazolam did not correlate significantly with the serum albumin or bilirubin or with the kinetics of antipyrine or indocyanine green. This study demonstrates significant delay in the elimination of midazolam and reduction in psychomotor function in patients with severe alcoholic liver disease. Caution should be exercised in using this drug for pre-medication in such patients prior to endoscopic examination.

12.2 INTRODUCTION

In chronic liver disease the disposition and elimination of many lipid soluble drugs are altered (HOYUMPA et al 1978, KOCH-WESER and WILLIAMS 1983). The hepatic metabolism of these agents may be determined by the capacity of the oxidising and conjugating enzyme systems and the liver blood flow (ROWLAND et al 1973), both of which may be impaired in the presence of cirrhosis (WILKINSON and SHAND 1976). The pharmacological response to a drug may also be abnormal in liver disease and, in particular, the cerebral sensitivity to sedative drugs may be increased (READ et al 1969).

Patients with chronic liver disease are frequently referred for upper gastrointestinal endoscopy either for the diagnostic assessment of gastrointestinal haemorrhage or dyspepsia or for therapeutic injection sclerotherapy of oesophageal varices (MacDOUGALL et al 1982). Diazepam is commonly used as the premedicating sedative, but in patients with liver disease the half life of this drug may exceed 100 hours (KLOTZ et al 1973), and some patients exhibit increased cerebral sensitivity (McCONNELL et al 1982, BRANCH et al 1976).

Midazolam is a new benzodiazepine consisting of an imidazole ring fused at the 1.2 position with a diazepine ring (Figure 12.1). Its hypnotic action is brief and its elimination half-life is under four hours and in some patients is as short as two hours (ALLONEN et al 1981, GREENBLATT et al 1981, SMITH et al 1981). These properties make it a potentially useful sedative for minor invasive procedures. It is metabolised in the liver by hydroxylation and conjugation with glucuronic acid (HEIZMANN and

ZEIGLER 1981). It has a high hepatic extraction ratio (ALLONEN et al 1981) and so its elimination would be expected to be dependent on liver blood flow.

The aims of this study were to compare the pharmacokinetic profile and pharmacodynamic response following an intravenous dose of midazolam in patients with hepatic cirrhosis and those with normal liver function. Secondly, to assess the value of antipyrine and indocyanine green kinetics in predicting midazolam pharmacokinetics and dynamics.

12.3 PATIENTS

Seven patients with hepatic cirrhosis and eight patient controls agreed to take part in the study. All gave written informed consent to inclusion in the study which was approved by the local hospital ethical committee.

The cirrhotic patients were aged between 39 and 54 years and all had biopsy proven alcoholic cirrhosis. They were referred for endoscopy for the assessment of portal hypertension. Five of the 7 patients had previously bled from oesophageal varices. Two had previous episodes of portosystemic encephalopathy, but there was no clinical evidence of this on entry to the study. Four of these patients died within six months of completion of the study from complications of their liver disease.

The patient controls were aged between 37 and 62 years, They showed no clinical evidence of liver disease and had normal biochemical liver function tests. They were all referred for diagnostic upper gastrointestinal endoscopy for suspected peptic ulcer disease.

No patient was receiving any drug known to alter hepatic drug metabolism or liver blood flow and all patients were instructed to abstain from ethanol for one week prior to the study.

12.4 METHODS

See Chapter 7.2 for antipyrine method.

See Chapter 7.3 for indocyanine green method.

See Chapter 7.5 for Midazolam method.

See Chapter 7.6 for pharmacokinetic analysis.

See Chapter 7.7 for pharmacodynamic assessment.

12.5 RESULTS

All patients became overtly sedated as a result of the administration of midazolam and endoscopy was accomplished with minimal difficulty. The standard biochemical liver function tests were all significantly deranged in the cirrhotic patients (TABLE 12.1).

Pharmacokinetics

The elimination of antipyrine and indocyanine green in the two groups is shown in TABLE 12.2; there was a highly significant prolongation of the half lives of both drugs in the cirrhotic patients ($p<0.001$), with a concomitant reduction in the clearance ($p<0.05$ and $p<0.001$).

The metabolism of midazolam was impaired in the cirrhotic group compared to the controls. In two patients (A and B in figure 12.2) high plasma levels of midazolam were found

throughout the duration of the study. If the values are true then the greatly prolonged estimated half life would preclude the calculation of acceptable kinetic parameters. Another possibility is that these results are due to some substance interfering with the assay, but attempts have failed to identify an interfering peak. The analytical data form these patients are therefore plotted separately and are not included in the statistical analysis of the midazolam kinetics. Using a two compartment model the clearances of midazolam were reduced in the cirrhotics (cirrhosis = 4.6 $\pm$ 5.7ml/min/kg vs controls = 15.5 $\pm$ 4.7ml/min/kg: $p<0.003$). There was no significant alteration in the volume of distribution between the two groups (cirrhotics = 29.1 $\pm$ 4.1 L; controls = 29.5 $\pm$ 6.5 L).

There were no significant correlations between the clearance of midazolam with the serum albumin, serum bilirubin, or with the clearances or half lives of antipyrine or indocyanine green.

Pharmacodynamics

All the control and cirrhotic patients were included in these analyses.

1. Choice Reaction Time

The CRT 1 (recognition time) and CRT 2 (total reaction time) values for both groups are compared in FIGURES 12.3 and 12.4. There was no significant difference in the mean baseline CRT 1 or CRT 2 between the cirrhotic and control groups. Neither the CRT 1 nor CRT 2 were significantly prolonged in the control patients at any time during the course of the study. In the cirrhotic patients both the CRT

1 and 2 were prolonged compared to the baseline values at all time points following the administration of midazolam and these differences were statistically significant at 1, 4 and 6 hours ($p<0.025$). Comparison of the cirrhotic and control patients showed significant prolongation of the CRT 1 at one hour ($p<0.025$), 4 hours ($p<0.05$) and 6 hours ($p<0.025$), and of the CRT 2 at 1, 2, and 6 hours ($p<0.025$ at all points) in the cirrhotic group (2 tailed Mann Whitney U-test).

2. Critical Flicker Fusion Time

CFFT values for both groups are shown in FIGURE 12.5. The base line values in the cirrhotic patients were significantly lower than in the control group ($p<0.05$). In the control group there was a reduction in the threshold at 60 minutes ($p<0.05$) after which the threshold returned to normal. In the cirrhotic patients the threshold was significantly reduced at 60, 120 and 240 minutes ($p<0.025$). Direct comparison between the groups was not performed because of the differing baseline values.

12.6 DISCUSSION

This study has demonstrated altered pharmacokinetics of midazolam in patients with chronic liver disease. There was a significant prolongation of the elimination half life of the drug with a concommitant fall in its clearance. The two patients with apparently high levels remain unexplained. If these are true levels the patients did not appear to be excessively sedated. Similar high levels have been demonstrated in critically ill patients receiving repeated doses of midazolam (BYATT et al 1984, BYRNE et al 1984).

The only objective evidence of psychomotor impairment in the control patients was a reduced CFFT at one hour. Subjectively they were sedated sufficiently to allow endoscopy to be performed. Using the recognition time and the total reaction time there was objective evidence of psychomotor impairment in the cirrhotic patients which was significant for up to 6 hours after the administration of midazolam. The maximum prolongation in CRT occurred in the cirrhotics at 2 hours (Figures 12.3 and 12.4). This occurred when there was a small but significantly higher plasma midazolam than in the control patients. These results could be interpreted to suggest that there maybe increased cerebral sensitivity to midazolam in these patients with chronic liver disease.

The results of the critical flicker fusion threshold are difficult to interpret because of the significantly reduced baseline in the cirrhotic patients (this problem has also occurred in a similarly designed study, with another psychoactive agent [PARKER and ROBERTS 1983]). If this apparent initial

abnormality represents subclinical portosystemic encephalopathy then the CFFT merits further study as a possible simple means of identifying and monitoring the early stages of this important complication.

The effect of chronic liver disease on the pharmacokinetics and pharmacodynamics of the benzodiazepines varies between the drugs (WILLIAMS and MAMELOCK 1980). The elimination half-life of diazepam is prolonged in cirrhotics, mainly due to a reduction in the volume of distribution (BRANCH et al 1976). A similar reduction in the elimination half-life of lorazepam has been attributed to a fall in the volume of distribution. (KRAUS et al 1978). Chlordiazepoxide has a low intrinsic clearance and a high level of protein binding. In cirrhosis its both are reduced and the volume of distribution is increased producing a half-life which is markedly prolonged (ROBERTS et al 1978). The elimination of oxazepam, a conjugated benzodiazepine, appears to be unaltered in both acute viral hepatitis or in cirrhosis (SHULL et al 1976). Direct comparisons of midazolam and diazepam in patients without liver disease undergoing diagnostic endoscopy suggest that midazolam produces a more rapid onset of sedation, The degree of sedation is similar and the patient recall is less (COLE et al 1983, WHITWAM et al 1983). This study demonstrates asignificant delay in the elimination of midazolam and increase in the degree of sedation produced for up to 6 hours following its administration to patients with severe alcoholic liver disease. Caution should therefore be exercised in administering the drug to patients with chronic liver disease. These changes, however, may be less than those occurring with

diazepam and midazolam may prove to be the benzodiazepine of choice in providing premedication for such patients who require to undergo a diagnostic or therapeutic endoscopic procedure.

TABLE 12.1

CLINICAL DETAILS AND BIOCHEMICAL LIVER FUNCTION TESTS (Mean ± SEM) IN CIRRHOTICS AND CONTROLS

	CONTROLS n = 8	CIRRHOTICS n = 7
AGE RANGE (YRS)	37 - 42	39 - 54
WEIGHT (KG)	60.6 ± 4.0	71.3 ± 4.3
DOSE OF MIDAZOLAM (MG)	4.5 ± 0.1	5.4 ± 0.3
BILIRUBIN (umol/L)	9.1 ± 0.2	71.7 ± 35.9 ***
ALKALINE PHOSPHATASE(iU/L)	87.9 ± 6.1	231.2 ± 61.0 ***
ALANINE TRANSFERASE (iU/L)	23.3 ± 1.2	60.0 ± 9.4 ***
ASPARTATE TRANSFERASE(iU/L)	22.6 ± 2.6	39.7 ± 7.4 *
GAMMA GLUTAMYL TRANSPEPTIDASE (iU/L)	24.9 ± 3.6	164.4 ± 54.2 ***
ALBUMIN (g/l)	44.0 ± 0.9	33.0 ± 2.9 *

Statistics obtained by Mann Whitney U tests

* = $p < 0.05$

** = $p < 0.025$

*** = $p < 0.001$

TABLE 12.2

ANTIPYRINE, INDOCYANINE GREEN AND MIDAZOLAM KINETICS (MEAN ± SEM) IN CIRRHOTICS AND CONTROLS

	CONTROLS n = 8	CIRRHOTICS n = 7
ANTIPYRINE		
Half life (hours)	9.8 ± 1.1	19.6 ± 1.6 ***
Volume of Distribution (litres)	45.5 ± 4.3	60.7 ± 7.2
Clearance (ml/min/kg)	1.0 ± 0.2	0.6 ± 0.1 *
INDOCYANINE GREEN		
Half life (mins)	4.1 ± 0.3	27.9 ± 8.3 ***
Volume of Distribution (litres)	4.1 ± 0.4	4.5 ± 0.3
Clearance (ml/min/kg)	12.4 ± 1.4	2.6 ± 0.7 ***
MIDAZOLAM[x]		
Clearance (ml/min/kg)	15.5 ± 4.7	4.0 ± 0.6 **
Volume of distribution (litres)	29.1 ± 4.1	29.5 ± 6.5

Statistics obtained by Mann Whitney U tests

* = $p < 0.05$
** = $p < 0.025$
*** = $p < 0.001$

[x] cirrhotics n = 5

FIGURE 12.1 CHEMICAL STRUCUTRE OF MIDAZOLAM

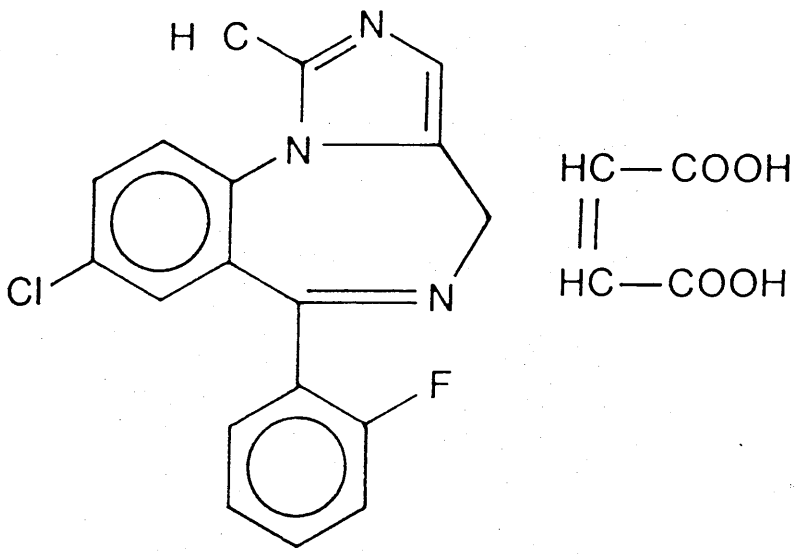


FIGURE 12.2: MIDAZOLAM PLASMA CONCENTRATIONS MEAN ±SEM) IN 8 CONTROL AND 5 CIRRHOTIC PATIENTS FOLLOWING AN INTRAVENOUS DOSE OF 0.075mg/kg BODY WEIGHT. ACTUAL PLASMA CONCENTRATIONS ARE PLOTTED FOR PATIENTS A AND B.

STATISTICAL ANALYSIS BY MANN WHITNEY U-TESTS.

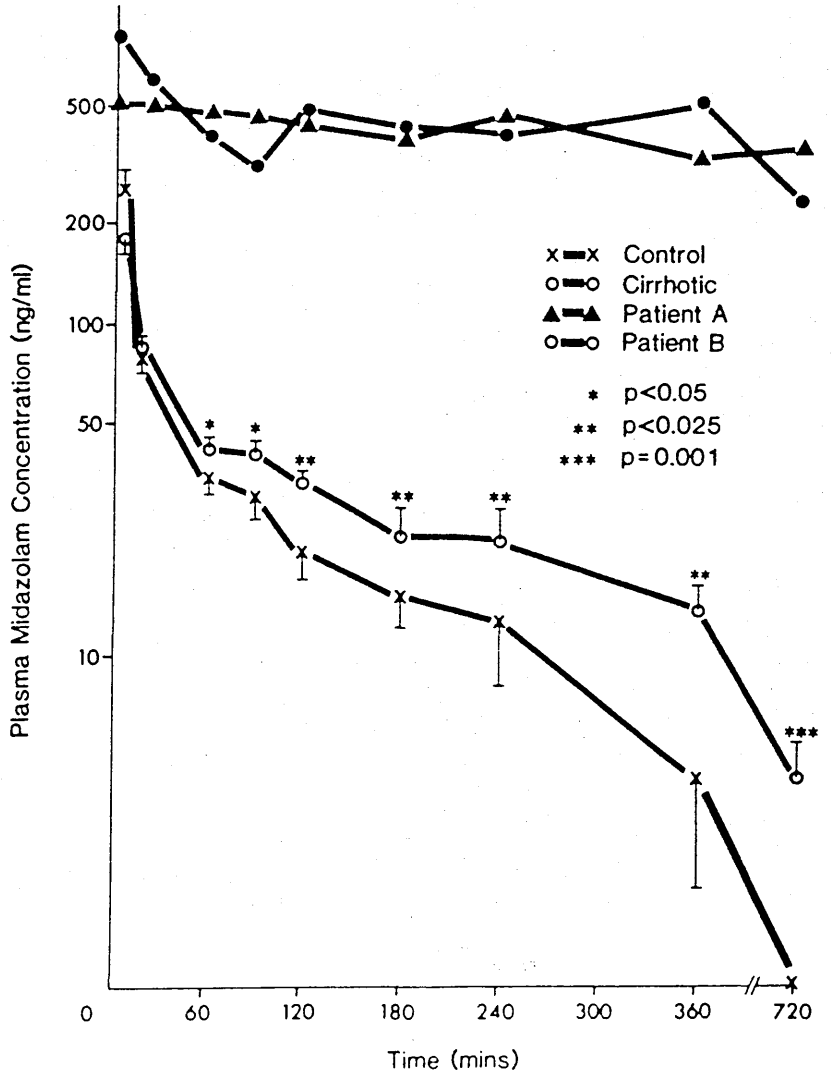


FIGURE 12.3: RECOGNITION TIME (CRT 1; MEAN + SEM) IN 8 CONTROL PATIENTS AND 7 CIRRHOTIC PATIENTS AFTER AN INTRAVENOUS BOLUS OF 0.075 MG/KG OF MIDAZOLAM.

STATISTICAL ANALYSIS BY MANN WHITNEY U-TESTS COMPARING THE DIFFERENCE OF THE RESULTS AND THE BASELINES IN EACH GROUP.

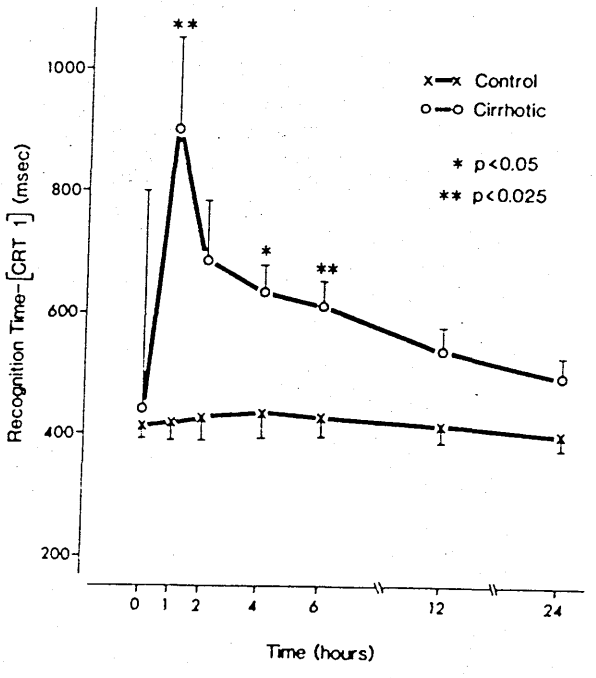


FIGURE 12.4: TOTAL REACTION TIME (CRT 2; MEAN + SEM) IN 8 CONTROL PATIENTS AND 7 CIRRHOTIC PATIENTS AFTER AN INTRAVENOUS BOLUS OF 0.075 MG/KG OF MIDAZOLAM.

STATISTICAL ANALYSIS BY MANN WHITNEY U-TESTS COMPARING THE DIFFERENCE OF THE RESULTS AND THE BASELINES BETWEEN EACH GROUP.

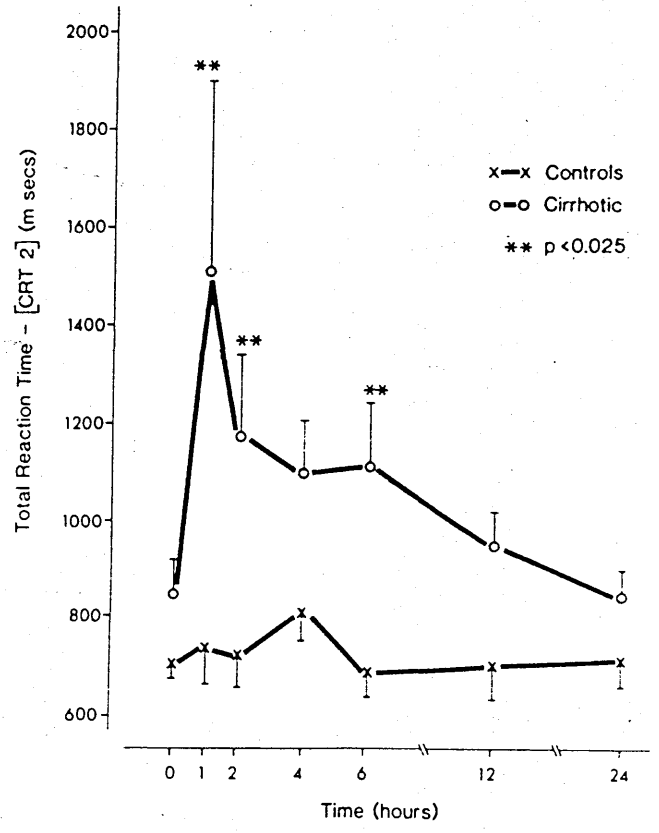
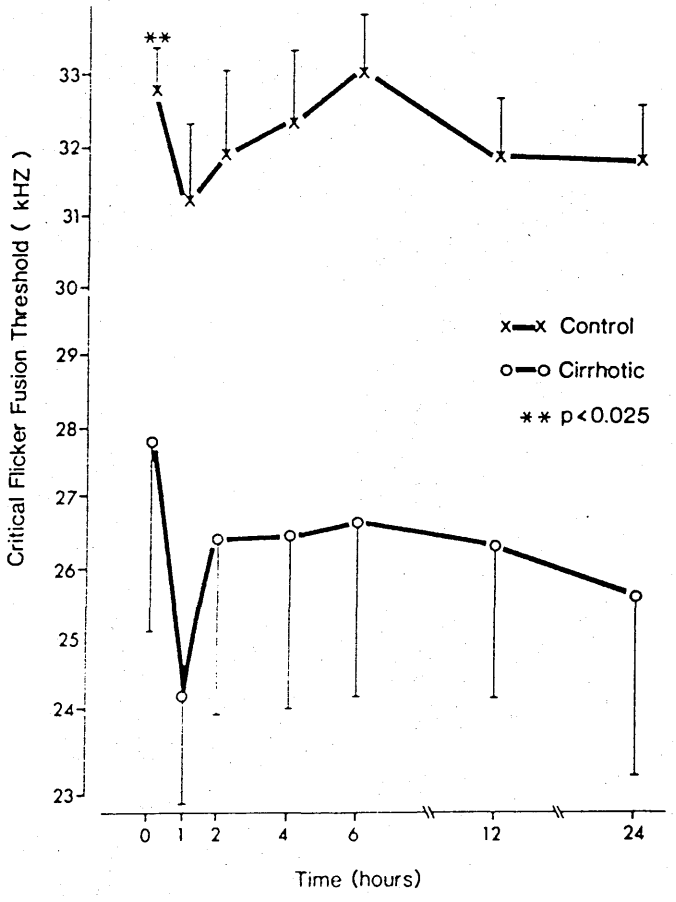


FIGURE 12.5: CRITICAL FLICKER FUSION THRESHOLD (CFFT; MEAN + SEM) IN 8 CONTROL PATIENTS AND 7 CIRRHOTIC PATIENTS AFTER AN INTRAVENOUS BOLUS OF 0.075 MG/KG OF MIDAZOLAM.

STATISTICAL ANALYSIS BY MANN WHITNEY U-TEST ON THE COMPARISONS WITH THE BASELINE RESULTS FOR EACH GROUP. THE BASELINE DIFFERED SIGNIFICANTLY ($P < 0.025$) BETWEEN THE GROUPS.



C H A P T E R 13

GASTROINTESTINAL INTOLERANCE TO MEPTAZINOL IN CIRRHOSIS - A PHARMACOKINETIC EXPLANATION ?

13.1 SUMMARY

Kinetic analysis was performed following single intravenous (25mg) and oral (200mg) doses of the novel partial opioid agonist meptazinol (Meptid) in patients with non-cirrhotic liver disease (NCLD) and biopsy-proven cirrhosis. Comparison was made with a group of patients with normal hepatic function. There was no significant alteration in the plasma clearance of the drug (cirrhotics = 83.5 $\pm$ 8.7 L/hr; NCLD = 98.4 $\pm$ 11.0 L/hr; control = 78.5 $\pm$ 7.3 L/hr). Following the oral dose, 7 out of 15 cirrhotic patients vomited but only 1 patient in each of the other groups was unable to tolerate the drug ($p = 0.06$). This may be explained by very much higher peak meptazinol concentrations in the cirrhotic (n=8; 184 $\pm$ 37ng/ml, $p<0.01$) and NCLD (n=8; 131 $\pm$ 38ng/ml, $p<0.05$) patients than those of the controls (n=7; 53$\pm$ 12ng/ml) reflecting a mean four fold and two fold increase in oral bioavailability respectively (cirrhotics: n=8; 27.9 $\pm$ 5.3%: $p< 0.001$; NCLD: n=7; 13.7 $\pm$3.9%: $p<0.05$; controls: n=7; 6.5 $\pm$ 1.3%). There was no evidence of accumulation following chronic dosing with 200mg meptazinol four times daily for 13 doses in 7 control, 7 NCLD and 6 cirrhotic patients as would be predicted by the lack of change in drug clearance. There were no detectable differences in psychomotor function measured objectively using the Leeds Psychomotor Tester or subjectively by linear analogue scoring between the groups in all three parts of the study.

The oral use of meptazinol in patients with chronic liver disease is limited by the development of nausea and vomiting rather than by the risk of excessive sedation. These data

suggest that dosage reduction in cirrhotic patients is advisable when the drug is taken by mouth as the bioavailability is markedly increased but that none is necessary when meptazinol is administered parenterally.

13.2 INTRODUCTION

Analgesics may precipitate episodes of portosystemic encephalopathy in patients with chronic liver disease (FESSEL & CONN 1972). This results from a combination of impairment of the hepatic and/or renal elimination mechanisms for the drug and increased cerebral sensitivity to its pharmacodynamic properties. The metabolism of many commonly used analgesics, including pethidine (KLOTZ et al 1974), methadone (NOVICK et al, 1980), paracetamol (FORREST et al, 1977) and pentazocine (NEAL et al, 1979), is impaired in patients with hepatic cirrhosis. The elimination of morphine is only minimally reduced in such patients (PATWARDHAN et al 1981), although there is evidence of increased cerebral sensitivity to the drug (LAIDLAW et al 1969). This apparent increase in sedation may be the result of an increase in the free (unbound) fraction of the drug (OLSEN et al 1975) or an increased density of opiate receptors in the frontal lobes and hypothalamus (ZENEROLI et al 1985).

Meptazinol (Meptid) (Figure 13.1) is a novel synthetic opioid analgesic which is effective in relieving pain associated with surgery (PAYMASTER 1977; HEDGES et al 1980), trauma (COPELAND 1983), renal colic (COUTINHO 1980), and childbirth (NICHOLAS and ROBSON 1983). Its use is associated with less psychomotor impairment than is seen with pentazocine (STACHER et al 1983) or with 0.8 mg/kg of ethanol (TEDESCHI et al 1984). Reported side effects have been minor, but about 10% of patients experience nausea and vomiting (DAVIES et al 1982; MOYES et al 1979). Following oral administration meptazinol is rapidly absorbed from the gastrointestinal tract and is subject to

substantial hepatic first pass metabolism with a bioavailability of around 9% in healthy subjects (NORBURY et al 1983). Within the liver, the major metabolic route is by conjugation with glucuronic acid and less than 5% of an administered dose is recovered unchanged from the urine (FRANKLIN et al 1976). Elimination half-life is around 2 hours and the binding to plasma protein is low at 27% (NORBURY et al 1983).

Meptazinol may be a suitable analgesic for use in patients with impaired liver function for two reasons. Firstly, hepatic conjugation is usually well maintained in liver disease (KRAUS et al 1978; SHULL et al 1976) and secondly, the low protein binding of the drug ensures that circulating concentrations of free drug would not be grossly altered from normal in patients with hypoproteinaemia. The aim of this study was to assess the pharmacokinetic profile and pharmacodynamic response to meptazinol in patients with cirrhotic and non-cirrhotic liver disease (NCLD) and to correlate any such changes with the standard biochemical liver function tests and the clearances of the model substances, indocyanine green and antipyrine.

13.3 PATIENTS

A total of ten patient controls, nine NCLD patients and fifteen patients with cirrhosis agreed to take part in the study. Eight of the cirrhotic patients were also taking spironolactone, but none of the other patients were on medication known to alter hepatic metabolism or liver blood flow. All gave written informed consent to their inclusion in the study, the protocol for which was approved by the Western Infirmary Ethical

Committee.

The cirrhotic patients were aged between 28 and 68 with a mean age of 53 years. All had biopsy proven hepatic cirrhosis. Eleven patients had alcoholic liver disease, two had primary biliary cirrhosis, and one each had chronic active hepatitis and primary sclerosis cholangitis. Eleven of these patients had episodes of bleeding from oesophageal varices and six had previous evidence of portosystemic encephalopathy. No patient was frankly encephalopathic on admission to the study.

The NCLD patients were aged from 24 to 81 with a mean age of 50 years. The aetiology of the liver disease was proven by liver biopsy in all cases and was due to alcohol in 6, pre-cirrhotic primary biliary cirrhosis in 2 and congenital hepatic fibrosis in 1. This last patient was included in the NCLD group because he did not fulfil the histolological criteria for the diagnosis of cirrhosis. However, he had severe portal hypertension with large oesophageal varices. None of the patients had a history of portosystemic encephalopathy.

The control patients were aged between 21 and 65 with a mean age of 39 years. Two patients had duodenal ulcers, four had chronic constipation and four were undergoing investigation of chronic abdominal pain. None had clinical evidence of liver disease and all had normal biochemical liver function tests.

13.4 METHODS

See Chapter 7.2 for antipyrine method.

See Chapter 7.4 for meptazinol method.

See Chapter 7.6 for pharmacokinetic methods.

See Chapter 7.7 for pharmacodynamic assessment.

The pharmacokinetics of meptazinol were studied after an intravenous dose of 25mg, and an oral dose of 200mg given in random order, with a delay of at least two weeks between each part of the study. The patients were fasted overnight prior to each study day and food was allowed 2 hours after meptazinol administration. The oral kinetics were then repeated following the chronic administration of the drug in a dose of 200mg four times daily for thirteen doses. Venous blood samples were taken at 0.25,0.5,0.75,1,1.5,2,3,4,6,8,12 and 24 hours after the intravenous dose and after the first and thirteenth oral dose of the drug. The samples were collected into glass lithium heparin tubes and centrifuged immediately. The plasma was separated and stored in glass tubes at -20 degrees Centigrade. Plasma concentrations of meptazinol were determined by a modified (NORBURY et al 1983) high pressure liquid chromatography method using fluorescence detection (FROST 1981). All samples for each patient were run in a single batch. The lower limit of detection of meptazinol was 10ng/ml and the coefficient of variation was 5% at 100ng/ml and 9.9% at of 10ng/ml.

The pharmacokinetic methods are described in Chapter 7.6. The data was fitted using a one and a two compartment model and

the comparison of these models is summarised in Table 13.4. For each patient the one compartment model was selected unless the F statistic indicated that a two compartment model was more appropriate.

13.5 RESULTS

Haemoglobin and creatinine concentrations together with the standard biochemical liver function tests are shown in Table 13.1. As expected evidence of impaired hepatic function was seen for both liver disease groups.

The pharmacokinetics of antipyrine and indocyanine green are shown in Table 13.2; there were substantial prolongations of the half lives of both drugs in the cirrhotic group ($p < 0.01$ and $p < 0.001$) compared with the controls indicating the severity of liver disease in this group of patients. The elimination of antipyrine was not significantly altered in the NCLD group but there was a small fall in the clearance of indocyanine green ($p < 0.01$) in these patients (Table 13.2).

13.5.1 Meptazinol Kinetics

Following the intravenous bolus of 25mg of meptazinol, there was no significant difference in the volume of distribution between the different patient groups (control = 175 $\pm$ 21.5 litres; NCLD = 144.0 $\pm$ 22.8 litres; cirrhotic = 186.0 $\pm$ 20.9 litres. There were no differences in the total plasma clearance of meptazinol between the groups (control = 78.5 $\pm$ 7.3 L/hr; NCLD = 98.4 $\pm$ 11.0 L/hr; cirrhotic = 83.5 $\pm$ 8.7 L/hr). Seven of the

cirrhotics, and one each of the NCLD and control patients were unable to complete the protocol because of severe nausea and vomiting following a single oral dose of the drug (Chi-Square Test : $p = 0.06$). The plasma concentration/time curves following the oral dose in those patients tolerating the drug are shown in Figure 13.3. The peak concentration attained was much higher in the patients with liver disease (cirrhosis: n=8, 184 $\pm$ 37ng/ml/; $p<0.002$; NCLD: n=8, 131 $\pm$ 38ng/ml; $p<0.05$; control: n=7, 53 $\pm$ 12ng/ml). The oral bioavailability of meptazinol was greatly increased in the cirrhotic patients (bioavailability = 27.9 $\pm$ 5.3%; $p<0.001$) and NCLD group (bioavailability = 13.7 $\pm$ 3.9%; $p<0.05$) compared to the controls (bioavailability = 6.5 $\pm$ 1.3%) [Figure 13.4]. There was a significant correlation between the bioavailability of meptazinol and the serum bilirubin ($r = 0.50$; $p < 0.05$) and negatively with serum albumin ($r = -0.46$; $p < 0.05$) but not with the antipyrine ($r = -0.37$) or indocyanine green ($r = -0.32$) clearance.

Following chronic oral dosing for three days there was no significant increase in the area under the concentration time curves, time to maximum concentration, or the maximum concentration achieved in any of the groups compared to the values obtained following the single dose (Table 13.3).

13.5.2 Pharmacodynamics

There were no significant alterations in the CRT 1, CRT 2 or the CFFT at any time point in any of the groups following the single intravenous and oral doses or chronic administration of meptazinol (Figures 13.5, 13.6, 13.7). Analysis of the visual

analogue scales showed no evidence of excessive sedation in any of the groups during any phase of the study.

13.6 DISCUSSION

This study has demonstrated the importance of assessing the oral bioavailability of drugs in patients with liver disease, particularly those which undergo a substantial degree of first pass elimination. In cirrhotics, the clearance of meptazinol was reduced by only 13% but there was a 300% increase in the oral bioavailability of the drug. Three factors could contribute towards this latter finding. Firstly, the bioavailability of meptazinol is dependent on the rate of absorption of the drug from the gastrointestinal tract (NORBURY et al 1983). When absorption is rapid the capacity of the conjugating enzymes may be saturated resulting in an increased bioavailability. In this study the time to maximum concentration did not differ significantly between the three groups indicating that it is unlikely that there were major differences in the rates of absorption. Secondly, the ability of the hepatocytes to remove the drug from the blood may be reduced. The primary route of metabolism of meptazinol is by conjugation. The elimination of drugs which are conjugated is usually little altered in liver disease e.g. oxazepam (SHULL et al 1976), morphine (PATWARDHAN et al 1980) and lorazepam (KRAUS et al 1978). In contradistinction, the hepatic clearance of oxidised drugs is invariably reduced in

patients with cirrhotic liver damage (WILLIAMS and KOCH-WESER 1983). In the present study there was no reduction in the clearance of meptazinol in cirrhotics. Thirdly, the intra- and extrahepatic portosystemic shunts which occur in cirrhosis can dramatically reduce the contact of the drug with the sites of hepatic elimination with a resulting increase in the bioavailability. More than 50% of the total portal blood flow may be shunted directly into the systemic circulation in cirrhotics (GROSZMANN et al 1972). In our study the majority of the cirrhotic patients studied had well established portal hypertension and 11/15 had previously bled from oesophageal varices. It is probable that this last factor explains the substantial increase in oral meptazinol bioavailability in cirrhosis. Interestingly one of the patients in the NCLD group had congenital hepatic fibrosis associated with large oesophageal varices and his meptazinol bioavailability was 26.1% which is comparable to the cirrhotic patients. Spironolactone was the only drug which these cirrhotic patients were receiving which may alter hepatic drug metabolism. This drug is a weak inducer of hepatic oxidation in healthy volunteers (TAYLOR et al 1972; HUFFMAN et al 1973), and much less so in patients with hepatic congestion associated with cardiac failure (OHNHAUS and GERBER-TARAS 1984). If spironolactone did influence meptazinol metabolism, it would be expected to reduce its oral bioavailability.

Antipyrine has a low hepatic extraction ratio and is extensively oxidised in the liver (BOOBIS et al 1981). Indocyanine green is a flow-dependent compound which is excreted

in the bile without being metabolised (WHEELER et al 1958; CHERRICK et al 1960). Both agents have been used as probes in the assessment of patients with liver disease and particularly in the detection of patients with altered drug metabolism (BRANCH 1982). Significant correlations between the metabolism of antipyrine and the elimination of lorcainide (KLOTZ et al 1979), lignocaine (PERRUCA et al 1980), phenylbutazone (DAVIES and THORGEIRSON 1971(a)), oxyphenylbutazone (DAVIES and THORGEIRSON 1971(b)), diazepam, prazepam, clonazepam, flurazepam (GREENBLATT et al 1981) and oxazepam (KELLERMAN and LUYTEN-KELLERMAN 1979), have been reported but not with the clearances of lorazepam, temazepam (GREENBLATT et al 1981) or triazolam (KELLERMAN and LUYTEN-KELLERMAN 1979). Indocyanine green clearance correlated poorly with the elimination of diazepam and aminopyrine (HEPNER et al 1977) but positively with the clearance of antipyrine (BRANCH et al 1976). In this study there was no useful relationship between the bioavailability or clearance of meptazinol and the clearance of antipyrine or indocyanine green. This lack of a correlation with antipyrine is not surprising as meptazinol is conjugated and antipyrine is oxidised within the liver. However, both meptazinol and indocyanine green are highly extracted by the liver and so a correlation between their clearances might be expected. Both the serum albumin and bilirubin were better predictors of meptazinol bioavailability.

The pharmacokinetic changes in meptazinol handling in the cirrhotic patients were accompanied by an increased incidence of vomiting when the drug was given orally. This occurred very shortly after administration on the upstroke of the absorption

curve. Despite the high plasma levels by patients tolerating the drug there was no evidence of excessive sedation in any of the groups measured subjectively by sedation scoring or objectively using reaction times.

In conclusion the oral bioavailability of meptazinol is greatly increased in patients with chronic liver disease. However, the drug can be used in such patients without producing excessive sedation. In order to avoid nausea and vomiting on oral administration in patients with cirrhosis or with portal hypertension the dose should be reduced to 25-50% of that normally prescribed. If such a dose is insufficient to produce analgesia the dose and/or frequency of administration can be increased to the limits of gastrointestinal tolerance. Meptazinol dosage need not be altered in patients with liver disease in whom the drug is administered parenterally.

ACKNOWLEDGEMENTS

We would like to thank Wyeth UK for financial support and, in particular, Dr. David Graham for his advice in the design of the study. We are grateful to Anne Macdonald for making the pharmacodynamic measurements.

TABLE 13.1

STANDARD LABORATORY TESTS (mean± SEM) IN ALL CONTROL NON-CIRRHOTIC LIVER DISEASE (NCLD) AND CIRRHOTIC PATIENTS

	Haemo globin (g/l)	Bili rubin (umol/l)	Alkaline Phosphatase (iu/l)	Albumin (g/l)	Creat inine (umol/l)	GGT (iu/l)
CONTROL	(n = 10)					
Mean	13.0	11.4	50	41.1	80.4	21
SEM	0.3	2.0	10	0.8	5.7	4
NCLD	(n = 9)					
Mean	13.6	18.3	141	41.7	70.7	108
SEM	0.6	6.4	56	2.1	3.4	27
CIRRHOTIC	(n = 15)					
Mean	12.1	32.6	172	34.5	90.2	161
SEM	0.5	15.4	38	2.0	7.1	39
KRUSKAL WALLIS						
p =	0.76	0.02	0.004	0.01	0.10	0.0001
MANN WHITNEY U TESTS						
CONTROL vs NCLD	NS	NS	NS	NS	NS	<0.001
CONTROL vs CIRRHOTIC	NS	<0.05	<0.05	<0.01	NS	<0.001
NCLD vs CIRRHOTIC	NS	<0.05	NS	<0.01	NS	NS

TABLE 13.2

ANTIPYRINE AND INDOCYANINE GREEN KINETICS (MEAN ± SEM) IN CONTROL, NON-CIRRHOTIC LIVER DISEASE (NCLD) AND CIRRHOTIC PATIENTS.

	<----ANTIPYRINE---------->				<------INDOCYANINE GREEN---->			
	Half life (hrs)	Volume of distribution (l)	Clearance (ml/min)	Clearance (ml/min/kg)	Half life (min)	Volume of distribution (l)	Clearance (ml/min)	Clearance (ml/min/kg)
CONTROL	(n = 10)							
Mean	12.2	25.6	29.0	0.43	3.8	3.8	704	11.7
SEM	1.4	1.7	4.6	0.04	0.2	0.4	98	2.0
NCLD	(n = 9)							
Mean	11.4	38.8	40.5	0.61	4.5	3.1	554	8.8
SEM	1.9	4.5	6.8	0.10	0.7	0.3	71	1.2
CIRRHOTIC	(n = 15)							
Mean	31.3	27.3	14.7	0.18	9.2	4.2	364	5.0
SEM	6.5	3.6	2.2	0.05	1.3	0.4	44	0.6
KRUSKAL WALLIS								
p =	0.003	0.07	0.004	0.0008	0.004	0.14	0.004	0.001
MANN WHITNEY U-TESTS								
CONTROL vs NCLD	NS	NS	NS	NS	NS	NS	<0.01	<0.01
CONTROL vs CIRRHOTIC	<0.01	NS	<0.01	<0.01	<0.001	NS	<0.001	<0.001
NCLD vs CIRRHOTIC	<0.01	NS	<0.001	<0.001	<0.01	NS	<0.01	<0.01

TABLE 13.3

MEPTAZINOL KINETICS (MEAN ± SEM) FOLLOWING SINGLE AND THIRTEENTH 200mg ORAL DOSE IN CONTROL, NON-CIRRHOTIC LIVER DISEASE (NCLD) AND CIRRHOTIC PATIENTS.

	IV	<-----SINGLE ORAL DOSE----->			<CHRONIC DOSING>	
	AREA UNDER CURVE (ng/hr/ml)	AREA UNDER CURVE (ng/hr/ml)	MAXIMUM CONCENTRATION CP(MAX) (ng/ml)	BIOAVAILABILITY (%)	AREA UNDER CURVE (ng/hr/ml)	MAXIMUM CONCENTRATION CP(MAX) (ng/ml)
CONTROLS		(n = 9)				
Mean	337	163	53	7	112	49
SEM	35	35	12	1	21	7
NCLD		(n = 8)				
Mean	299	311	131	14	105	42
SEM	25	78	38	4	17	5
CIRRHOTIC		(n = 8)				
Mean	391	794	184	28	903	302
SEM	44	148	37	5	247	92
KRUSKAL WALLIS						
p =	0.5	0.003	0.02	0.01	0.03	0.06
MANN WHITNEY U TESTS						
CONTROL vs NCLD	NA	0.09	0.04	0.1	0.4	NS
CONTROL vs CIRRHOTIC	NA	0.0001	0.002	0.001	0.02	NS
NCLD vs CIRRHOTIC	NA	0.01	0.12	0.04	0.007	NS

NA = not applicable

TABLE 13.4 MEPTAZINOL STUDY - Intravenous dose. Comparison of One and Two Compartment Models by Comparison of Residual Sum of Squares.

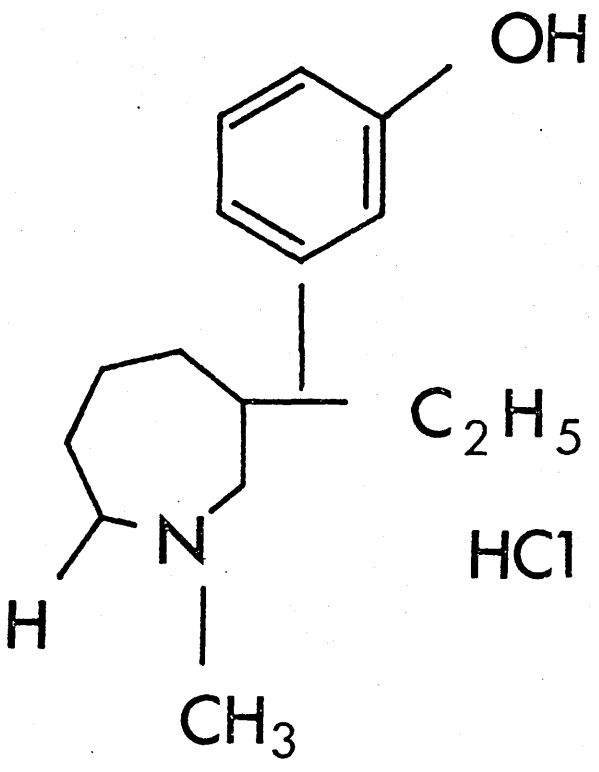
	Residual Sum of Squares		F	Compartment	Cl	vd
	Two Compartment	One Compartment	Statistic	Selected	L/hr	L
1.	109.8	461.7	6.4*	Two	116	269
2.	502.2	711.5	0.8	One	58	138
3.	136.2	135.9	0.0	One	57	225
4.	214.6	258.8	0.4	One	92	204
5.	54.5	991.2	33.9*	Two	80	114
6.	129.4	121.5	0.0	One	60	215
7.	128.3	1840.0	36.6*	Two	91	102
8.	269.1	1618.0	10.1	One	74	134
9.	65.1	1246.0	36.9*	Two	87	119
10.	130.1	471.7	5.2*	Two	79	198
11.	35.6	1132.0	61.6	Two	104	45
12.	196.4	403.8	2.1	One	173	92
13.	36.5	538.7	27.6*	Two	85	170
14.	953.5	1232.0	0.6	One	85	125
15.	192.7	312.0	1.2	One	81	254
16.	187.4	197.4	0.1	One	93	145
17.	124.5	123.4	0.0	One	42	231
18.	190.4	201.3	0.1	One	66	211
19.	69.0	884.1	23.5*	Two	54	178
20.	143.8	288.8	2.0	One	114	278
21.	932.2	166.8	0.0	One	72	105
22.	80.2	167.1	2.2	One	126	237
23.	133.6	311.5	2.7	One	99	206
24.	145.4	282.6	1.9	One	104	200
25.	78.0	2000.0	49.3*	Two	65	54
26.	3699.0	4658.0	0.5	One	93	158

(V1 = 2 V2 = 6)

* = $p < 0.05$

FIGURE 13.1

THE CHEMICAL STRUCTURE OF MEPTAZINOL



Half-life 2hours
Bioavailability 9%

FIGURE 13.2

PLASMA CONCENTRATION TIME CURVES (MEAN ± SEM) FOLLOWING AN ORAL DOSE OF 200mg OF MEPTAZINOL IN CONTROL (n=7), NON-CIRRHOTIC LIVER DISEASE (NCLD) (n=8) AND CIRRHOTIC PATIENTS (n=8) Statistics by Kruskal Wallis analysis of variance and Mann Whitney U-tests.

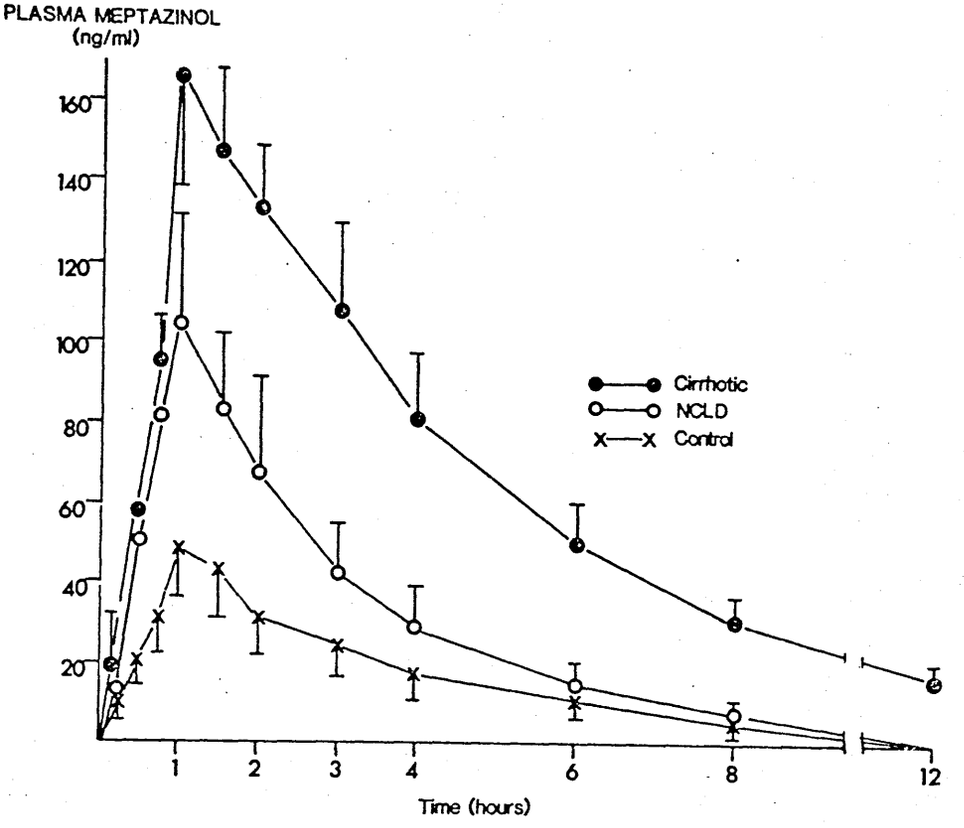


FIGURE 13.3

PERCENTAGE ORAL BIOAVAILABILITY OF MEPTAZINOL (MEAN ± SEM) IN CONTROL, NON-CIRRHOTIC LIVER DISEASE (NCLD) AND CIRRHOTIC PATIENTS.

Statistics by Kruskal Wallis analysis of variance and Mann Whitney U-tests.

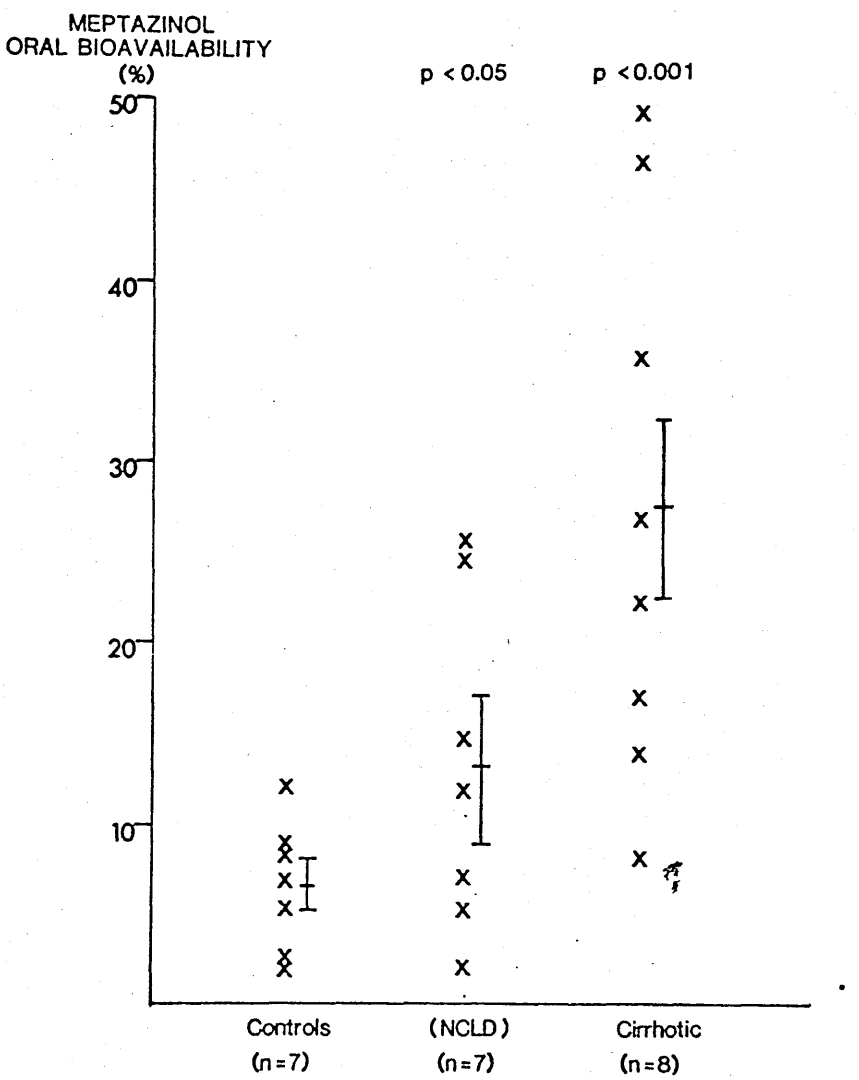


FIGURE 13.4 RECOGNITION TIME (CRT 1) IN ALL PATIENT GROUPS FOLLOWING A SINGLE ORAL DOSE, AN INTRAVENOUS DOSE AND CHRONIC ADMINISTRATION OF MEPTAZINOL

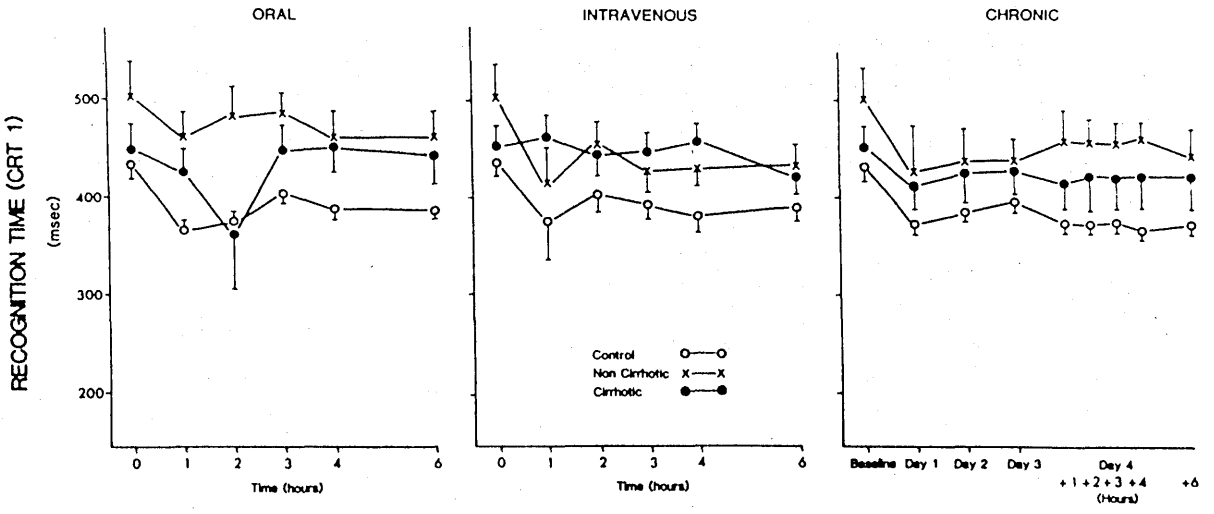


FIGURE 13.5 TOTAL REACTION TIME (CRT 2) IN ALL PATIENT GROUPS FOLLOWING A SINGLE ORAL DOSE AN INTRAVENOUS DOSE AND CHRONIC ADMINISTRATION OF MEPTAZINOL

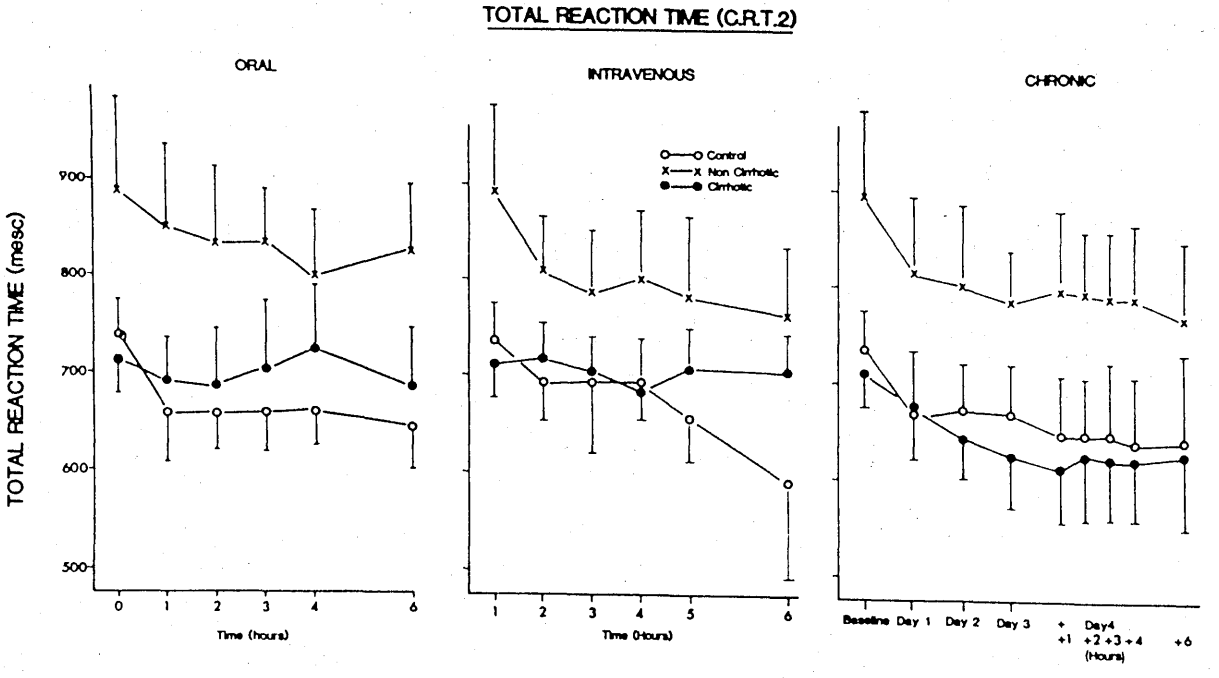
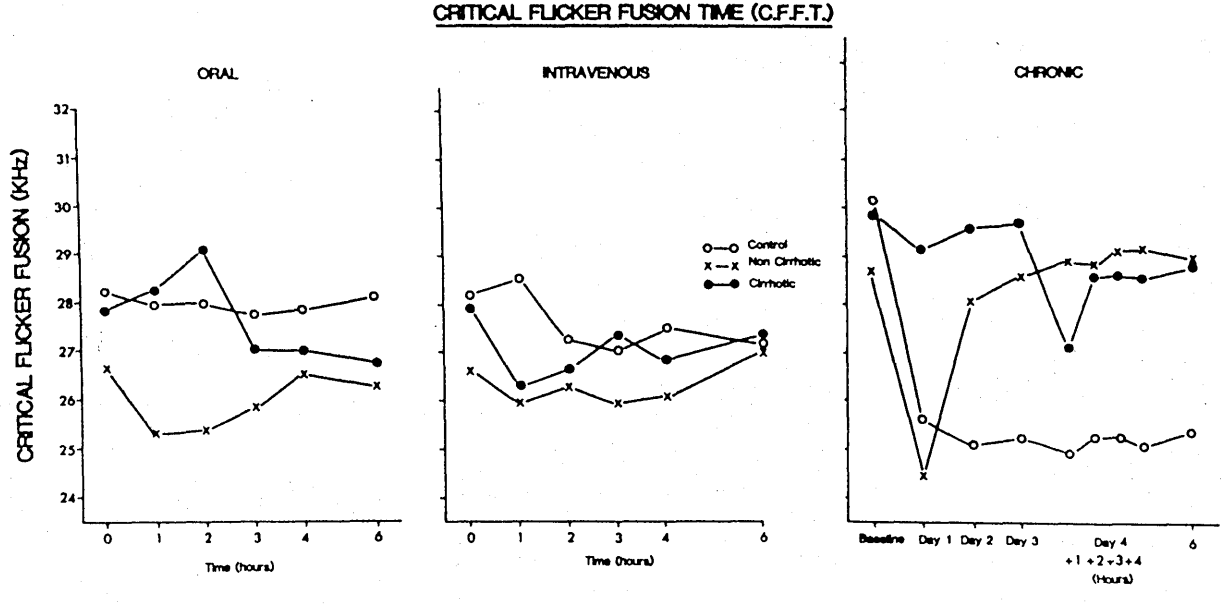


FIGURE 13.6 CRITICAL FLICKER FUSION (CFFT) IN ALL PATIENT GROUPS FOLLOWING A SINGLE ORAL DOSE, AN INTRAVENOUS DOSE AND CHRONIC ADMINISTRATION OF MEPTAZINOL



C H A P T E R 14

IMPAIRED DRUG METABOLISM IN PATIENTS WITH CARDIAC FAILURE: STUDIES WITH ANTIPYRINE AND INDOCYANINE GREEN.

14.1 SUMMARY

The disposition of antipyrine (AP) and indocyanine green (ICG) was studied in 11 patients with congestive cardiac failure (CCF) before and after treatment and 32 control patients. The antipyrine distribution was not significantly altered in patients with CCF. The indocyanine green half life was significantly prolonged in patients with CCF (CCF = 10.0 $\pm$ 8.0 min; Control = 4.2 $\pm$ 1.1 mins: $p < 0.01$). The indocyanine green disposition was not significantly altered in a further 12 patients with valvular heart disease but without evidence of CCF. There was a close correlation between the ICG half life and the clinical assessment ($r = 0.99$; $p < 0.001$).

In the 12 patients without CCF there was no correlation between cardiac pressure measurements and the disposition of antipyrine or indocyanine green.

14.2 INTRODUCTION

The disposition and elimination of many drugs are altered in patients with congestive CCF (BENOWITZ & MEISTER 1976). Two mechanisms for these alterations have been suggested. Firstly, there is a reduction in cardiac output and an increase in hepatic venous pressure. These changes result in a fall in the total liver blood flow (BRAUER 1963). This is one of the important determinants of the elimination of drugs, particularly those with a high hepatic ratio (See Chapter 4.2.5). Secondly, as a result of ischaemia and hepatic necrosis there is necrosis of the centrilobular hepatocytes (SHERLOCK 1951). These hepatocytes have particularly high concentrations of Cytochrome P-450 (SWEENEY et al 1978) which is the major enzyme complex responsible for drug metabolism within the liver. (GUMUCIO and MILLER 1981). Reduction in the Cytochrome P-450 activity of the liver leads to a reduced capacity to eliminate drugs which are extensively oxidised within the liver, for example, antipyrine.

The aims of this study are to investigate the relative importance of these two mechanisms in determining drug elimination in patients with CCF. The elimination of a low hepatic extraction ratio drug (antipyrine) and a high hepatic extraction ratio drug (indocyanine green) has been studied in patients with CCF before and after treatment.

14.3 METHODS AND PATIENTS

Three groups of patients were studies. Group 1 consisted of 11 patients urgently admitted to hospital because of congestive cardiac failure. These patients were studied within 24 hours of admission to hospital and were re-studied after there was clinical improvement in the cardiac failure at the time of study. Group 2 consisted of 12 patients with valvular heart disease who did not have clinical evidence of cardiac failure. Group 3 is a control group and consisted of 37 patients admitted to hospital for the investigation of various gastrointestinal symptoms. These patients had no clinical or biochemical evidence of liver disease and no clinical evidence of congestive cardiac failure.

The patients in Group 1 were graded for the severity of cardiac failure according to the scheme in Table 14.1. Each sign is graded on a score of 1-3 and the scores for each patient are summed to give a "Cardiac Failure Index" (CFI). Patients had to have a CFI of at least 5 to enter the study. A subtotal of the right ventricular features (jugular venous pressure, oedema, hepatomegaly) has also been calculated and designated as the "Right Ventricular Index" (RVI). The patients were treated for congestive cardiac failure with the drugs summarised in Table 14.2. Following treatment the clinical grading assessment was repeated.

Standard liver function tests, antipyrine kinetics and indocyanine green kinetics have been obtained using the protocols and methods described in Chapter 7.

The patients in Group 2 all had valvular heart disease and

were in hospital for cardiac catheterisation to assess the severity of their valvular disease.

14.3 RESULTS

In Group 1 there was a significant improvement in the "Cardiac Failure Index" ($p < 0.001$) and the "right ventricular index ($p < 0.004$) following treatment for congestive cardiac failure (Table 14.3).

Prior to treatment the serum bilirubin, aspartate transaminase, and alanine transaminase were all outwith the normal laboratory range. There was a tendency for these tests to return to normal following treatment (Table 14.4). This trend was statistically significant for the serum bilirubin. Prior to treatment = 23.1 $\pm$ 14.9 mmol/l: After treatment = 18.8 $\pm$ 14.6 mmol/l: $P < 0.05$).

The antipyrine half life was significantly prolonged in the Group 1 patients prior to treatment in comparison to the healthy controls (Group 1 = 19.3 $\pm$ 15.0 hrs: Healthy Controls = 11.8 $\pm$ 3.5 hrs: $P < 0.05$). The antipyrine clearance was also reduced (Group 1 = 25.9 $\pm$ 10.1ml/min: Healthy Controls = 37.2 $\pm$ 15.1 ml/min: $P < 0.05$). There was no significant alteration in the antipyrine volume of distribution (Table 14.5).

A similar pattern was seen with indocyanine green, although the magnitude of the differences was greater. In patients with CCF the half life of ICG was prolonged by 138% compared to 33% for antipyrine. Similarly the ICG clearance was reduced by 37% compared to a 29% reduction for antipyrine (Table 14.5).

In the Group 1 patients after treatment of CCF there was a tendency for the half lives to fall and the clearances to increase but these changes failed to reach statistical significance (Table 14.5, Fig. 14.1).

The correlation of the kinetic parameters of antipyrine and ICG with the clinical assessment of the degree of cardiac failure is shown in Table 14.6. There were no significant correlations between the clinical indices of CCF and antipyrine kinetics but there was a close correlation of the ICG half life and the CFI (Fig. 14.2) and the RVI.

The patients in Group 2 all had cardiac catheterisation studies performed to determine the nature of their heart disease. The results of the pressure study are shown in Table 14.7 and the antipyrine and ICG kinetic data in Table 14.8. There were no significant correlations between the kinetic parameters and the mean right atrial pressure or the mean wedged and free pulmonary artery pressure.

14.4 DISCUSSION

Congestive cardiac failure is associated with a reduced capacity to eliminate various drugs including Lignocaine (THOMSON et al 1973; PRESCOTT et al 1976; BAX et al 1980), Aminopyrine (HEPNER et al 1978, PIROTTE et al 1983), Antipyrine (PRESCOTT et al 1976, RISSAM et al 1983) and Theophylline (PIAFSKY et al 1974). The elimination of other drugs is little altered including Digoxin (DOHERTY et al 1961, 1962; MARCUS 1964). The mechanisms by which changes occur in the disposition of drugs in

congestive cardiac failure include reduced absorption, hepatocellular damage secondary to hepatic congestion and reduced liver blood flow (BENOWITZ & MEISTER 1976).

This study demonstrates that in CCF the clearance of ICG is reduced by 37% and the half life prolonged by 138%. There was a good correlation between the clearance of ICG and the clinical severity of the CCF. ICG is not metabolised within the liver but has a high hepatic extraction ratio so that its elimination is primarily dependent on liver blood flow. A major determinant of liver blood flow is the cardiac output (STENSON et al 1971). A previous study failed to demonstrate any alteration in ICG elinination in patients with CCF (BAX et al 1980).

In the same group of patients the clearance of antipyrine was reduced by 30% and the half life prolonged by 33%. These changes are less marked than was seen with ICG. Antipyrine is extensively oxidised within the liver and has a low hepatic extraction ratio. Its elimination is primarily dependent on the rate of hepatic oxidation and it is relatively independent of liver blood flow.

This study demonstrates that the elimination of high and low extraction ratio drugs is reduced in CCF. The changes are greatest for high extraction ratio drugs, and for these molecules the changes correlate closely with the clinical severity of the cardiac failure. These data suggest that alterations in liver blood flow are relatively more important than reduced hepatic metabolic capacity in determining changes in liver blood flow. The magnitude of the changes in the elimination of antipyrine and

indocyanine green in CCF are similar to those seen on a large group of patients with mixed liver disease (Table 14.5). If these alterations are primarily due to changes in liver blood flow then it is likely that they may alter rapidly as the heart fails further or responds to therapy. This suggests that the elimination of high hepatic ratio drugs is likely to be particularly variable and unpredictable in patients with CCF.

TABLE 14.1 CLINICAL GRADING OF THE SEVERITY OF CARDIAC FAILURE

	1	2	3
PULSE (Beats/min)	> 90	> 100	-
JVP (cms)	> 5	> 10	
OEDEMA	MILD	MODERATE	SEVERE
HEPATOMEGALY	PRESENT	-	-
PLEURAL EFFUSION	PRESENT	-	-
BREATHLESSNESS	WALKING	DRESSING	AT REST
CARDIOMEGALY	PRESENT	-	-
TRIPLE RHYTHM	PRESENT	-	-
BASAL CREPITATIONS	PRESENT	-	-

TABLE 14.2 DRUGS TAKEN BY 11 PATIENTS WITH CONGESTIVE CARDIAC FAILURE BEFORE AND AFTER TREATMENT

	AMILORIDE	AMPICILLIN	BENDROFLUAZIDE	BUMETANIDE	DIGOXIN	DIPYRIDAMOLE	FRUSEMIDE	FUROSEMIDE	INDAPAMIDE	METHYLDOPA	PROPRANOLOL	SPIRONOLACTONE	TEMAZEPAM	VERAPAMIL	WARFARIN
1 - BEFORE					*		*			*					
1 - AFTER					*		*			*					
2 - BEFORE				*			*								
2 - AFTER				*			*								
3 - BEFORE			*		*	*					*				
3 - AFTER			*		*	*					*				
4 - BEFORE		*					*	*			*		*		
4 - AFTER	*		*					*							
5 - BEFORE	*		*					*							
5 - AFTER	*		*					*							
6 - BEFORE							*					*			
6 - AFTER							*					*			
7 - BEFORE	*														
7 - AFTER	*						*								
8 - BEFORE	*						*	*							
8 - AFTER	*						*	*							
9 - BEFORE			*				*			*					
9 - AFTER			*				*			*					
10 - BEFORE	*	*		*	*									*	
10 - AFTER	*	*		*	*									*	
11 - BEFORE					*		*								
11 - AFTER					*		*								

TABLE 14.3 CLINICAL ASSESSMENT OF 11 PATIENTS WITH CARDIAC FAILURE BEFORE AND AFTER TREATMENT

	<-------BEFORE TREATMENT------->											*	<----------AFTER TREATMENT---------->										
	PULSE	J.V.P.	OEDEMA	HEPAR	EFFUSION	BREATHLESSNESS	CARDIOMEGALY	TRIPLE RHYTHM	CREPITATION	R. V. SCORE	TOTAL SCORE	*	PULSE	J.V.P.	OEDEMA	HEPAR	EFFUSION	BREATHLESSNESS	CARDIOMEGALY	TRIPLE RHYTHM	CREPITATION	R. V. TOTAL	TOTAL SCORE
1	0	2	2	0	0	1	0	0	1	4	6	*	0	1	1	0	0	1	0	0	1	2	4
2	0	2	2	1	0	3	1	0	1	5	10	*	2	1	1	0	0	2	1	0	0	2	7
3	2	2	1	0	0	3	1	0	1	3	10	*	1	1	1	0	0	1	1	0	0	2	5
4	0	1	1	0	0	3	0	0	1	2	15	*	0	2	0	0	0	2	0	0	1	2	5
5	0	2	3	1	1	2	1	0	1	7	11	*	0	0	1	0	0	0	1	0	1	1	3
6	2	0	0	1	0	2	0	0	0	1	5	*	2	0	0	0	0	0	1	0	1	0	4
7	2	1	1	0	0	2	1	0	1	2	8	*	0	0	0	0	0	0	0	0	1	0	1
8	0	2	2	1	1	3	1	0	1	6	11	*	1	1	1	0	0	0	1	0	1	2	5
9	2	1	3	1	0	2	0	0	1	5	10	*	0	0	3	0	0	2	0	0	1	3	5
10	1	1	2	0	1	2	1	0	1	4	9	*	0	1	1	0	1	2	1	0	1	3	7
11	2	2	2	0	1	2	0	0	0	4	9	*	1	0	0	0	1	0	0	0	0	1	2
MEDIAN										4	9											2+	5++

Statistics by Mann-Whitney U Test

\+ p = 0.005
++ p = 0.001

TABLE 14.4 STANDARD BIOCHEMICAL TESTS OF LIVER FUNCTION IN 11 PATIENTS BEFORE AND AFTER TREATMENT OF CONGESTIVE CARDIAC FAILURE.

	<---BEFORE TREATMENT--->					<---AFTER TREATMENT--->				
	BILI RUBIN	AST	ALT	ALK PHOS	ALBU MIN	BILI RUBIN	AST	ALT	ALK PHOS	ALBU MIN
	MMOL/L	IU/L	IU/L	IU/L	G/L	MMOL/M	IU/L	IU/L	G/L	G/L
1	13	9	24	114	34	7	21	21	112	34
2	32	57	158	148	36	44	52	139	129	35
3	13	79	46	125	36	7	14	20	112	37
4	14	20	16	94	33	8	19	13	83	38
5	12	22	26	97	40	6	27	25	71	45
6	40	45	70	129	34	21	19	24	119	40
7	14	324	63	119	42	15	64	72	121	33
8	13	121	52	115	39	5	14	26	115	40
9	35	22	13	135	37	25	26	13	145	37
10	55	77	138	163	32	16	23	35	98	28
11	13	17	15	65	36	13	14	9	76	41
MEAN	23.1	72.1	56.5	117.6	36.3	18.8*	26.6	36.1	107.4	37.1
S.D.	14.9	90.3	49.5	27.8	3.1	14.6	16.4	38.1	23.0	4.6

Statistics by Paired Wilcoxon Sign Rank Test

*$p < 0.05$

TABLE 14.5 ANTIPYRINE AND INDOCYANINE GREEN KINETICS IN PATIENTS BEFORE AND AFTER TREATMENT FOR CONGESTIVE CARDIAC FAILURE (GROUP 1): CARDIAC CONTROLS (GROUP 2): PATIENT CONTROLS AND PATIENTS WITH LIVER DISEASE

	GROUP 1		GROUP 2	CONTROL GROUP	LIVER DISEASE GROUP
	BEFORE TREATMENT (n=11)	AFTER TREATMENT (n=11)	(n-12)	(n=37)	(n=104)
ANTIPYRINE					
Half Life (hrs)	19.3+	17.4	14.5	11.8	21.7
Standard Deviation	15.0	9.8	5.4	3.5	16.1
Volume of Distribution(l)	34.1	32.9	40.1	36.3	33.0
Standard Deviation	8.8	7.8	8.0	13.7	12.7
Clearance (ml/min)	25.9+	27.3	36.5	37.2	24.1
Standard Deviation	10.1	13.6	15.7	15.1	14.2
INDOCYANINE GREEN				(n=32)	(n=102)
Half Life (mins)	10.0++	7.4+	4.2	3.7	12.4
Standard Deviation	8.0	4.7	1.1	0.7	11.7
Volume of Distribution(l)	3.3	3.1	3.0	3.8	3.8
Standard Deviation	1.0	0.8	0.6	1.1	1.5
Clearance (ml/min)	339.7++	359.6+	542.1	714.4	358.2
Standard Deviation	173.0	177.0	153.0	230.0	234.0

Statistics by Mann Whitney U Test

Versus Control Group

+ $p < 0.05$
++ $p < 0.01$

TABLE 14.6 CORRELATION OF ANTIPYRINE AND INDOCYANINE GREEN KINETIC DATA WITH INDICES OF CONGESTIVE CARDIAC FAILURE AND RIGHT VENTRICULAR FAILURE. (r VALUES)

	ANTIPYRINE		INDOCYANINE GREEN		Congestive Cardiac Index
	Half Life	Clearance	Half Life	Clearance	
Antipyrine Clearance	0.83***				
I.C.G. Half Life	0.25	0.29			
I.C.G. Clearance	-0.35	0.47*	0.81**		
CCF INDEX	0.27	-0.32	0.99**	0.81**	
RV Index	0.21	-0.15	0.50*	-0.39	0.49*

Statistics by Spearman Rank Correlation

* = $p < 0.05$

** = $p < 0.001$

TABLE 14.7 PRESSURE MEASUREMENTS (mmHg) IN 12 PATIENTS UNDERGOING CARDIAC CATHETERISATION

	DIAGNOSIS	LEFT VENTRICLE			AORTA		RIGHT ATRIUM			RIGHT VENTRICLE		PULMONARY ARTERY			PULMONARY WEDGE		
		S	D	EDP	S	D	a	v	Mean	S	D	S	D	Mean	a	v	Mean
1.	MS	200	0	20	200	100	-	-	16	70	0	70	30	50	-	-	24
2.	MS	110	0	-	130	80	3	3	3	30	0	30	10	13	-	-	6
3.	MS/MI	160	0	8	130	60	10	6	6	40	0	32	10	18	12	18	11
4.	MI	140	0	12	120	70	8	8	5	24	0	28	8	16	-	14	13
5.	AI	-	-	-	180	80	8	4	4	30	0	28	12	18	-	-	10
6.	MS	-	-	-	-	-	10	6	4	50	0	36	20	25	20	16	16
7.	VSD	140	0	8	120	80	5	7	6	80	0	20	8	14	16	14	12
8.	MI/AI	110	0	14	110	60	14	12	10	28	0	28	12	16	-	-	8
9.	MS/AS	190	0	14	190	60	12	6	6	75	0	80	30	52	-	-	30
10.	ASD	120	0	12	120	80	-	-	-	50	0	50	20	25	-	-	10
11.	MS	-	-	-	-	-	5	3	3	22	0	23	8	13	14	10	9
12.	NORMAL	120	0	8	120	80	12	8	8	20	0	28	12	20	16	16	14

MS = Mitral Stenosis
MI = Mitral Incompetence
AI = Aortic Incompetence
VSD = Ventricular septal defect
ASD = Atrial septal defect

S = Systolic
D = Diastolic
EDP= End diastolic pressure
a =
v = Viral

TABLE 14.8 INDOCYANINE GREEN AND ANTIPYRINE KINETIC DATA ON 12 PATIENTS UNDERGOING CARDIAC CATHETERISATION

	Half Life (min)	Vd (l)	Clearance (ml/min)	Half Life (hrs)	Vd (l)	Clearance (ml/min)
1.	5.9	3.2	378.2	22.9	38.7	19.5
2.	3.8	2.8	512.2	25.0	32.2	14.9
3.	3.8	3.5	634.4	18.0	40.9	26.2
4.	4.0	4.3	736.4	15.1	37.7	28.8
5.	3.0	2.6	565.4	15.6	37.1	27.4
6.	4.0	2.3	402.0	10.1	43.8	50.0
7.	3.4	3.9	795.5	11.8	59.7	58.5
8.	4.8	2.6	380.0	10.4	35.2	39.2
9.	3.2	2.8	620.9	6.0	35.7	68.4
10.	6.7	3.0	309.3	11.7	32.2	31.8
11.	4.1	3.2	542.9	15.5	50.6	37.6
12.	3.5	2.1	411.9	12.1	37.7	35.6

Vd = Volume of Distribution

FIGURE 14.1 ANTIPYRINE AND INDOCYANINE GREEN HALF LIVES IN ALL PATIENTS BEFORE AND AFTER TREATMENT OF CONGESTIVE CARDIAC FAILURE.

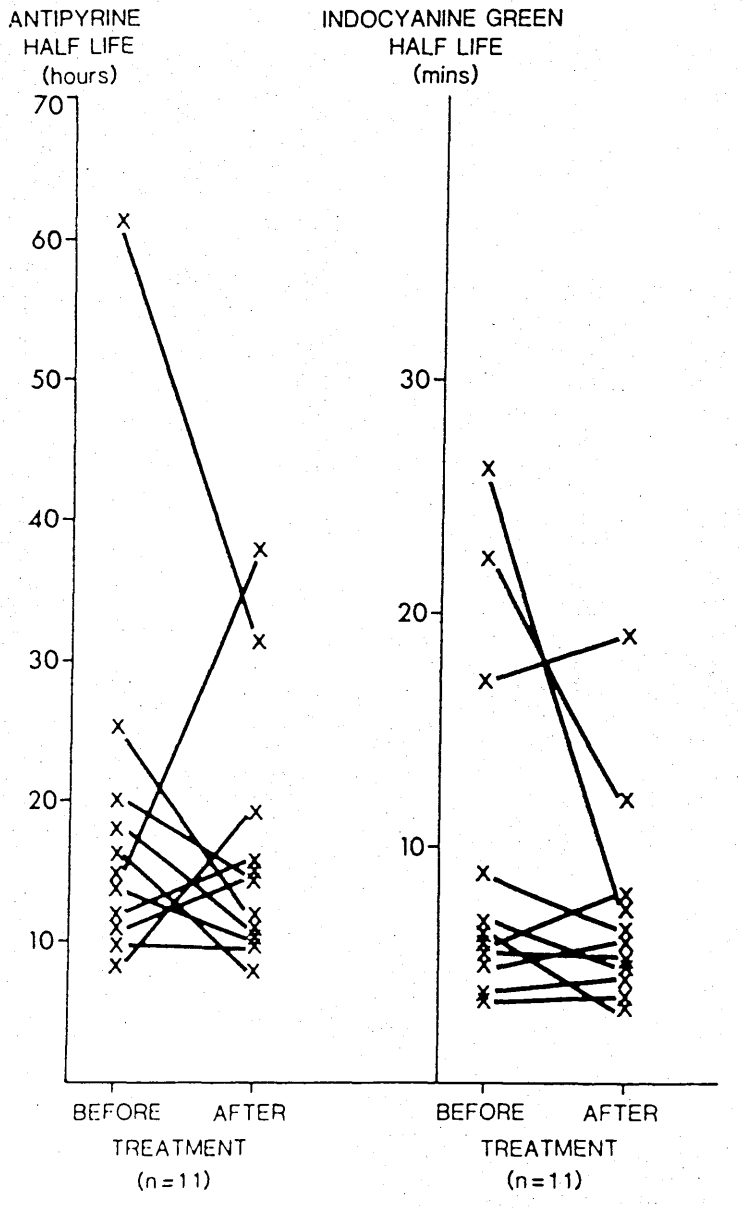
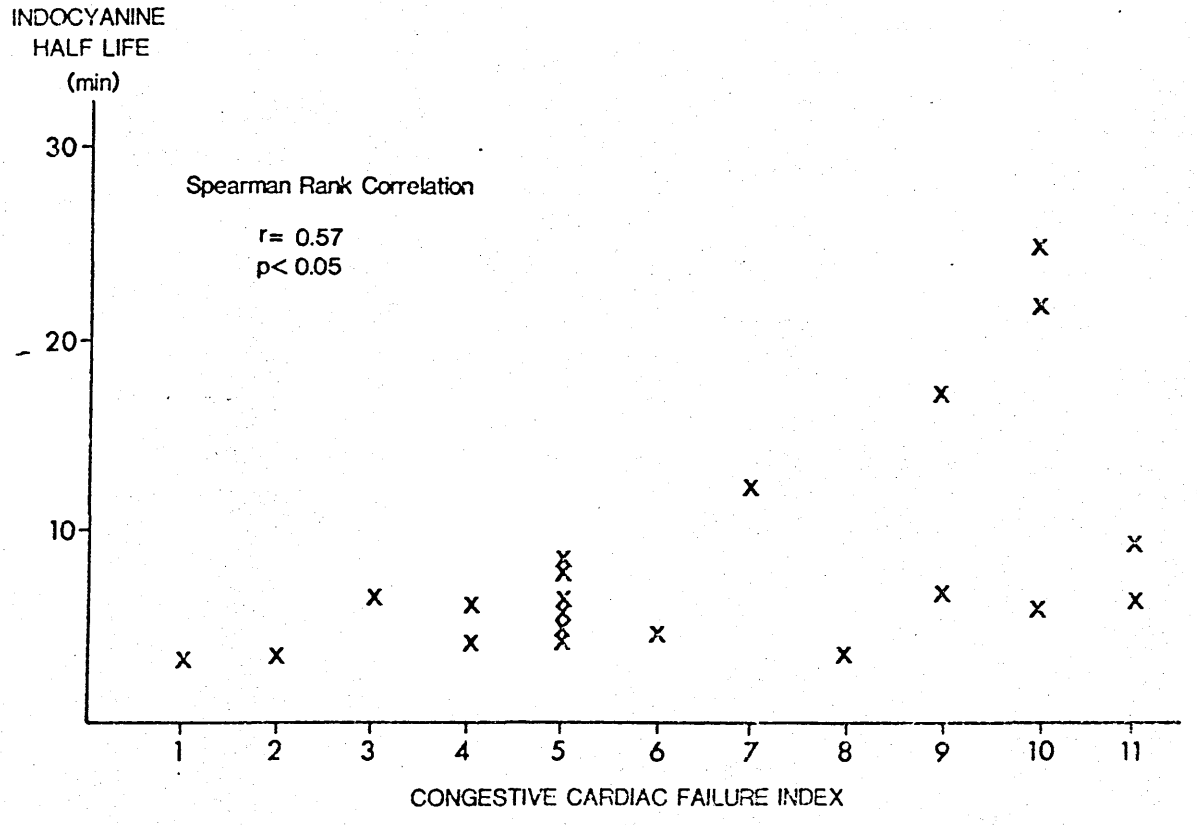


FIGURE 14.2 CORRELATION BETWEEN INDOCYANINE GREEN HALF LIFE AND CONGESTIVE CARDIAC FAILURE INDEX



C H A P T E R 15

CONCLUSION AND FURTHER RESEARCH

The severity of liver disease has traditionally been described in histological terms. Patients who had progressed to cirrhosis were considered to have severe liver disease, with severe functional impairment and a poor prognosis. As knowledge has progressed it has become obvious that this is not an accurate assessment. Many patients with cirrhosis survive for many years with very little or no evidence of functional impairment. The biochemical liver function tests have not been much more satisfactory. Many of these tests do not even reflect a liver function at all but are dependent on hepatocellular destruction and bile duct patency. Only the serum bilirubin and albumin concentrations together with the prothrombin time have been found to have prognostic importance. These tests can be difficult to interpret because they are dependent on several different factors extraneous to the liver. These difficulties have given rise to the concept of studying liver function using the clearance of probe molecules. A further stimulus to this area of research has been the increasing need for an accurate test of the severity of liver disease. This need has been created by the increasing sophistication and cost of the treatment available, including the possibility of hepatic transplantation. For a new liver function test to be accepted into clinical practice it must satisfy two major criteria:-

Firstly, it must have an advantage over the currently available tests as either a screening test, a diagnostic test or as a test of the severity of liver disease.

Secondly, it must be simple to perform.

This thesis demonstrates that indocyanine green clearance is sensitive to the subtle changes in liver function that occur in

patients on methotrexate. However this is not a particularly typical form of liver disease in that the histological abnormality is a progressive hepatic fibrosis. This results in distortion of the liver architecture without gross hepatocellular destruction. Indocyanine green clearance is primarily dependent on liver blood flow which is likely to be sensitive to changes in liver architecture. So that while ICG clearance may be a suitable screening test for methotrexate associated liver disease it is unlikely that this observation can be extrapolated to liver disease in general. In most "civilised" populations the most common form of liver disease in the community is related to alcohol abuse. This can be sensitively detected by measuring the serum gamma glutamyl transpeptidase. It is unlikely that a relatively complex clearance test such as ICG clearance, which requires seven blood samples, could replace a simple single sample test like the measurement of GGT as a screening test in these populations.

Another major area of interest in the use of clearance tests of hepatic function has been in their use as model drugs to predict the elimination of similar molecules. This thesis provides further evidence that Antipyrine and Indocyanine green clearance perform poorly in this function. The correlation of the elimination of these drugs with Midazolam and Meptazinol elimination was poor. For both these drugs the pharmacokinetics were markedly abnormal in patients with liver disease. With Midazolam this predictably led to excessive sedation, but for Meptazinol the result was gastrointestinal intolerance. These two studies again emphasis the importance of examining the pharmacokinetic and dynamic responses of new drugs in

patients with liver disease.

The chapter on the effect of Nadolol on wedged portal vein pressure provides evidence that this may be a suitable beta-blocker to use in patients with portal hypertension. The concept that portal hypertension could be treated like systemic hypertension arose in the early 1980's from the observations of Lebrec. He demonstrated that propranolol reduced portal pressure, and that this was of clinical benefit to patients who had bled from oesophageal varices. However propranolol it extensively metabolised within the liver, so that the pharmacodynamic response may be difficult to predict in patients with liver disease. Nadolol is primarily excreted by the kidney so that it its effect should be easier to predict in the presence of hepatic impairment. Unfortunately other workers have been unable to confirm the clinical benefit of beta blocker therapy in portal hypertension. There is a need for more evidence in this area. A study has been in progress in Glasgow for the past four years to study the effect of propranolol on the secondary prevention of variceal bleeding. Although this study is not yet complete an interim analysis, following the randomisation of 80 patients, suggests that propranolol reduced the incidence of rebleeding by approximately 20%. Further studies are required especially to assess if beta-blockade has any part to play in the primary prevention of variceal bleeding. The data on Nadolol in this thesis suggests that it may be a suitable drug for such a study.

The study in porphyric patients shows the value of antipyrine as a noninvasive assessment of hepatic drug oxidation. This study suggests that porphyric patients have a deficiency of hepatic haem. This observation requires is confirmation by direct measurement of

cytochrome P450 in liver biopsy specimens from porphyric patients.

The study in patients with cardiac failure shows that the changes in the elimination of antipyrine and indocyanine green are as marked in this condition as they are in liver disease. Interestingly there is a close correlation between the severity of the cardiac failure and the clearance if indocyanine green. This suggests that patients with CCF may be highly sensitive to drugs with a high hepatic extraction ratio, and that this sensitivity has the potential to alter rapidly in response to the patients cardiac output.

The chapter on the natural history of liver disease shows that indocyanine green is a powerful liver function test with independent prognostic value. This is a surprising result because it suggests that the complications and prognosis of liver disease are primarily dependent on changes in functional liver blood flow rather than hepatic metabolic capacity. This observation support's the "intact hepatocyte" model of liver dysfunction. In that it is not the function of individual hepatocytes that determines the severity of liver disease, rather it is the mismatching of liver blood flow to functional hepatocytes which is important. Further research into the use of high hepatic extraction ratio drugs requires to be done in particular several important questions remain.

What is the rate limiting step in the excretion of indocyanine green ? In this thesis it has been assumed that because ICG is not metabolised within the liver that the limiting factor for its elimination is the rate of delivery of the drug to functioning hepatocytes. This assumption is not proven and it is possible that the "function" which these changes reflect is not the functional liver

blood flow but a change in the permeability of the hepatocyte membrane.

The value of indocyanine green elimination in specific situations requires further exploration. Is there a critical level of ICG elimination from which death is inevitable ? Can ICG elimination be used as a day to day assessment of liver function in patients with fulminant hepatic failure ? If this were possible then a critical level of liver function could defined to logically select a group of patients for transplantation.

Are there other high hepatic extraction ratio drugs which provide similar results ? In particular an oral clearance test would theoretically be more sensitive, provided that no changes in absorption occured. For a clearance test to become widely adopted in hepatology the sampling method should be as simple as possible. Traditionally ICG clearance is deduced from 7 blood samples over a 21 minute period. This has been simplified in some centres to a retention test requiring only two samples. A further modification to the test uses a dichromatic light sensor attached to the patients ear lobe instead of blood sampling. Research needs to be done to assess other high hepatic extraction ratio drugs as clearance tests in hepatology. In particular HIDA is an interesting compound. This radiopharmaceutical can be administered intravenously with the clearance measure by scanning over the liver. A good correlation exists between the clearance of HIDA measure by this method and both the plasma clearance of HIDA and ICG clearance. A clearance test based on this molecule would provide the advantage of a simultaneous imaging and functional assessment, which require no blood sampling.

Medicine has advanced to the state where accurate liver function

testing is required. Clinical and histological assessment of liver function does not provide accurate functional information. It is hoped that such a test will soon be validated because it is likely that it will open the door to improvements in the therapy for liver disease.

...oooOooo...

A P P E N D I C E S

APPENDIX ONE

THE EFFECT OF DRUGS ON ANTIPYRINE KINETICS

t 1/2	=	Half-Life
vd	=	Apparent Volume of Distribution
cl	=	Clearance
cl/k	=	Clearance/Kilogram

Drug	Dose		Units	Controls	Subjects	% Change	Reference
ACTH	40 units	t 1/2	hrs	11.5	11.2	2.6	SAENGER et al 1978
		vd	l/kg	0.6	0.6	1.7	
		cl/kg	ml/min/kg				
ALLOPURINOL	5mg/kg for 2/52	t 1/2	hrs	11.6	19.1	-64.7	VESELL et al 1970
ALLOPURINOL	5mg/kg for 4/52	t 1/2	hrs	11.6	35.0	-201.7	VESELL et al 1970
ALLOPURINOL	5mg/kg	t 1/2	hrs	11.6	31.0	-167.2	VESELL & PASSANANTI 1973
AMINOPYRINE	9mg/kg	t 1/2	hrs	13.3	21.3	-60.2	VESELL & PASSANANTI 1976
		vd	litres	63.1	61.2	3.0	
		cl	ml/min	56.1	34.3	38.9	
	0.5g	t 1/2	hrs	3.1	4.7	-51.6	BRODIE et al 1959

Drug	Dose		Units	Controls	Subjects	% Change	Reference
AMITRYITYLINE	7 days	t 1/2	hrs	12.7	11.8	7.1	O'MALLEY et al 1973
AMITRYITYLINE	28 days	t 1/2	hrs	12.7	16.9	14.2	O'MALLEY et al 1973
AMYLOBARBITONE	200mg	t 1/2	hrs	12.1	7.8	35.5	STEVENSON et al 1972
AMYLOBARBITONE	200mg	t 1/2	hrs	12.3	8.7	29.3	BALLINGER et al 1972
ANTIPYRINE	500mg	t 1/2	hrs	9.6	8.1	15.6	DANHOF, VERBEEK et al 1982
		cl	l/hr	3.2	3.7	-15.6	
ANTIPYRINE	1000mg	t 1/2	hrs	12.5	8.4	32.8	OHNHAUS & PARK 1979
		vd	litres	40.5	37.5	7.4	
		cl	ml/min	37.5	53.6	-42.9	
ANTIPYRINE	1200mg	t 1/2	hrs	11.9	8.0	32.8	OHNHAUS & PARK 1979
		vd	litres	44.6	42.6	4.5	
		cl	ml/min	45.5	65.0	-42.9	
ANTIPYRINE & PHENOBARBITONE	100mg	t 1/2	hrs	10.4	7.0	32.7	OHNHAUS et al 1983
		vd	litres	39.8	49.4	-24.1	
		cl	ml/min	45.6	82.5	-80.9	

Drug	Dose		Units	Controls	Subjects	% Change	Reference
ANTIPYRINE & RIFAMPICIN	600mg	t 1/2	hrs	12.5	4.6	63.2	OHNHAUS et al 1983
		vd	litres	41.2	36.3	11.9	
		cl	ml/min	40.5	92.5	-128.4	
ASTEMIZOLE	600mg	t 1/2	hrs	11.0	10.8	1.8	BATEMAN & RAWLINS 1983
		vd	litres	52.8	49.7	5.9	
		cl	l/hr	3.6	3.4	5.6	
ATENOLOL	200mg	t 1/2	hrs	11.9	14.2	-19.3	DANESHMEND et al 1982
		vd	litres	40.1	40.5	-1.0	
		cl	ml/min	41.3	34.5	16.3	
CANNABIS	27g	t 1/2	hrs	9.3	4.2	54.9	UPPAL et al 1981
		vd	litres	0.4	0.5	-25.0	
		cl/kg	ml/min/kg	0.6	1.0	-66.7	
CARBAMAZEPINE	15mg/kg	t 1/2	hrs	6.2	2.8	54.8	MORELAND et al 1980
		vd	ml/kg	584.0	582.0	0.3	
		cl/kg		65.2	147.4	-126.1	
CHLORIMIPRAMINE	7 days	t 1/2	hrs	11.8	10.5	11.0	O'MALLEY et al 1973
CHLORIMIPRAMINE	28 days	t 1/2	hrs	11.8	9.3	21.2	O'MALLEY et al 1973

Drug	Dose		Units	Controls	Subjects	% Change	Reference
CHLORINATED HYDROCARBONS	10/15mg	t 1/2	hrs	13.1	7.7	41.2	KALMADIN et al 1969
CIMETIDINE	1g/d	t 1/2	hrs	12.5	14.7	-17.6	KLOTZ et al 1980
		cl	ml/min	40.9	31.8	22.2	
CIMETIDINE	1600mg	t 1/2	hrs	12.2	16.8	-37.7	SERLIN et al 1979
		vd	litres	39.1	42.4	-8.4	
		cl	ml/min	37.1	29.7	20.0	
CIMETIDINE	20mg/kg	t 1/2	hrs	7.4	9.6	-29.7	BRADBEAR et al 1982
		vd	l/kg	0.9	0.8	11.1	
		cl	ml/min/kg	1.2	0.9	20.1	
CIMETIDINE	1g	t 1/2	hrs	10.0	11.5	-15.0	ROBERTS et al 1981
		vd	litres	45.8	47.6	-3.9	
		cl	ml/min	53.7	48.1	10.4	
CIMETIDINE	1g	t 1/2	hrs	10.8	13.2	-22.2	STAIGER et al 1981
		vd	litres	41.3	40.2	2.7	
		cl	ml/min	43.3	32.0	26.1	

Drug	Dose		Units	Controls	Subjects	% Change	Reference
CIMETIDINE	1200mg	t 1/2	hrs	12.3	16.8	-36.6	SLUSHER & VESELL 1984
		vd	litres	51.8	51.5	0.6	
		cl	ml/min	49.1	37.2	24.2	
CIMETIDINE	1g	t 1/2	hrs	12.2	14.3	-17.2	DANESHMEND et al 1984
		vd	litres	38.1	36.8	5.5	
		cl	ml/min	36.5	30.9	1.5	
COMBINED ORAL CONTRACEPTIVE		t 1/2	hrs	10.0	17.3	-73.0	ABERNETHY & GREENBLATT 1981
		vd	ld/kg	0.6	0.6	0.0	
		cl/k	ml/kg/hr	0.7	0.4	43.0	
COMBINED ORAL CONTRACEPTIVE		t 1/2	hrs	9.1	14.7	-61.5	CHAMBERS et al 1982
		vd	ml/kg	483.0	524.0	-8.5	
		cl/k	ml/kg/hr	37.7	26.6	29.4	
COMBINED ORAL CONTRACEPTIVE		t 1/2	hrs	10.8	14.1	-30.6	O'MALLEY et al 1972
COMBINED ORAL CONTRACEPTIVE		t 1/2	hrs	10.6	13.6	28.3	CARTER et al 1973

Drug	Dose		Units	Controls	Subjects	% Change	Reference
COMBINED ORAL CONTRACEPTIVE		t 1/2	hrs	10.0	15.4	-54.0	HOMEIDA et al 1978(a)
		vd	litres	33.6	35.4	-5.4	
		cl	ml/min	39.3	31.0	21.1	
COMBINED ORAL CONTRACEPTIVE (1 month after stopping)	1200mg/kg	t 1/2	hrs	12.6	15.7	-24.6	HOMEIDA et al 1978(a)
		vd	litres	35.5	34.2	3.7	
		cl	ml/min	36.6	28.4	22.4	
COMBINED ORAL CONTRACEPTIVES Ethinyoestradiol	50ug	t 1/2	hrs	9.6	13.3	-38.5	OCHS et al 1984
		vd	l/kg	0.6	0.5	16.0	
		cl	ml/min/kg	0.7	0.5	28.6	
DELTA-9-Tetrahydrocannibinol	180mg	t 1/2	hrs	7.9	9.6	-21.5	BENOWITZ et al 1977
		vd	litres	36.0	39.2	-8.9	
		cl	ml/hr	60.3	52.9	12.3	
DESIMIPRAMINE	7 days	t 1/2	hrs	12.4	10.6	17.0	O'MALLEY et al 1973
DESIMIPRAMINE	28 days	t 1/2	hrs	12.4	11.3	8.9	O'MALLEY et al 1973
DEXAMETHASONE	2mg	t 1/2	hrs	7.6	7.8	-2.6	SAENGER et al 1978
		vd	l/kg	0.5	0.6	-2.0	
		cl/k	ml/min/kg	0.9	0.8	11.1	

Drug	Dose		Units	Controls	Subjects	% Change	Reference
DIPHENHYDRAMINE-METHAQUALONE (MANDRAX)	275-500mg	t 1/2	hrs	14.8	10.8	27.0	STEVENSON et al 1982
DIPHENHYDRAMINE	50mg	t 1/2	hrs	11.0	11.9	-8.2	STEVENSON et al 1982
DISULFIRAM	7mg/kg	t 1/2	hrs	11.0	19.1	-73.6	VESELL & PASSANANTI 1975
		vd	litres	62.0	59.0	4.8	
		cl	ml/min	69.9	44.5	36.3	
DISULFIRAM - 10 days	7.5 mg/kg	t 1/2	hrs	15.0	23.5	-56.6	VESELL & PASSANANTI 1973
DISULFIRAM - 4 days	7.5mg/kg	t 1/2	hrs	14.1	22.9	-62.4	VESELL & PASSANANTI 1973
ENFLURANE		t 1/2	hrs	9.8	8.9	9.2	DUVALDESTIN et al 1981
		vd	l/kg	0.5	0.6	-2.0	
		cl	ml/min -2	28.5	30.2	-6.0	
ETHANOL	15 mg/kg/hr	t 1/2	hrs	10.6	11.7	-10.4	DOSSING & ANDREASEN 1981
		vd	litres	47.7	42.5	10.9	
		cl	ml/min	54.7	47.7	12.8	

Drug	Dose		Units	Controls	Subjects	% Change	Reference
FENFLURAMINE		t 1/2	hrs	11.9	12.1	-1.7	O'MALLEY et al 1975
FLUPENTHIXOL	20-70mg	t 1/2	hrs	12.0	7.3	39.1	SALEM et al 1982
GENERAL ANAESTHESIA for > 4 hrs		cl	ml/min/kg	1.0	0.5	50.0	PESSAYRE et al 1978
GENERAL ANAESTHETIA for 2-4 hrs		cl	ml/min/kg	0.8	0.5	37.5	PESSAYRE et al 1978
GENERAL ANAESTHESIA for < 2 hrs		cl	ml/min/kg	0.8	1.2	50.0	PESSAYRE et al 1978
GLUTETHEMIDE	250mg	t 1/2 cl	hrs ml/min	11.8 42.1	9.0 56.3	23.7 -33.7	FARRELL et al 1979
GLUTETHEMIDE	500mg	t 1/2	hrs	13.0	9.0	30.8	JACKSON et al 1978
HALOFENATE	5g/d	t 1/2	hrs	13.0	10.0	23.1	VESELL & PASSANANTI 1975 (b)

Drug	Dose		Units	Controls	Subjects	% Change	Reference
HYDROCORTISONE		t 1/2	hrs	9.7	12.6	-30.0	FLANAGAN & RICHENS 1974
		vd	l	51.2	52.3	-2.1	
IMIPRAMINE	7 days	t 1/2	hrs	10.3	10.0	2.9	O'MALLEY et al 1973
IMIPRAMINE	28 days	t 1/2	hrs	10.3	9.5	7.8	O'MALLEY et al 1973
INDUSTRIAL SOLVENTS		t 1/2	hrs	8.7	8.1	6.9	SOTANIEMI et al 1982
		vd	l/kg	54.0	48.0	11.1	
		cl	ml/min	52.6	46.2	12.2	
ISONAZID	1gm	t 1/2	hrs	12.7	12.5	1.6	GRECH-BELANGER et al 1983
		vd	ml/kg	1469.0	905.3	38.4	
		cl	ml/min/kg	1.4	0.8	42.9	
ISONAZID	180mg	t 1/2	hrs	9.6	11.3	20.0	OCHS et al 1984
		vd	l/kg	0.5	0.6	-20.0	
		cl	ml/min/kg	0.7	0.6	14.3	
LABETALOL	300mg	t 1/2	hrs	11.9	13.0	-9.2	DANESHMEND et al 1982
		vd	litres	40.1	38.9	3.0	
		cl	ml/min	41.3	35.2	14.8	

Drug	Dose		Units	Controls	Subjects	% Change	Reference
LEVODOPA	250mg/d	t 1/2	hrs	12.6	12.5	0.8	VESELL et al 1971
LEVODOPA METHYLHYDRAZINE	2gms 150mg	t 1/2	hrs	10.2	13.6	-33.3	VESELL et al 1971
LORAZEPAM	4gms	t 1/2	hrs	8.9	9.5	-6.7	GREENBLATT et al 1979
		vd	l/kg	0.6	0.6	-15.6	
		cl	ml/min/kg	0.8	0.8	-11.6	
MEDROXYPROGESTERONE	250g	t 1/2	hrs	11.7	9.8	16.2	RAUTIO et al 1979
		vd	l/kg	0.4	0.4	0.0	
		cl	ml/min	30.5	34.6	-13.4	
METHAQUALONE	250-500mg	t 1/2	hrs	13.2	12.0	9.1	STEVENSON et al 1972
METHYLHYDRAZINE	150mg	t 1/2	hrs	10.0	10.8	-8.0	VESELL et al 1971
METOPROLOL	200mg	t 1/2	hrs	10.7	12.9	-20.6	BAX et al 1981
		vd	litres	43.1	43.4	-0.7	
		cl	l/hr	2.9	2.4	17.3	

Drug	Dose		Units	Controls	Subjects	% Change	Reference
METOPROLOL	100mg	t 1/2	hrs	10.8	12.1	-12.0	PARKER et al 1984
		vd	litres	35.2	36.2	-0.03	
		cl	l/hr	42.0	37.0	0.12	
NADOLOL	40g	t 1/2	hrs	10.8	11.9	-10.2	PARKER et al 1984
		vd	litres	35.2	35.6	-0	
		cl	l/hr	42.0	37.0	0.12	
NITRAZEPAM	5-10mg	t 1/2	hrs	12.6	14.4	-14.3	STEVENSON et al 1982
NORTRIPTYLINE	0.6mg/kg	t 1/2	hrs	8.4	20.7	-146.4	VESELL et al 1970
NORTRIPTYLINE	0.6mg/kg	t 1/2	hrs	12.3	9.7	21.1	VESELL & PASSANANTI 1975 (a)
NORTRIPTYLINE	0.6mg/kg	t 1/2	hrs	14.0	13.3	5.0	VESELL & PASSANANTI 1975 (a)
NORTRIPTYLINE	0.6mg	t 1/2	hrs	12.5	14.7	-17.6	KLOTZ et al 1980
NORTRIPTYLINE	7 days	t 1/2	hrs	10.2	9.0	11.2	O'MALLEY et al 1973
NORTRIPTYLINE	28 days	t 1/2	hrs	10.2	9.3	8.8	O'MALLEY et al 1973

Drug	Dose		Units	Controls	Subjects	% Change	Reference
PENTOBARBITONE	500mg	t 1/2	hrs	10.5	6.8	35.2	DANHOF, VERBEEK et al 1982
		cl	l/hr	3.0	4.8	-60.0	
PHENELZINE	45-90mg/d	cl	ml/min	36.4	30.0	17.6	SMITH et al 1980
PHENOBARBITONE	100mg	t 1/2	hrs	13.8	8.9	35.5	OHNHAUS & PARK 1979
		vd	litres	45.1	44.9	0.4	
		cl	ml/min	38.9	60.6	-55.8	
PHENOBARBITONE	120mg	t 1/2	hrs	12.2	6.6	45.9	ROBERTS et al 1976
		vd	litres	42.1	42.6	-1.2	
		cl	ml/min	42.8	77.9	-82.0	
PHENOBARBITONE	18mg/kg	t 1/2	hrs	13.2	6.9	47.7	MADDOCK et al 1975
		vd	litres	39.8	39.7	0.3	
PHENOBARBITONE	16mg/kg	t 1/2	hrs	12.7	8.0	37.0	VESELL & PAGE 1969
PHENOBARBITONE	1.4 - 6g	t 1/2	hrs	15.1	10.5	30.5	KAMPFFMEYER et al 1971
PHENOBARBITONE	3.6g	t 1/2	hrs	15.1	8.7	42.4	KAMPFFMEYER et al 1971

Drug	Dose		Units	Controls	Subjects	% Change	Reference
PHENYTOIN	200-300g	t 1/2	hrs	10.9	4.5	58.7	NEUVONEN et al 1981
		vd	l/kg	0.6	0.6	0.0	
		cl/k	ml/min/kg	0.7	1.6	-128.6	
PHENYTOIN + CIMETIDINE		t 1/2	hrs	10.9	6.1	44.0	NEUVONEN et al 1981
		vd	l/kg	0.6	0.5	16.6	
		cl/kg	ml/min/kg	0.7	1.0	-42.9	
PIRENZEPINE	20mg/kg	t 1/2	hrs	10.4	10.7	-2.9	PAXTON & PATON 1983
		vd	l/kg	0.6	0.6	-0.0	
		cl/kg	ml/kg/hr	40.6	41.7	-2.7	
PROGESTERONE Only ORAL CONTRACEPTIVE		t 1/2	hrs	9.2	9.1	1.1	CHAMBERS et al 1982
		vd	ml/kg	547.0	569.0	-4.0	
		cl/kg	ml/kg/hr	44.2	47.6	-7.7	
PROPRANOLOL	120mg	t 1/2	hrs	11.9	12.7	-6.7	DANESHMEND & ROBERTS 1982
		vd	litres	40.1	35.8	10.7	
		cl	ml/min	41.3	35.0	15.3	
PROPRANOLOL	160mg	t 1/2	hrs	10.8	14.9	-37.9	GREENBLATT et al 1978
		vd	l/kg	0.6	0.6	0.0	
		cl/kg	ml/min/kg	0.7	0.5	28.6	

Drug	Dose		Units	Controls	Subjects	% Change	Reference
PROPRANOLOL	60g	t 1/2	hrs	10.8	15.9	-42.2	PARKER et al 1984
		vd	litres	35.2	35.1	0	
		cl	ml/min	42.0	27.0	35.7	
PROPRANOLOL	160mg/d	t 1/2	hrs	10.7	17.6	-64.5	BAX et al 1981
		vd	litres	43.1	45.0	-4.4	
		cl	l/hr	2.9	1.8	37.9	
QUININE	325mg	t 1/2	hrs	12.7	10.3	18.9	BERLIN et al 1975
		vd	litres	44.1	44.1	0.0	
		cl	l/hr	2.4	3.0	-25.0	
QUININE	650mg	t 1/2	hrs	17.1	12.4	27.5	BERLIN et al 1975
		vd	litres	38.6	41.2	6.7	
		cl	l/hr	1.7	2.4	-41.2	
RANITIDINE	300mg	t 1/2	hrs	12.6	12.0	4.8	STAIGER et al 1980
		vd	litres	38.2	38.7	-1.3	
		cl	ml/min	36.6	39.1	-6.8	
RANITIDINE	1.2gm	t 1/2	hrs	11.6	11.5	0.9	ABERNETHY et al 1984
		vd	l/kg	0.7	0.7	0.0	
		cl/k	ml/min/kg	0.8	0.8	0.0	

Drug	Dose		Units	Controls	Subjects	% Change	Reference
RIFAMPICIN	600mg	t 1/2	hrs	11.7	7.1	39.3	OHNHAUS & PARK 1979
		vd	litres	53.2	50.9	4.3	
		cl	ml/min	52.9	84.3	-59.4	
RIFAMPICIN	1200mg	t 1/2	hrs	11.7	5.6	52.1	OHNHAUS & PARK 1979
		vd	litres	41.7	45.8	-9.8	
		cl	ml/min	42.7	95.1	-122.0	
RIFAMPICIN	1200mg	t 1/2	hrs	6.9	7.2	-4.4	BREIMER et al 1977
		cl/kg	ml/min/kg	0.6	0.7	-16.7	
RIFAMPICIN	600mg	t 1/2	hrs	11.7	6.9	41.0	MIGUET et al 1977
		vd	litres	32.2	32.2	0.0	
		cl	ml/min	59.4	72.3	-21.7	
RIFAMPICIN	1200mg	t 1/2	hrs	11.3	6.0	46.9	OHNHAUS,GERBER TERAS
		vd	litres	48.4	51.1	-5.6	et al 1983
		cl	ml/min	49.6	101.1	-103.8	
SPIRONOLACTONE	800mg	t 1/2	hrs	12.4	7.60	38.7	HUFFMAN et al 1973
SPIRONOLACTONE	150mg	t 1/2	hrs	14.5	12.89	11.1	TAYLOR et al 1972

Drug	Dose		Units	Controls	Subjects	% Change	Reference
SPIRONOLACTONE	150g	t 1/2	hrs	13.6	14.4	-5.8	OHNHAUS & GERBER TARAS
		vd	litres	31.0	31.0	0.0	1984
		cl	ml/min	30.5	30.5	0.0	
SULPHINPYRAZONE	800mg	t 1/2	hrs	13.2	7.7	41.7	STAIGER et al 1983
		vd	litres	49.1	51.6	-5.1	
		cl	l/hr	2.7	4.7	-74.1	
TERBUTALINE	15mg	t 1/2	hrs	10.7	11.2	-4.7	BAX et al 1981
		vd	litres	43.1	42.4	1.6	
		cl	l/hr	2.9	2.8	3.4	
TESTOSTERONE	400mg	t 1/2	hrs	8.0	5.7	28.8	JOHNSEN et al 1976
VITAMIN C	1 gram	t 1/2	hrs	17.0	10.0	41.2	GINTER & VEJMOLOVA 1981
		vd	l/kg	0.6	0.5	16.7	
		cl	ml/kg/hr	25.2	37.7	-49.6	
VITAMIN C	10mg/kg	t 1/2	hrs	10.0	7.9	21.0	HOUSTON 1977
		vd	l/kg	0.5	0.5	0.0	
		cl/k	ml/kg/hr	39.7	49.6	-24.9	

Drug	Dose		Units	Controls	Subjects	% Change	Reference
VITAMIN A,B,C,D		t 1/2	hrs	12.1	12.0	0.8	SMITHARD & LANGMAN 1978
SUPPLEMENTS IN NON		vd	ml/kg	509.0	499.0	1.9	
VITAMIN DEFICIENT		cl/k	ml/kg/hr	29.8	30.0	-0.7	
GERIATRICS							
VITAMIN A,B,C,D		t 1/2	hrs	12.5	10.6	15.2	SMITHARD & LANGMAN 1978
SUPPLEMENTS IN		vd	ml/kg	530.0	551.0	-3.9	
VITAMIN DEFICIENT		cl/k	ml/kg/hr	33.4	41.5	-24.2	
GERIATRICS							

APPENDIX TWO

THE EFFECT OF LIVER DISEASE ON THE ELIMINATION OF DRUGS

DRUG/DISEASE	DOSE	PARAMETER/UNITS		CONTROLS	SUBJECT	% CHANGE	REFERENCE
AMPICILLIN							
Cirrhosis	600mg	t 1/2	hrs	1.31	1.90	-45	LEWIS & JUSKO 1975
		vd	litres	13.40	20.40	-52	
		cl	ml/min	342.00	280.00	18	
AMYLOBARBITONE							
Mixed chronic liver disease and reduced albumin	3.23mg/kg	t 1/2	hrs	21.10	39.40	-87	MAWER et al 1972
Mixed chronic liver disease with normal serum albumin	3.23mg/kg	t 1/2	hrs	21.10	17.74	16	MAWER et al 1972
BROTIZOLAM							
Cirrhosis	0.5mg	t 1/2	hrs	6.90	12.80	-86	JOCHEMSEN et al 1983
CAFFEINE							
Cirrhosis	125mg	t 1/2	hrs	3.80	17.50	-361	RENNER et al 1984
		vd	l/kg	0.64	0.57	11	
		cl	ml/min/kg	2.02	0.67	67	
Mixed liver disease	125mg	t 1/2	hrs	3.80	4.70	-24	RENNER et al 1984
		vd	l/kg	0.64	0.55	14	
		cl	ml/min/kg	2.02	1.52	25	

DRUG/DISEASE	DOSE	PARAMETER/UNITS		CONTROLS	SUBJECT	% CHANGE	REFERENCE
CAFFEINE							
Primary Biliary Cirrhosis	125mg	t 1/2	hrs	3.80	9.40	-147	RENNER et al 1984
		vd	l/kg	0.64	0.57	11	
		cl	ml/min/kg	2.02	0.87	57	
CARBENECILLIN							
Mixed liver disease	2g	t 1/2	hrs	1.00	1.90	-90	HOFFMAN et al 1970
CEFTRIAZONE							
Cirrhosis	1g	t 1/2	hrs	8.40	8.00	5	STOECKEL et al 1984
		vd	l/kg	0.16	0.15	3	
		cl/k	ml/min/kg	0.23	0.24	-4	
Fatty Liver	1g	t 1/2	hrs	8.40	9.70	-15	STOECKEL et al 1984
		vd	l/kg	0.16	0.17	-9	
		cl/k	ml/min/kg	0.23	0.18	19	
Ascites	1g	t 1/2	hrs	8.40	9.70	-15	STOECKEL et al 1984
		vd	l/kg	0.16	0.32	-100	
		cl/k	ml/min/kg	0.23	0.39	-73	
CHLORAMPHENICOL							
Cirrhosis	10mg/kg	t 1/2	hrs	2.30	4.04	-76	AZZOLLINI et al 1972
Cirrhosis	20mg/kg	t 1/2	hrs	4.61	10.45	-127	NARANG et al 1981
		vd	litres	68.89	49.95	24	
		cl	ml/min	168.60	59.17	65	

DRUG/DISEASE	DOSE	PARAMETER/UNITS		CONTROLS	SUBJECT	% CHANGE	REFERENCE
CHLORAMPHENICOL							
Acute Hepatitis	20mg/kg	t 1/2	hrs	4.61	11.60	-152	NARANG et al 1981
		vd	litres	65.89	51.86	21	
		cl	ml/min	168.60	52.36	69	
Idiopathic Portal Hypertension	20mg/kg	t 1/2	hrs	4.61	7.60	-65	NARANG et al 1981
		vd	litres	65.89	47.91	27	
		cl	ml/min	168.60	77.73	54	
Extrahepatic Obstruction	20mg/kg	t 1/2	hrs	4.61	7.22	-57	NARANG et al 1981
		vd	litres	65.89	46.65	29	
		cl	ml/min	168.60	86.59	49	
Budd Chiari Syndrome	20mg/kg	t 1/2	hrs	4.61	8.25	-79	NARANG et al 1981
		vd	litres	65.89	52.77	20	
		cl	ml/min	168.60	80.44	52	
Amoebic Liver Disease	20mg/kg	t 1/2	hrs	4.61	7.28	-58	NARANG et al 1981
		vd	litres	65.89	55.54	16	
		cl	ml/min	168.60	92.38	45	
CHLORDIAZEPOXIDE							
Cirrhosis	0.6mg/kg	t 1/2	hrs	23.80	62.70	-163	ROBERTS et al 1978
		vd	1/kg	0.17	0.29	-71	
		cl	ml/min	15.30	7.70	50	
Acute Hepatitis	0.6mg/kg	t 1/2	hrs	11.10	91.00	-720	ROBERTS et al 1978
		vd	1/kg	0.15	0.18	-20	
		cl	ml/min	18.10	6.10	66	

DRUG/DISEASE	DOSE	PARAMETER/UNITS		CONTROLS	SUBJECT	% CHANGE	REFERENCE
CHLORDIAZEPOXIDE							
Alcoholic	25mg	t 1/2	hrs	16.50	40.10	-143	MORGAN et al 1981
Hepatitis		vd	ml/kg	321.00	428.00	-33	
		cl	ml/kg/hr	13.80	7.60	45	
CHLORMETHIAZOLE							
Cirrhosis	192/300mg	t 1/2	hrs	6.60	8.70	-32	PENTIKAINEN et al 1978
		cl	ml/min/kg	18.10	12.80	29	
CHLORPROMAZINE							
Cirrhosis	25mg	t 1/2	hrs	31.00	24.00	23	MAXWELL et al 1972
CIMETIDINE							
Cirrhosis	200mg	t 1/2	hrs	2.30	2.90	-26	SCHENTAG et al 1981
		vd	l/kg	1.10	1.40	-27	
		cl	ml/min	511.00	463.00	9	
Cirrhosis	100/400mg	vd	l/kg	2.10	1.00	52	GRAHNEN et al 1984
		cl	ml/min	789.00	262.00	67	
CLINDAMYCIN							
Cirrhosis	300mg	t 1/2	hrs	3.42	4.46	-30	AVANT et al 1975
		vd	l/kg	0.25	0.24	6	
		cl	ml/min	159.20	121.70	24	
CYCLOBARBITONE							
Cirrhosis	200mg	t 1/2	hrs	13.40	35.20	-163	BREYER-PFAFF et al 1984
		cl	ml/min	39.10	16.30	58	

DRUG/DISEASE	DOSE	PARAMETER/UNITS		CONTROLS	SUBJECT	% CHANGE	REFERENCE
CYCLOBARBITONE							
Acute Hepatitis	200mg	t 1/2	hrs	13.40	22.40	-67	BREYER-PFAFF et al 1984
		cl	ml/min	39.10	23.40	40	
Mixed Liver Disease	200mg	t 1/2	hrs	13.40	20.60	-54	BREYER-PFAFF et al 1984
		cl	ml/min	39.10	33.40	15	
Fatty Liver	200mg	t 1/2	hrs	13.40	22.10	-65	BREYER-PFAFF et al 1984
		cl	ml/lmin	39.10	51.20	-31	
D-PROPRANOLOL							
Cirrhosis	0.4mg/kg	vd	l/kg	5.00	5.00	0	
		cl	ml/min/kg	21.00	8.00	62	
Alcoholic Fibrosis	0.4mg/kg	vd	l/kg	5.00	5.00	0	PESSAYRE et al 1978
		cl/k	ml/min/kg	21.00	18.00	14	
DIAZEPAM							
Mixed Liver Disease	10mg	t 1/2	hrs	38.00	127.60	-2-236	HENDEL et al 1976
Cirrhosis	0.1mg/kg	t 1/2	hrs	46.60	105.60	-127	KLOTZ et al 1975
		cl	ml/min	26.60	13.80	48	
Cirrhosis	5mg	t 1/2	hrs	32.10	164.00	-411	ANDREASEN et al 1976
		cl	ml/min	35.00	17.10	51	
Acute Hepatitis	0.1mg/kg	t 1/2	hrs	32.70	74.50	-128	KLOTZ et al 1975
Mixed Liver Disease		t 1/2	hrs	53.10	116.00	-118	HEPNER et al 1977(b)
		cl	ml/min	15.10	9.80	35	

DRUG/DISEASE	DOSE	PARAMETER/UNITS		CONTROLS	SUBJECT	% CHANGE	REFERENCE
DIAZEPAM							
Mixed Liver		t 1/2	hrs	53.10	116.00	-118	HEPNER et al 1977(b)
Disease		cl	ml/min	15.10	9.80	35	
Cholestasis		t 1/2	hrs	53.10	59.00	-11	HEPNER et al 1977(b)
		cl	ml/min	15.10	16.90	-12	
Chronic Active Hepatitis	0.1mg/kg	t 1/2	hrs	32.70	59.70	-83	KLOTZ et al 1975
Hepatic Neoplasm		t 1/2	hrs	53.10	77.10	-45	HEPNER et al 1977(b)
		cl	ml/min	15.10	10.83	28	
DICUMAROL							
Cirrhosis		t 1/2	hrs	30.7	50.6	-65	BRODIE et al 1959
FRUSEMIDE							
Cirrhosis	80mg	t 1/2	hrs	0.79	2.20	-178	ALLGULANDER et al 1980
		vd	ml/kg	210.00	533.00	-154	
		cl	ml/min	194.00	192.00	1	
Fatty Liver	80mg	t 1/2	hrs	0.79	1.15	-46	ALLGULANDER et al 1980
		vd	ml/kg	210.00	245.00	-17	
		cl	ml/min	194.00	246.00	-27	

DRUG/DISEASE	DOSE	PARAMETER/UNITS		CONTROLS	SUBJECT	% CHANGE	REFERENCE
GLYCOFUROL							
Cirrhosis	6.486g	t 1/2	hrs	1.06	2.14	-102	BURY et al 1984
		vd	l/kg	0.52	0.46	13	
		cl		0.60	0.31	49	
HEXOBARBITAL							
Extrahepatic Cholestasis	7.32mg/k	t 1/2	min	323.00	344.00	-7	RICHTER et al 1980
		vd	l/kg	0.54	0.42	22	
		cl	ml/min/kg	3.41	3.81	-12	
Intrahepatic Cholestasis	7.32mg/k	t 1/2	min	323.00	357.00	-11	RICHTER et al 1980
		vd	l/kg	0.54	0.53	2	
		cl	ml/min/kg	3.41	4.08	-20	
Compensated Cirrhosis		t 1/2	min	340.00	509.00	-50	ZILLY et al 1978
		vd	l/kg	1.25	1.14	9	
		cl	ml/min/kg	3.32	1.88	43	
Acute Hepatitis	2.97-7.32 mg/kg	t 1/2	min	261.00	490.00	-88	BREIMER et al 1976
		vd	l/kg	0.43	0.33	30	
		cl	ml/min/kg	3.57	1.94	46	
Decompensated Cirrhosis		t 1/2	min	340.00	1017.00	-199	ZILLY et al 1978
		vd	l/kg	1.25	1.57	-26	
		cl	ml/min/kg	3.32	1.26	62	
Mixed Enzyme Inducer in Mixed LiverDisease	7.32mg/kg	t 1/2	min	399.00	227.00	43	RICHTER et al 1980
		cl	ml/min/kg	3.44	7.58	-120	

DRUG/DISEASE	DOSE	PARAMETER	UNITS	CONTROLS	SUBJECT	% CHANGE	REFERENCE
HEXOBARBITAL							
Rifampicin in Mixed Liver Disease	7.32mg/kg	t 1/2	min	624.00	291.00	53	ZILLY et al 1977
		cl	ml/min/kg	2.80	0.60	79	
ISONIAZID							
Cirrhosis		t 1/2	hrs	3.24	6.74	-108	ACOCELLA et al 1972
LABETALOL							
Cirrhosis	0.5mg/kg	t 1/2	min	187.00	170.00	9	HOMEIDA et al 1978
		vd	litres	805.00	526.00	35	
Cirrhosis	100mg	t 1/2	min	154.00	156.00	-1	HOMEIDA et al 1978(b)
LIGNOCAINE							
Cirrhosis		t 1/2	min	108.00	343.00	-218	THOMSON et al 1973
		vd	l/kg	1.70	2.22	-31	
		cl	ml/min/kg	9.20	5.20	43	
Cirrhosis Vs Chronic Hepatitis		t 1/2	min	84.30	227.50	-170	HUET & VILLENEUVE et al 1983
		vd	l/kg	2.40	2.10	13	
		cl	ml/min/kg	19.40	7.30	62	
Severe Alcoholic Liver Disease	50mg	t 1/2	min	107.80	296.00	-175	THOMSON et al 1973
		vd	litres	37.00	43.00	-16	
		cl	l/min	0.70	0.42	40	
		cl/k	ml/min/kg	10.00	6.00	40	

DRUG/DISEASE	DOSE	PARAMETER/UNITS		CONTROLS	SUBJECT	% CHANGE	REFERENCE
LIGNOCAINE							
Chronic Active Hepatitis	100mg	t 1/2	min	105.00	93.00	11	HUET & LE LORIER 1980
		vd	l/kg	2.44	4.30	-76	
		cl/k	ml/min/kg	49.70	113.20	-128	
Viral Hepatitis	100mg	t 1/2	min	90.00	160.00	-78	WILLIAMS et al 1976
		vd	l/kg	0.60	1.00	-67	
		cl	ml/min/kg	20.00	13.00	35	
Mixed Liver Disease	400mg	t 1/2	hrs	1.40	6.60	-371	FORREST et al 1977
LORAZEPAM							
Cirrhosis	2mg	t 1/2	hrs	21.70	41.20	-90	KRAUS et al 1978
		cl/k	ml/min/kg	0.75	9.81	-8	
Acute Hepatitis	2mg	t 1/2	hrs	21.70	28.30	-30	KRAUS et al 1978
		cl/k	ml/min/kg	0.75	0.74	1	
LORCAINIDE							
Cirrhosis	1.5mg/kg	t 1/2	hrs	7.70	12.50	-62	KLOTZ et al 1979
		vd	l/kg	9.40	11.80	-27	
		cl	ml/min	1002.00	814.00	19	
METHADONE							
Alcoholic Liver Disease		t 1/2	hrs	19.70	32.00	-62	NOVICK et al 1985
		vd	L	438.00	716.00	-63	
		cl	ml/L	246.20	279.20	-13.4	

DRUG/DISEASE	DOSE	PARAMETER/UNITS		CONTROLS	SUBJECT	% CHANGE	REFERENCE
MEPTAZINOL							
Non Cirrhotic	25mg	t 1/2	hrs	2.7	3.2	-19	SEE CHAPTER 13
		vd	L	308.0	408.0	32	
		cl	ml/L	83.0	89.0	7	
Cirrhotic	25mg	t 1/2	hrs	2.7	4.2	-56	SEE CHAPTER 13
		vd	L	308.0	450.0	46	
		cl	ml/L	83.0	72.0	11	
METOPROLOL							
Cirrhosis	20mg	t 1/2	hrs	4.20	7.20	-71	REGARDH et al 1981
		vd	l/kg	0.96	1.90	-98	
		cl		0.80	0.61	24	
Cirrhosis	50mg	t 1/2	hrs	4.30	6.20	-44	REGARDH et al 1981
METRONIDAZOLE							
Mixed Liver	8mg/kg	t 1/2	hrs	7.90	19.90	-152	FARREL et al 1984
Disease		cl	ml/min	51.90	17.50	66	
MIDAZOLAM							
Cirrhosis	0.075ng/kg	t 1/2	min	1.60	4.80	-200	SEE CHAPTER 12
		vd	L	80.70	106.19	-32	
		cl	ml/min/kg	10.40	5.4	48	

DRUG/DISEASE	DOSE	PARAMETER/UNITS		CONTROLS	SUBJECT	% CHANGE	REFERENCE
MORPHINE							
Cirrhosis	0.15mg/kg	t 1/2	hrs	1.50	1.50	0	PATWARDHAN et al 1981
		vd	l/kg	2.80	2.70	4	
		cl	ml/min	1239.00	1183.00	5	
NAPROXEN							
Cirrhosis		vd	l/hr	1.21	16.80	-1288	CALVO et al 1982
		cl	l/hr	0.55	0.75	-37	
Mixed Liver Disease	250mg	t 1/2	hrs	14.14	20.36	-44	CALVO et al 1982
OXAZEPAM							
Cirrhosis	2mg	t 1/2	hrs	6.40	7.80	-22	SHULL et al 1976
		vd	litres	61.20	60.90	0	
		cl	ml/min	136.00	155.50	-14	
Acute Hepatitis	45mg	t 1/2	hrs	7.10	6.10	14	SHULL et al 1976
		vd	litres	47.70	51.70	-8	
		cl	ml/min	113.50	137.40	-21	
PARACETAMOL							
Cirrhosis	15mg/kg	t 1/2	min	172.00	285.00	-66	ARMAN & OLSSON 1978
Cholestasis	1gram	t 1/2	min	2.40	4.20	-75	BRODIE et al 1982
Ascites	15mg/kg	t 1/2	min	172.00	311.00	-81	ARMAN & OLSSON 1978
Hepatic Neoplasm	15mg/kg	t 1/2	min	172.00	282.00	-64	ARMAN & OLSSON 1978

DRUG/DISEASE	DOSE	PARAMETER/UNITS		CONTROLS	SUBJECT	% CHANGE	REFERENCE
PARACETAMOL							
Gilberts Syndrome	1 gram	t 1/2	hrs	0.28	0.32	-14	DOUGLAS et al 1978
		vd	l/kg	0.60	0.69	-15	
		cl	ml/min	352.00	255.00	28	
Mixed Liver Disease	1.5mg	t 1/2	hrs	2.00	2.90	45	FORREST et al 1977
PAS							
Cirrhosis	20mg	t 1/2	min	30.80	27.00	12	HELD & FRIED 1977
		vd		98.00	100.00	-2	
		cl	ml/min/kg	2.62	3.01	-15	
PEFLOXACIN							
Cirrhosis	400mg/8mg/kg	t 1/2	hrs	11.00	35.10	-219	DANAN et al 1985
		vd	L/kg	1.54	1.88	22	
		cl	L/hr	8.19	2.66	553	
PENTAZOCINE							
Cirrhosis	0.4mg/k	t 1/2	min	230.00	396.00	-72	NEAL et al 1979
		vd	litres	415.00	356.00	14	
		cl	ml/min	1246.00	675.00	46	
PETHIDINE							
Cirrhosis	0.8mg/kg	t 1/2	min	213.00	359.00	-69	NEAL et al 1978
		vd	litres	270.00	285.00	-6	
		cl	ml/min	900.00	573.00	36	

DRUG/DISEASE	DOSE	PARAMETER/UNITS		CONTROLS	SUBJECT	% CHANGE	REFERENCE
PETHIDINE							
Cirrhosis	0.8mg/kg	t 1/2	hrs	3.21	7.04	-119	KLOTZ et al 1974
		vd	l/kg	1.54	2.48	-61	
		cl	ml/min	1316.00	664.00	50	
Acute Hepatitis	0.8mg/kg	t 1/2	hrs	3.37	6.99	-107	McHORSE et al 1975
		vd		5.94	5.56	6	
		cl	ml/min	1261.00	649.00	49	
PHENACTIN							
Cirrhosis		t 1/2	hrs	0.72	1.92	-167	BREEN et al 1984
		cl	ml/min/kg	22.88	11.95	48	
PHENOBARBITONE							
Cirrhosis	0.85mg/kg	t 1/2	hrs	86.00	130.00	-51	ALVIN et al 1974
Acute Hepatitis	0.85mg/kg	t 1/2	hrs	86.00	104.00	-21	ALVIN et al 1974
PHENPROCOUMON							
Cirrhosis	0.12-0.25mg/kg	cl	ml/l/kg	0.90	1.64	-82	KITTERINGHAM et al 1984
PHENYLBUTAZONE							
Mixed Liver Disease	400-600	t 1/2	min	70.90	78.10	-10	LEVI et al 1968
Cirrhosis	0.8gms	t 1/2	hrs	72.20	50.60	30	BRODIE et al 1959

DRUG/DISEASE	DOSE	PARAMETER/UNITS		CONTROLS	SUBJECT	% CHANGE	REFERENCE
PHENYTOIN							
Acute Hepatitis	250mg	t 1/2	hrs	13.50	13.20	0	BLASCKE et al 1975
		vd	l/kg	0.64	0.68	0	
		cl	l/hr	2.50	2.60	0	
PREDNISOLONE							
Portocaval Shunt	20mg	t 1/2	hrs	3.06	2.66	13	DU SOUICH & ERILL 1977
PROCAINAMIDE							
Cirrhosis	500mg	t 1/2	min	0.70	2.90	-314	DU SOUICH & ERILL 1977
Ascites	50mg	t 1/2	min	2.40	3.50	-46	
PROPRANOLOL							
Cirrhosis	80mg	t 1/2	hrs	4.00	11.20	-180	WOOD et al 1978
		vd	litres	290.00	380.00	-31	
		cl	ml/min	860.00	580.00	33	
PROPRANOLOL							
Mild Liver Disease	40g	t 1/2	hrs	2.90	9.80	183	BRANCH et al 1976
Severe Liver Disease	40g	t 1/2	hrs	2.90	22.70	683	BRANCH et al 1976
RANITIDINE							
Cirrhosis	50mg	t 1/2	min	81.40	97.50	-20	OKOLICSANYI et al 1984
		vd	litres	73.50			
		cl	ml/min	566.00	548.00	3	

DRUG/DISEASE	DOSE	PARAMETER/UNITS		CONTROLS	SUBJECT	% CHANGE	REFERENCE
RANITIDINE							
Cirrhosis	150mg	t 1/2	min	158.00	142.00	10	OKOLICSANYI et al 1984
RIFAMPICIN							
Cirrhosis		t 1/2	hrs	2.80	5.42	-94	ACOCELLA et al 1972
SALICYLAMIDE							
Cirrhosis		t 1/2	min	12.00	19.00	-58	NEAL et al 1979
SALICYLIC ACID							
Cirrhosis	1.3g	t 1/2	hrs	6.10	6.60	-8	BRODIE et al 1959
THEOPHYLLINE							
Cirrhosis	2.25mg/kg	t 1/2	hrs	6.70	25.60	-282	PIAFSY et al 1977
		vd	l/kg	0.51	0.33	35	
		cl		0.06	0.04	32	
THEOPHYLLINE							
Cirrhosis		t 1/2	hrs	6.00	28.80	-380	MANGIONE et al 1978
		vd	l/kg	0.48	0.56	-17	
		cl/k	ml/kg/hr	63.00	18.80	71	
TOCAINIDE							
Cirrhosis	100mg	t 1/2	hrs	13.50	27.40	-103	OLTMANNS et al 1983
		vd	l/kg	2.90	3.82	-32	
		cl	ml/min/kg	2.60	1.84	29	

DRUG/DISEASE	DOSE	PARAMETER/UNITS		CONTROLS	SUBJECT	% CHANGE	REFERENCE
TOLBUTAMIDE							
Cirrhosis	1gm	t 1/2	min	339.20	353.40	04	IBER et al 1981
Acute Hepatitis		t 1/2	hrs	4.00	5.90	-48	WILLIAMS et al 1976
		vd	l/kg	0.15	0.15	0	
		cl	ml/kg/hr	26.00	18.00	31	
TRIAMTERENE							
Cirrhosis	200mg	cl	ml/min	1617	134	92	VILLENEUVE et al 1984
VERAPAMIL							
Cirrhosis	5mg	t 1/2	min	170.00	815.00	-379	WOODCOCK et al 1979(a)
		vd	litres	296.00	481.00	-63	
		cl		1.57	0.55	65	
WARFARIN							
Acute Hepatitis	15mg	t 1/2	hrs	25.00	23.00	8	WILLIAMS et al 1976
		vd	l/kg	0.21	0.19	10	
		cl/k	ml/kg/hr	6.10	6.10	0	
ZOPICLONE							
Cirrhosis	7.5mg	t 1/2	hrs	3.50	8.53	-144	PARKER & ROBERTS 1983

A P P E N D I X 3

(Data for Chapter 10)

REPORT 1 - Clinical details, standard biochemistry

REPORT 2 - Antipyrine kinetics, Histological details

REPORT 3 - Indocyanine green kinetics, Drugs

CODES FOR REPORT ONE

DIAGNOSIS	CODE	1	=	PRIMARY BILIARY CIRRHOSIS
		2	=	CHRONIC ACTIVE HEPATITIS
		3	=	ALCOHOLIC LIVER DISEASE
		4	=	IDIOPATHIC PORTAL HYPERTENSION
		6	=	CRYPTOGENIC CIRRHOSIS
		7	=	PRIMARY SCLEROSING CHOLANGITIS
		8	=	HAEMACHROMATOSIS
		9	=	DIAGNOSIS OBSCURE
		100	=	CONTROL
SEX	CODE	0	=	FEMALE
		1	=	MALE
PHT	CODE	0	=	NO EVIDENCE OF PORTAL HYPERTENSION
		1	=	OESOPHAGEAL VARICES PRESENT
		2	=	BLEEDING OESOPHAGEAL VARICES
		3	=	PORTACAVAL SHUNT
ASCITES	CODE	0	=	NO ASCITES
		1	=	ASCITES
ENCEPH	CODE	0	=	NO ENCEPHALOPATHY
		1	=	ENCEPHALOPATHY
CHILDS	CODE	1	=	CHILD'S GRADE A
		2	=	CHILD'S GRADE B
		3	=	CHILD'S GRADE C
		4	=	CONTROL

REPORT 1

NO	DIAGNOSIS	SEX	AGE	WT	LIVER	SPLEEN	PHT	ASCITES	ENCEPH	HAEMOGLOBIN	PT	CONTROL	BILIRUBIN	SGOT	SGPT	GGT	A.P.	ALBUMIN	GLOBULIN	CREATININE	AL/D	FOLLOWUP	HIST	CHILD
001	1	0	67	43	6	6	1	1	0	8.6	16	14	103	78	81	110	411	33	43	75	2	36	2	2
003	1	0	72	59	1	0	1	1	0	10.4	17	15	85	82	47	17	332	20	30	110	2	8	2	3
011	1	0	62	54	8	0	0	0	0	13.0	12	14	27	63	95	669	1122	41	33	102	1	41	2	1
019	1	0	72	55	0	0	0	0	0	12.8	13	15	26	140	232	3000	1668	34	16	110	1	30	1	1
028	1	0	61	65	0	0	0	0	0	15.0	15	14	15	90	131	1029	1311	38	30	78	1	36	1	1
035	1	0	65	67	1	0	0	0	0	13.8	14	15	16	55	59	825	528	38	34	82	1	35	1	1
045	1	0	60	70	0	0	0	0	0	12.1	13	13	15	4	22	27	93	36	28	93	1	34	1	1
047	1	0	65	53	1	2	0	0	1	11.1	12	14	43	100	77	456	696	32	47	88	1	34	2	2
048	1	0	51	75	0	0	1	0	0	13.6	13	15	19	118	13	466	429	39	35	53	1	28	1	1
054	1	0	50	60	0	0	0	0	0	13.9	12	15	12	94	147	445	550	39	54	63	1	38	1	1
055	1	0	74	47	0	0	0	0	0	9.6	13	14	3	43	42	288	446	27	46	77	1	28	1	1
057	1	0	38	46	0	0	0	0	0	11.9	14	15	23	121	264	374	1029	41	26	67	1	28	1	1

NO	DIAGNOSIS	SEX	AGE	WT	LIVER	SPLEEN	PHT	ASCITES	ENCEPH	HAEMOGLOBIN	PT	CONTROL	BILIRUBIN	SGOT	SGPT	GGT	A.P.	ALBUMIN	GLOBULIN	CREATINE	AL/D	FOLLOWUP	HIST	CHILD
058	1	0	40	57	0	0	1	0	0	10.4	15	14	19	91	83	226	332	35	35	74	1	29	2	1
062	1	0	57	62	0	0	0	0	0	13.0	14	14	6	58	75	157	489	45	32	79	1	28	1	1
068	1	0	67	63	4	0	0	0	0	15.0	15	15	24	71	66	402	408	36	34	89	1	29	1	1
071	1	0	67	69	3	0	1	0	0	12.7	13	15	28	131	135	385	1071	35	39	58	1	30	1	1
072	1	0	56	62	0	0	0	0	0	13.2	12	14	23	92	149	413	451	43	22	74	1	27	1	1
079	1	0	71	73	0	0	0	0	0	13.1	14	15	16	39	35	220	293	41	40	78	1	28	1	1
130	1	1	64	50	10	1	1	1	1	14.8	12	14	195	103	120	292	550	32	48	67	2	20	2	2
133	1	0	58	64	2	0	0	0	0	13.8	13	14	7	84	90	493	565	39	35	114	1	4	1	1
134	1	0	65	70	0	1	0	0	0	13.0	13	15	13	66	79	180	348	44	24	153	1	5	1	1
138	1	0	55	70	0	0	2	0	0	13.3	14	15	7	37	61	153	186	35	25	68	1	5	2	1
153	1	0	60	58	3	0	0	0	0	10.8	14	14	32	169	183	624	1509	40	50	62	1	19	1	1
154	1	0	64	58	0	0	0	0	0	13.5	12	14	6	71	87	666	535	37	33	69	1	0	1	1
228	1	0	72	76	0	0	0	0	0	13.5	14	14	19	58	69	418	190	43	24	110	1	20	1	1

NO	DIAGNOSIS	SEX	AGE	WT	LIVER	SPLEEN	PHT	ASCITES	ENCEPH	HAEMOGLOBIN	PT	CONTROL	BILIRUBIN	SGOT	SGPT	GGT	A.P.	ALBUMIN	GLOBULIN	CREATINE	AL/D	FOLLOWUP	HIST	CHILD
002	2	0	74	43	0	0	0	0	1	11.4	15	15	20	20	14	128	213	36	30	122	2	15	2	1
017	2	1	69	73	6	0	0	0	0	12.6	15	15	11	105	61	58	147	34	32	81	1	39	2	1
032	2	0	39	45	0	0	3	1	1	11.4	20	15	59	33	52	0	85	28	27	59	2	17	2	3
050	2	0	44	94	0	0	0	0	0	14.0	13	14	5	56	116	96	92	36	25	84	1	30	1	1
059	2	0	50	46	0	0	0	0	0	13.3	14	14	7	64	55	354	400	44	23	68	1	29	1	1
067	2	0	56	70	0	0	0	0	0	15.7	11	13	11	32	3	714	180	35	24	71	1	29	1	1
074	2	0	63	50	1	0	0	0	0	14.6	13	15	8	34	24	36	94	46	25	110	1	28	2	1
080	2	0	57	50	0	0	0	0	0	14.4	15	14	12	23	21	12	67	41	25	110	1	28	1	1
108	2	1	25	82	6	7	1	1	0	11.2	18	14	59	84	68	68	252	24	50	144	1	26	2	2
111	2	1	58	63	2	0	0	1	1	12.8	25	13	54	177	198	57	241	21	64	82	2	4	2	3
150	2	0	63	57	4	0	0	1	0	10.0	28	14	70	299	174	143	233	16	89	67	2	1	2	3
191	2	0	45	57	0	0	0	0	0	12.6	17	14	45	998	645	134	332	32	55	61	3	14	2	2
004	3	1	39	65	9	4	2	1	1	7.7	18	14	48	147	19	483	225	28	54	63	1	40	2	3

NO	DIAGNOSIS	SEX	AGE	WT	LIVER	SPLEEN	PHT	ASCITES	ENCEPH	HAEMOGLOBIN	PT	CONTROL	BILIRUBIN	SGOT	SGPT	GGT	A.P.	ALBUMIN	GLOBULIN	CREATININE	AL/D	FOLLOWUP	HIST	CHILD
006	3	0	50	82	8	3	2	0	0	13.3	18	14	65	454	376	172	84	35	41	91	2	32	2	2
010	3	1	58	84	0	0	2	1	0	15.0	14	14	9	25	20	222	104	41	38	127	3	20	2	1
012	3	1	36	75	4	0	0	1	1	16.2	15	15	85	288	193	3000	116	40	31	0	1	28	1	2
015	3	0	39	58	12	0	0	1	0	10.0	18	15	61	96	33	943	232	31	44	42	1	40	1	3
016	3	0	65	59	4	0	2	0	1	11.9	16	15	49	130	75	873	197	35	34	85	2	32	2	2
023	3	1	51	76	4	3	1	0	0	13.3	13	15	35	65	55	484	153	41	33	114	1	38	2	2
024	3	0	58	46	6	0	0	0	0	12.2	13	13	16	74	53	319	118	33	29	111	3	35	1	1
025	3	1	62	79	4	2	2	1	1	11.0	16	15	45	51	26	88	112	32	22	0	2	24	2	3
027	3	1	48	77	6	0	0	1	1	12.1	37	15	109	176	76	56	227	26	54	63	1	38	2	3
029	3	0	54	43	0	0	0	1	1	12.8	15	15	34	58	25	146	189	26	34	110	1	37	2	3
038	3	1	62	75	2	0	2	0	0	12.4	16	14	63	90	44	225	205	28	41	85	1	11	2	3
051	3	1	51	71	14	0	0	0	0	15.7	15	15	34	84	52	882	132	38	31	95	1	32	2	1
052	3	0	64	67	1	0	0	0	0	12.0	18	15	26	261	189	125	296	25	52	111	1	31	2	2

NO	DIAGNOSIS	SEX	AGE	WT	LIVER	SPLEEN	PHT	ASCITES	ENCEPH	HAEMOGLOBIN	PT	CONTROL	BILIRUBIN	SGOT	SGPT	GGT	A.P.	ALBUMIN	GLOBULIN	CREATINE	AL/D	FOLLOWUP	HIST	CHILD
053	3	0	66	37	0	0	0	0	0	13.3	13	14	11	25	13	106	116	41	17	85	3	27	1	1
056	3	0	40	70	6	1	0	1	0	12.0	20	15	37	55	11	236	219	22	44	83	1	30	2	3
060	3	1	52	70	0	0	0	0	0	17.0	12	15	7	19	13	52	94	44	25	0	1	41	1	1
061	3	0	51	46	2	0	0	1	1	12.2	19	15	74	56	36	111	206	22	32	95	1	29	2	3
063	3	1	68	71	2	7	0	1	0	13.0	15	14	30	35	24	54	93	39	42	111	2	4	2	1
070	3	1	30	71	0	0	0	0	0	15.7	13	12	11	60	113	1140	185	39	28	110	1	29	1	1
073	3	1	49	76	3	0	0	0	0	15.7	15	14	13	39	44	125	64	43	33	80	1	31	1	1
076	3	0	62	51	0	0	0	1	1	13.5	21	15	115	166	62	278	226	28	40	57	2	1	2	3
087	3	1	62	63	7	0	0	0	0	12.8	14	14	10	29	34	600	214	33	40	76	1	27	1	1
094	3	1	61	78	0	0	2	1	1	13.1	16	14	30	49	8	48	23	29	27	110	2	4	2	3
098	3	1	63	61	2	0	0	0	0	13.3	14	15	15	235	264	579	548	30	52	80	1	25	2	1
100	3	1	43	60	5	0	0	0	0	13.4	14	14	24	46	26	1331	247	30	27	89	1	28	1	1
112	3	1	29	88	7	0	1	0	0	13.0	17	13	48	154	123	338	101	42	38	70	1	24	2	1

NO	DIAGNOSIS	SEX	AGE	WT	LIVER	SPLEEN	PHT	ASCITES	ENCEPH	HAEMOGLOBIN	PT	CONTROL	BILIRUBIN	SGOT	SGPT	GGT	A.P.	ALBUMIN	GLOBULIN	CREATINE	AL/D	FOLLOWUP	HIST	CHILD
123	3	0	51	44	5	0	0	1	1	10.3	18	13	21	85	43	79	110	27	49	140	1	23	2	2
127	3	1	50	98	0	0	0	1	1	13.7	23	15	326	181	128	62	236	29	31	115	2	1	2	3
128	3	1	37	94	0	0	0	0	0	12.7	13	13	8	135	302	206	61	50	25	96	1	22	1	1
135	3	1	60	66	4	0	2	0	0	12.6	17	15	59	52	21	260	121	28	32	88	1	4	2	2
139	3	1	56	80	0	0	1	1	0	10.9	20	14	49	49	26	35	131	21	58	81	2	1	2	3
143	3	1	57	71	0	0	2	1	1	9.7	16	14	112	21	12	33	136	25	41	62	1	19	2	2
144	3	1	61	60	0	0	0	1	1	11.3	21	14	438	123	66	261	210	23	65	82	2	1	2	3
145	3	1	46	55	2	0	1	0	0	14.3	17	13	44	45	33	29	104	42	32	76	1	13	2	1
146	3	1	56	92	0	0	0	1	1	12.9	13	14	22	33	40	209	121	45	31	81	1	19	1	1
147	3	0	63	55	0	0	1	1	1	15.6	16	14	58	55	33	165	226	24	41	81	1	19	1	1
148	3	1	59	46	6	0	0	0	0	14.2	14	14	25	85	70	324	99	41	24	95	1	16	1	1
151	3	1	53	56	6	0	0	0	0	12.7	14	14	133	155	69	2448	531	29	26	65	1	19	2	2
152	3	1	61	71	0	0	0	1	1	10.6	21	14	57	48	22	34	103	21	59	113	2	3	2	3

NO	DIAGNOSIS	SEX	AGE	WT	LIVER	SPLEEN	PHT	ASCITES	ENCEPH	HAEMOGLOBIN	PT	CONTROL	BILIRUBIN	SGOT	SGPT	GGT	A.P.	ALBUMIN	GLOBULIN	CREATININE	AL/D	FOLLOWUP	HIST	CHILD
156	3	0	38	42	3	0	0	1	0	8.7	17	14	10	27	13	226	209	36	36	65	1	4	2	1
157	3	0	38	42	3	0	0	1	0	8.7	17	14	10	27	13	226	209	36	36	65	1	4	2	1
158	3	1	61	59	4	0	0	0	0	13.9	14	14	21	59	98	482	433	34	33	0	1	3	1	1
159	3	0	0	95	2	3	2	1	1	13.2	17	14	78	69	102	234	107	25	20	136	2	10	2	3
165	3	1	53	77	10	2	1	1	1	12.1	17	13	5	25	70	52	49	34	26	72	1	23	2	2
168	3	1	52	77	6	0	2	0	0	10.0	19	14	103	76	25	107	53	28	45	106	1	3	2	2
201	3	1	41	85	0	0	0	1	1	12.3	21	14	420	74	33	246	381	23	66	126	1	24	2	3
203	3	0	61	44	0	0	0	0	0	12.2	15	14	14	85	45	137	118	33	28	58	1	13	2	1
205	3	1	67	79	0	0	2	0	0	12.6	14	14	20	36	20	53	145	28	44	93	2	16	2	1
210	3	0	48	51	0	5	1	1	1	11.9	17	14	231	119	59	459	219	34	27	145	2	3	1	3
214	3	1	35	58	0	0	2	0	1	11.6	0	0	28	53	33	0	114	40	0	96	1	21	2	2
220	3	1	41	58	6	0	0	0	0	14.7	13	14	14	98	98	122	124	53	20	79	1	18	1	1
221	3	1	69	67	5	0	0	0	0	10.9	12	14	8	57	28	178	107	33	24	57	1	18	1	1

NO	DIAGNOSIS	SEX	AGE	WT	LIVER	SPLEEN	PHT	ASCITES	ENCEPH	HAEMOGLOBIN	PT	CONTROL	BILIRUBIN	SGOT	SGPT	GGT	A.P.	ALBUMIN	GLOBULIN	CREATINE	AL/D	FOLLOWUP	HIST	CHILD
222	3	1	54	67	0	0	0	0	0	16.0	13	14	16	132	86	84	14	39	24	75	1	17	1	1
223	3	0	35	70	5	0	0	0	0	11.1	13	14	21	39	22	810	81	43	33	74	1	17	1	1
224	3	1	24	58	0	0	0	0	0	13.5	13	14	7	141	138	90	79	44	29	74	1	16	1	1
225	3	1	59	70	3	2	1	1	0	11.8	15	12	15	41	34	113	87	37	40	110	1	18	2	1
227	3	1	28	60	0	0	0	1	1	12.9	15	14	6	39	2	202	90	42	32	89	1	16	2	1
229	3	1	65	65	0	2	2	0	0	12.0	20	14	22	26	29	41	99	31	48	99	1	14	2	2
230	3	1	55	90	10	10	0	0	0	11.7	19	14	18	67	70	93	162	33	33	64	1	14	2	2
233	3	0	40	73	0	0	0	1	1	12.8	26	15	201	174	46	54	153	21	40	111	2	0	1	3
236	3	1	59	38	5	0	1	0	0	11.5	12	14	7	95	31	540	234	32	27	50	1	3	1	1
789	3	0	67	70	0	0	0	0	0	13.4	14	14	5	20	22	37	71	38	26	45	1	33	1	4
798	3	0	42	75	0	0	0	0	0	13.3	15	15	6	13	1	16	167	46	37	67	1	33	1	4
005	4	1	58	78	0	6	2	0	0	11.0	18	15	57	23	24	16	42	33	22	115	2	28	1	1
014	6	0	64	49	0	0	3	0	1	12.0	15	15	20	58	8	77	72	32	28	89	2	14	2	2

NO	DIAGNOSIS	SEX	AGE	WT	LIVER	SPLEEN	PHT	ASCITES	ENCEPH	HAEMOGLOBIN	PT	CONTROL	BILIRUBIN	SGOT	SGPT	GGT	A.P.	ALBUMIN	GLOBULIN	CREATINE	A/D	FOLLOWUP	HIST	CHILD
026	6	0	64	49	0	0	3	0	1	12.0	15	15	20	58	8	77	72	32	28	89	2	14	2	2
069	6	1	42	65	0	2	2	0	0	13.2	14	14	12	57	48	37	101	37	25	113	1	29	2	1
077	6	1	37	67	0	0	2	0	0	12.8	14	14	33	86	92	115	70	42	21	90	1	28	2	1
086	6	1	62	76	3	0	0	1	1	10.0	16	15	36	127	87	157	314	20	35	113	2	12	2	3
093	6	0	53	93	0	0	2	1	1	13.6	14	14	11	0	13	62	88	35	47	69	1	26	2	1
034	7	1	45	72	5	2	0	0	0	16.1	14	15	4	87	180	68	306	41	27	0	1	36	1	1
312	7	1	49	67	0	0	0	0	0	12.2	13	14	8	34	74	80	104	46	23	111	1	14	1	1
036	8	1	60	80	4	0	0	0	0	14.6	14	15	8	80	166	39	55	39	23	0	1	32	2	1
037	8	1	54	65	3	0	0	0	0	12.9	14	14	5	52	78	51	97	43	33	72	1	35	2	1
075	9	0	56	57	0	0	0	0	0	14.1	12	15	14	29	60	109	180	40	35	110	1	28	1	1
101	9	1	21	58	0	0	0	0	0	12.7	15	13	28	320	720	63	111	38	23	77	1	25	1	1
132	9	0	0	62	0	0	0	1	1	12.1	13	14	5	41	94	197	352	39	29	57	1	21	1	1
007	100	1	66	53	0	0	0	0	0	15.6	15	14	9	24	17	4	84	35	31	111	1	40	3	4

NO	DIAGNOSIS	SEX	AGE	WT	LIVER	SPLEEN	PHT	ASCITES	ENCEPH	HAEMOGLOBIN	PT	CONTROL	BILIRUBIN	SGOT	SGPT	GGT	A.P.	ALBUMIN	GLOBULIN	CREATININE	AL/D	FOLLOWUP	HIST	CHILD
008100	1	71	53	0	0	0	0	0	11.7	14	15	9	40	21	15	79	37	27	76	1	40	3	4
013100	0	79	35	0	0	0	0	0	13.6	13	14	14	24	35	24	100	40	0	0	1	25	3	4
018100	1	67	61	0	0	0	0	0	17.1	14	14	22	31	48	75	42	42	28	129	1	38	3	4
020100	1	69	90	0	0	0	0	0	14.3	14	14	8	31	47	33	74	40	28	110	1	38	3	4
030100	0	74	64	0	0	0	0	0	12.7	14	15	13	23	27	71	82	43	23	84	1	36	3	4
041100	0	74	64	0	0	0	0	0	12.8	15	15	15	29	27	8	80	40	25	0	1	35	3	4
043100	0	42	63	0	0	0	0	0	13.2	15	14	6	13	19	0	48	44	22	60	1	38	3	4
082100	1	67	60	0	0	0	0	0	14.5	14	15	11	20	2	9	78	41	21	98	1	27	3	4
114100	0	54	75	0	0	0	0	0	12.4	13	14	5	39	41	24	130	41	27	93	1	24	3	4
115100	1	65	83	1	0	0	0	0	15.0	14	14	5	22	40	23	62	40	24	110	1	10	3	4
121100	0	54	64	0	0	0	0	0	14.2	14	14	12	34	25	23	104	42	23	74	1	24	3	4
141100	1	30	73	0	0	0	0	0	14.1	14	14	11	23	25	23	76	42	0	0	1	16	3	4
169100	0	45	70	0	0	0	0	0	14.7	14	14	9	23	34	25	121	43	23	76	1	24	3	4

NO	DIAGNOSIS	SEX	AGE	WT	LIVER	SPLEEN	PHT	ASCITES	ENCEPH	HAEMOGLOBIN	PT	CONTROL	BILIRUBIN	SGOT	SGPT	GGT	A.P.	ALBUMIN	GLOBULIN	CREATINE	AL/D	FOLLOWUP	HIST	CHILD
207100	1	43	63	0	0	0	0	0	18.1	0	0	9	18	20	29	45	0	0	81	1	22	3	4	
208100	1	52	58	0	0	0	0	0	15.3	0	0	11	28	31	31	105	47	0	94	1	22	3	4	
209100	0	35	36	0	0	0	0	0	14.1	0	0	11	20	11	12	95	40	0	71	1	22	3	4	
211100	1	42	67	0	0	0	0	0	14.9	0	0	11	29	32	24	101	24	0	92	1	22	3	4	
212100	1	52	82	0	0	0	0	0	15.6	0	0	7	22	24	16	75	46	0	86	1	22	3	4	
215100	1	46	71	0	0	0	0	0	15.4	0	0	7	22	24	16	75	46	0	86	1	21	3	4	
216100	1	55	57	0	0	0	0	0	14.3	0	0	8	20	15	29	68	44	0	94	1	21	3	4	
226100	1	47	67	0	0	0	0	0	12.8	14	14	12	13	13	62	62	42	29	63	1	17	3	4	
232100	0	0	40	0	0	0	0	0	12.1	14	13	7	18	0	12	53	43	23	79	1	3	4	4	
234100	0	65	56	0	0	0	0	0	13.9	14	14	6	28	36	26	97	38	22	75	1	3	3	4	
235100	1	20	52	0	0	0	0	0	16.4	14	14	17	46	44	15	108	42	20	81	1	3	4	4	
600100	0	72	51	0	0	0	0	0	14.0	0	0	4	37	38	74	191	40	33	0	1	36	3	4	
601100	1	48	95	0	0	0	0	0	13.7	0	0	17	56	34	48	127	48	26	96	1	32	3	4	

NO	DIAGNOSIS	SEX	AGE	WT	LIVER	SPLEEN	PHT	ASCITES	ENCEPH	HAEMOGLOBIN	PT	CONTROL	BILIRUBIN	SGOT	SGPT	GGT	A.P.	ALBUMIN	GLOBULIN	CREATINE	AL/D	FOLLOWUP	HIST	CHILD
722100	0	72	85	0	0	0	0	0	0.0	14	14	7	34	36	23	106	42	30	0	1	31	3	4
773100	1	59	65	0	0	0	0	0	14.3	0	0	5	16	22	50	115	36	32	80	1	32	3	4
775100	1	60	70	0	0	0	0	0	12.2	14	15	5	38	17	31	73	40	40	110	1	33	1	1
777100	1	37	70	0	0	0	0	0	15.2	0	0	7	33	73	93	72	45	20	99	1	33	3	4
778100	0	45	75	0	0	0	0	0	12.8	0	0	6	21	28	16	64	41	23	80	1	35	3	4
779100	0	44	50	0	0	0	0	0	14.6	0	0	7	0	28	5	87	45	22	90	1	34	3	4
780100	0	62	80	0	0	0	0	0	15.4	0	0	20	0	33	27	101	47	31	77	1	34	3	4
781100	1	41	90	0	0	0	0	0	15.8	0	0	7	33	56	56	66	76	22	88	1	34	3	4
783100	0	65	58	0	0	0	0	0	0.0	0	0	13	18	18	21	74	43	0	0	1	33	3	4
784100	1	58	80	0	0	0	0	0	16.9	0	0	7	25	29	23	80	38	29	10	1	35	3	4
785100	0	56	59	0	0	0	0	0	0.0	0	0	26	23	29	28	63	39	0	0	1	33	3	4
786100	0	47	75	0	0	0	0	0	13.0	13	14	9	11	23	27	126	41	26	77	1	34	3	4

REPORT 2

NO.	DATE	T 1/2	CORR ELAT	VOL DI	V/KG	TOT B.	CL/KG	HISTOLOGY	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
<----------ANTIPYRINE---------->																									
001	11-01-81	15.55	1.00	27.10	0.57	20.14	3.00	00-00-82	0	0	1	0	0	0	0	1	1	0	1	0	0	0	0	0	0
003	11-04-81	38.09	1.00	22.47	0.38	6.81	0.12	00-00-77	0	0	1	0	0	0	0	1	1	0	0	1	0	0	0	0	0
011	11-09-81	5.70	1.00	26.19	0.48	53.05	0.98	00-00-82	0	0	1	0	0	0	0	1	1	1	0	0	1	0	0	0	0
019	01-09-82	16.04	0.99	26.68	0.49	19.22	0.35	00-00-81	1	0	0	0	0	0	0	1	1	0	1	0	0	0	0	0	0
028	02-02-82	7.23	0.99	24.03	0.32	38.40	0.51	00-00-82	0	1	0	0	0	0	0	1	1	0	0	1	0	0	1	0	0
035	04-27-82	19.94	0.99	31.98	0.48	18.52	0.28	00-00-82	0	1	0	0	0	0	0	1	1	0	1	0	0	0	0	0	0
045	05-02-92	14.98	0.98	32.08	0.46	24.74	0.35	00-00-78	1	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0
047	00-00-82	21.80	1.00	25.57	0.51	13.55	0.27	83-82-62	0	0	1	0	0	0	0	1	1	0	0	1	0	0	1	0	1
048	10-05-82	6.09	1.00	18.08	0.37	34.30	0.70	00-00-79	0	1	0	0	0	0	0	1	1	0	1	0	0	0	1	0	0
054	02-12-82	10.14	0.99	38.63	0.64	44.01	0.73	01-12-83	0	1	0	0	0	0	0	0	1	0	1	0	0	0	0	0	0
055	11-26-82	11.21	0.99	24.21	0.52	24.96	0.53	11-26-82	1	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0
057	11-24-82	8.75	1.00	26.56	0.58	35.06	0.76	18-63-82	0	1	0	0	0	0	0	1	1	0	1	0	0	0	0	0	0

NO.	DATE	T 1/2	CORR ELAT	VOL DI	V/KG	TOT B.	CL/KG	HISTOLOGY	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
<----------ANTIPYRINE---------->																									
058	10-11-82	19.23	0.99	25.15	0.44	15.11	0.27	88-60-82	0	0	1	0	0	0	0	1	1	0	0	1	0	0	0	0	0
062	11-24-82	11.54	0.99	31.21	0.50	31.25	0.50	82-52-41	0	1	0	0	0	0	0	1	1	0	1	0	0	0	0	0	0
068	99-99-99	0.00	0.00	0.00	0.00	0.00	0.00	99-99-99	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
071	11-09-82	10.73	0.99	20.96	0.43	22.34	0.46	41-52-82	0	1	0	0	0	0	0	1	1	0	1	0	0	0	0	0	0
072	12-14-82	15.93	0.96	35.56	0.57	25.78	0.42	14-12-82	1	0	0	0	0	0	0	1	0	0	1	0	0	0	0	0	0
079	11-27-82	12.12	0.96	28.37	0.39	27.04	0.37	77-00-00	0	1	0	0	1	0	0	0	0	0	1	0	0	0	0	0	0
130	99-99-99	0.00	0.00	0.00	0.00	0.00	0.00		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
133	11-02-84	8.93	1.00	17.33	9.27	22.41	0.35	83-75-86	0	1	0	0	0	0	0	1	1	0	1	0	0	0	0	0	0
134	09-05-84	7.00	1.00	13.92	0.21	22.95	0.35	82-53-06	0	1	0	0	0	0	0	1	0	0	1	0	0	0	0	0	0
138	10-26-84	12.49	1.00	12.95	0.18	11.97	0.17	84-64-31	0	0	1	0	0	0	0	1	1	0	1	0	0	0	0	0	0
153	08-23-83	13.79	0.99	28.13	0.48	23.56	0.41	82-34-80	1	0	0	0	0	0	0	1	1	0	1	0	0	0	0	0	0
154	01-02-85	10.40	1.00	10.67	0.18	11.83	0.20		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
228	07-09-83	17.36	0.99	35.94	0.48	23.90	0.32	83-83-62	1	0	0	0	0	0	0	1	0	0	1	0	0	0	1	0	0
002	11-05-81	24.19	1.00	17.81	0.41	8.51	0.20	02-15-81	0	0	1	0	0	0	0	1	1	0	1	0	0	0	1	0	0

NO.	DATE	T 1/2	CORR ELAT	VOL DI	V/KG	TOT B.	CL/KG	HISTOLOGY	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
<----------ANTIPYRINE---------->																									
017	12-06-81	23.28	0.98	33.17	0.46	16.46	0.23	78-42-81	0	0	1	0	0	0	0	1	1	0	0	1	0	0	1	0	1
032	11-28-82	31.33	1.00	24.30	0.54	8.96	0.20		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
050	09-10-82	11.76	1.00	27.77	0.40	27.73	0.39	82-57-03	1	0	0	0	0	0	0	1	0	0	0	0	0	0	1	0	0
059	10-14-82	12.05	0.99	32.23	0.78	30.80	0.75	61-62-82	1	0	0	0	0	0	0	1	1	0	1	0	0	0	0	0	0
067	10-18-82	9.72	1.00	33.32	0.48	39.62	0.57	47-64-82	1	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0
074	11-17-82	10.51	1.00	25.91	0.52	28.49	0.57	96-70-82	0	1	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0
080	11-28-82	11.55	1.00	28.73	0.36	28.73	0.36	28-11-83	1	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0
108	03-01-83	24.55	0.96	27.15	0.33	12.78	0.16	99-99-99	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
111	03-17-83	15.50	0.94	64.22	1.20	47.80	0.84	83-20-97	0	0	1	0	0	0	0	1	0	0	1	0	0	0	0	1	0
150	12-01-84	76.31	0.99	30.08	0.53	4.55	0.08	84-08-34	0	0	1	0	0	0	0	0	1	0	0	1	0	0	0	0	0
191	10-19-83	32.26	0.98	31.34	0.55	11.22	0.20	83-69-34	0	0	1	0	0	0	0	0	1	1	0	0	0	1	0	0	0
004	11-16-81	50.33	0.98	33.17	0.51	7.61	0.12	00-00-78	0	1	0	0	0	0	0	1	1	0	0	1	0	0	1	0	1
006	11-17-81	35.36	0.94	48.08	0.59	15.71	0.19	63-76-81	0	0	1	0	0	0	0	1	1	0	0	0	0	1	1	0	0
010	11-16-81	30.50	1.00	33.48	0.40	12.67	0.15	81-02-70	0	0	1	0	0	0	0	1	1	1	0	0	1	0	0	0	1

NO.	DATE	T 1/2	CORR ELAT	VOL DI	V/KG	TOT B.	CL/KG	HISTOLOGY	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
<----------ANTIPYRINE---------->																									
012	11-25-81	31.91	0.99	33.18	0.44	12.01	0.16	61-80-81	0	1	0	0	0	0	1	1	0	0	0	1	0	0	1	0	1
015	11-19-81	32.59	1.00	25.68	0.44	9.10	0.16	36-41-81	0	1	0	0	0	0	1	0	0	0	0	0	0	1	1	0	1
016	12-02-81	14.94	1.00	28.38	0.48	21.94	0.37	57-80-81	0	0	1	0	0	0	0	1	0	0	0	0	0	1	0	1	0	0
023	01-20-82	20.35	1.00	37.47	0.49	21.27	0.28	96-01-81	0	0	1	0	0	0	0	1	0	1	0	0	0	1	1	0	1
024	01-20-82	12.57	1.00	20.40	0.44	18.75	0.41	96-04-82	1	0	0	0	0	0	0	1	0	0	1	0	0	0	1	0	0
025	10-13-82	21.12	0.97	35.67	0.45	19.51	0.24	42-25-81	0	0	1	0	0	0	0	0	1	0	1	0	0	0	0	0	0
027	01-22-82	60.23	1.00	47.44	0.62	9.10	0.12		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
029	02-22-82	23.04	0.99	21.81	0.51	10.94	0.25	27-10-82	0	0	1	0	0	0	0	1	0	1	0	0	1	0	1	1	1
038	04-28-84	39.29	0.99	25.52	0.34	7.50	0.10		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
051	07-11-82	21.10	1.00	39.04	0.55	21.37	0.30	00-00-82	0	0	1	0	0	0	1	1	1	0	0	0	1	0	1	0	1
052	99-99-99	0.00	0.00	0.00	0.00	0.00	0.00	08-07-82	0	0	1	0	0	0	0	1	1	0	0	0	1	0	1	0	0
053	07-12-82	7.76	1.00	16.24	0.44	24.18	0.65		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
056	09-23-82	30.70	0.99	31.09	0.44	11.70	0.17	20-10-82	0	0	1	0	0	0	0	1	1	0	0	1	0	0	1	0	1
060	10-20-82	26.07	0.99	33.25	0.48	14.74	0.21		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

NO.	DATE	T 1/2	CORR ELAT	VOL DI	V/KG	TOT B.	CL/KG	HISTOLOGY	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
<----------ANTIPYRINE---------->																									
061	10-27-82	26.37	0.99	15.57	0.84	6.82	0.15	37-65-82	0	0	0	1	0	0	0	0	1	0	0	0	1	0	0	0	1
063	11-10-82	18.84	0.97	30.55	0.44	18.73	0.27	06-69-82	0	0	1	0	0	0	0	1	0	0	1	0	0	0	0	0	0
070	10-21-82	31.90	0.96	37.02	0.52	13.41	0.19	10-29-82	0	1	0	0	0	0	0	1	0	0	1	0	0	0	1	0	0
073	12-08-83	7.36	0.99	33.81	0.44	53.06	0.70		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
076	11-20-83	60.39	0.94	36.35	0.71	6.95	0.14	81-04-68	0	0	1	0	0	0	0	0	1	0	0	0	3	0	1	1	0
087	99-99-99	0.00	0.00	0.00	0.00	0.00	0.00	21-12-83	0	1	0	0	0	0	0	1	1	0	1	0	0	0	1	0	0
094	02-04-83	32.63	0.99	30.35	0.39	10.75	0.14	83-08-07	0	0	1	0	0	0	0	0	1	0	1	0	0	0	1	0	1
098	02-19-83	29.88	0.92	49.60	0.81	19.18	0.31	83-10-67	1	0	0	0	0	0	0	1	0	0	1	0	0	0	0	0	1
100	01-10-83	21.14	1.00	34.39	0.56	18.78	0.31	11-02-82	0	1	0	0	0	0	0	1	1	0	1	0	0	0	1	0	0
112	03-16-83	29.65	1.00	39.46	0.45	15.38	0.17		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
123	04-13-83	20.01	0.99	28.51	0.65	16.46	0.37	83-24-00	0	0	1	0	0	0	1	1	0	0	1	0	0	0	1	0	0
127	04-20-83	14.02	1.00	51.82	0.53	42.69	0.44	99-99-99	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
128	05-27-83	4.34	0.99	24.51	0.26	65.30	0.70	82-00-00	1	0	0	0	1	0	0	0	0	0	1	0	0	0	1	0	0
135	10-30-84	32.22	1.00	27.46	0.42	9.85	0.15	99-99-99	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

NO.	DATE	T 1/2	CORR ELAT	VOL DI	V/KG	TOT B.	CL/KG	HISTOLOGY	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
<----------ANTIPYRINE---------->																									
139	09-06-83	12.08	0.99	34.15	0.43	32.64	0.41	99-99-99	0	0	0	1	0	0	0	1	0	0	0	1	0	0	0	0	0
143	08-08-83	12.87	0.98	62.81	0.84	56.38	0.75	99-99-99	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
144	18-11-83	65.22	0.94	35.12	0.59	6.22	0.10	15-12-83	0	0	1	0	0	0	1	0	0	0	0	1	0	0	0	0	0
145	02-13-84	34.50	0.98	28.01	0.51	9.39	0.17	84-09-78	0	0	0	1	0	1	0	0	0	0	1	0	0	0	0	0	1
146	08-07-83	11.78	1.00	42.59	0.45	41.78	0.44	83-51-18	0	1	0	0	0	0	0	1	1	0	1	0	0	0	1	0	0
147	08-07-83	12.26	0.98	45.94	0.84	43.28	0.79	99-99-99	0	0	1	0	0	0	0	0	1	0	0	0	1	0	0	0	0
148	11-24-83	14.78	0.99	51.78	0.68	40.55	0.53	83-80-61	0	1	0	0	0	0	0	1	0	1	0	1	0	0	1	0	1
151	21-08-83	9.08	1.00	35.30	0.63	44.91	0.80	83-54-70	0	1	0	0	0	0	1	1	0	0	0	1	0	0	1	0	1
152	11-18-83	40.51	0.96	41.79	0.59	11.92	0.17	17-11-83	0	0	1	0	0	0	1	0	0	0	0	1	0	0	0	0	1
156	27-11-84	111.50	0.99	14.33	0.28	0.00	0.03	99-99-99	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
157	11-27-84	49.92	1.00	12.72	0.30	2.94	0.07	84-82-09	0	0	0	1	0	0	0	1	0	0	0	1	0	0	1	0	0
158	06-12-84	13.39	1.00	14.50	0.25	12.51	0.21	84-85-06	0	1	0	0	0	0	0	1	0	0	0	0	1	0	1	0	0
159	04-17-84	16.34	1.00	19.83	0.25	14.01	0.18	99-99-99	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
165	04-13-83	18.55	0.98	47.98	0.62	29.89	0.39	04-13-83	0	0	1	0	0	1	0	0	1	0	0	1	0	0	0	0	1

NO.	DATE	T 1/2	CORR ELAT	VOL DI	V/KG	TOT B.	CL/KG	HISTOLOGY	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
<----------ANTIPYRINE---------->																									
168	99-99-99	0.00	0.00	0.00	0.00	0.00	0.00	99-99-99	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
201	23-03-83	17.18	0.97	93.40	1.10	62.79	0.74	83-27-41	0	0	1	0	0	0	0	1	0	1	0	0	1	0	1	1	1
203	99-99-99	0.00	0.00	0.00	0.00	0.00	0.00	84-02-02	0	0	1	0	0	0	0	1	0	1	0	0	1	0	1	1	1
205	99-99-99	0.00	0.00	0.00	0.00	0.00	0.00	99-99-99	0	0	0	1	0	0	1	0	0	0	0	1	0	0	1	0	0
210	24-05-83	16.24	0.98	64.57	1.20	45.93	0.88	83-84-88	0	1	0	0	0	0	0	1	0	1	0	1	0	0	1	1	1
214	06-07-83	17.02	0196	53.31	0.92	36.17	0.62	83-37-78	0	0	1	0	0	0	0	1	0	0	0	1	0	0	1	0	1
220	09-08-83	10.56	0.98	43.22	0.75	47.26	0.81	83-59-76	1	0	0	0	1	0	0	0	0	0	0	0	0	0	0	1	1	0
221	08-09-83	14.89	0.98	24.64	0.40	19.11	0.31	83-59-77	0	1	0	0	0	0	1	1	0	1	0	0	1	0	1	1	1
222	15-09-83	12.26	0.98	48.74	0.73	45.89	0.68	83-61-67	1	0	0	0	0	0	0	1	0	0	1	0	0	0	1	0	0
223	10-10-84	9.32	0.99	25.38	0.36	31.43	0.45	10-10-83	1	0	0	0	1	0	0	0	0	0	1	0	0	0	1	0	0
224	01-27-84	9.26	1.00	35.42	0.57	44.18	0.71	83-69-62	1	0	0	0	0	0	0	1	0	0	1	0	0	0	1	0	0
225	01-04-84	11.76	1.00	37.04	0.53	36.36	0.52	83-30-12	0	0	1	0	0	0	0	1	1	0	1	0	0	0	0	0	0
227	11-28-84	15.89	0.99	37.17	0.62	27.01	0.45	83-42-54	0	0	1	0	0	0	0	1	1	0	1	0	0	0	1	0	0
229	01-12-84	25.00	1.00	33.43	0.51	15.47	0.24	99-99-99	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

NO.	DATE	T 1/2	CORR ELAT	VOL DI	V/KG	TOT B.	CL/KG	HISTOLOGY	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
<----------ANTIPYRINE---------->																									
230	01-18-84	46.46	0.99	45.78	0.51	11.38	0.13	99-99-99	0	0	1	0	0	1	1	0	0	0	0	1	0	0	1	0	0
233	99-99-99	0.00	0.00	0.00	0.00	0.00	0.00		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
236	99-99-99	0.00	0.00	0.00	0.00	0.00	0.00	01-28-85	0	1	0	0	0	0	0	1	0	0	0	1	0	0	1	0	0
789	06-09-82	14.44	1.00	30.78	0.45	24.62	0.36	00-00-82	1	0	0	0	0	0	0	1	0	0	1	0	0	0	1	0	0
798	06-02-82	14.00	1.00	37.37	0.50	30.81	0.41	74-50-82	1	0	0	0	1	0	0	0	0	0	0	0	0	0	0	1	0	0
005	11-09-81	19.55	1.00	38.79	0.50	22.47	0.29	00-00-81	1	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0
014	99-99-99	0.00	0.00	0.00	0.00	0.00	0.00	99-99-99	0	0	1	0	0	0	1	0	0	0	0	1	0	0	0	0	0
026	01-18-82	32.71	0.99	27.24	0.56	9.62	0.20		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
069	10-28-82	15.56	0.99	39.79	0.57	29.54	0.42	13-64-13	0	1	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0
077	11-18-82	15.72	1.00	33.93	0.51	24.93	0.37	11-18-82	0	1	0	0	0	0	0	1	1	0	1	0	0	0	1	0	0
086	12-07-82	58.21	0.93	56.96	0.75	11.30	0.15	44-37-82	0	0	1	0	0	0	0	1	1	0	1	0	0	0	0	0	1
093	01-23-83	15.42	1.00	22.09	0.24	16.54	0.18	01-20-83	0	0	1	0	0	0	0	1	1	0	1	0	0	0	1	0	0
034	03-31-82	12.17	1.00	25.65	0.37	24.34	0.35	40-23-82	0	1	0	0	0	0	0	0	1	0	1	0	0	0	1	0	1
312	01-07-84	15.56	1.00	33.02	0.49	24.51	0.37	84-17-74	1	0	0	0	0	0	0	1	0	0	0	0	0	0	1	0	0

NO.	DATE	T 1/2	CORR ELAT	VOL DI	V/KG	TOT B.	CL/KG	HISTOLOGY	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
<----------ANTIPYRINE---------->																									
036	07-27-82	20.78	0.98	40.98	0.51	11.74	0.28	00-00-82	0	0	1	0	0	0	0	1	1	0	1	0	0	0	1	1	0
037	04-28-82	10.04	1.00	31.62	0.49	36.40	0.56	93-47-81	0	0	1	0	0	0	0	1	1	0	1	0	0	0	0	1	0
075	11-19-82	17.91	1.00	30.15	0.53	19.45	0.34	05-71-82	1	0	0	0	0	0	0	1	0	0	1	0	0	0	1	0	0
101	02-25-83	8.03	0.99	18.43	0.32	26.51	0.46	20-02-83	1	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0
132	06-01-83	9.86	0.99	50.05	0.81	58.64	0.95	83-32-75	1	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0
007	11008-81	11.79	0.00	27.95	0.47	27.38	0.46	99-99-99	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
008	11-06-81	11.65	1.00	22.18	0.42	21.99	0.41	99-99-99	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
013	02-08-83	8.24	1.00	25.76	0.74	36.10	1.03		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
018	01-04-82	16.58	0.99	34.65	0.57	24.15	0.40	99-99-99	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
020	01-20-82	10.04	0.96	44.85	0.50	51.60	0.57	99-99-99	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
030	03-02-82	7.56	1.00	23.78	0.40	36.34	0.61		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
041	04-28-82	15.95	0.97	26.74	0.42	19.36	0.30		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
043	00-00-82	15.69	1.00	29.51	0.47	21.72	0.35		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
082	12-01-82	15.09	1.00	24.54	0.42	26.43	0.32		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

NO.	DATE	T 1/2	CORR ELAT	VOL DI	V/KG	TOT B.	CL/KG	HISTOLOGY	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
<----------ANTIPYRINE---------->																									
114	12-18-83	8.65	1.00	25.88	0.43	34.56	0.58		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
115	05-08-84	6.48	0.98	16.66	0.20	29.69	0.36	99-99-99	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
121	06-09-83	18.20	1.00	38.52	0.60	24.45	0.38		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
141	29-11-84	11.71	0.99	39.97	0.55	39.42	0.54		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
141	02-12-83	14.60	0.97	47.53	0.65	37.61	0.52		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
169	30-03-83	18.20	1.00	38.52	0.60	24.45	0.38	99-99-99	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
207	05-10-83	12.66	0.99	32.44	0.51	29.60	0.47		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
208	05-16-83	6.40	0.97	40.47	0.70	72.85	1.26		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
209	05-24-83	12.67	0.96	43.73	1.20	39.86	1.10		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
211	05-31-83	9.38	0.99	43.11	0.64	53.12	0.79		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
212	05-31-83	5.99	0.99	30.51	0.37	58.87	0.72		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
215	06-14-83	12.21	0.99	62.13	0.88	58.76	0.83		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
216	06-14-83	12.31	0.94	48.21	0.85	45.21	0.83		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
226	11-01-83	10.38	1.00	26.16	0.39	29.10	0.43		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

NO.	DATE	T 1/2	CORR ELAT	VOL DI	V/KG	TOT B.	CL/KG	HISTOLOGY	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
<----------ANTIPYRINE---------->																									
232	99-99-99	0.00	0.00	0.00	0.00	0.00	0.00	99-99-99	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
234	99-99-99	0.00	0.00	0.00	0.00	0.00	0.00	99-99-99	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
235	99-99-99	0.00	0.00	0.00	0.00	0.00	0.00	99-99-99	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
600	03-22-82	11.05	0.99	29.27	0.57	30.59	0.60	47-52-82	1	0	0	0	1	0	0	0	0	0	1	0	0	0	0	0	0
601	99-99-99	0.00	0.00	0.00	0.00	0.00	0.00	99-99-99	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
722	08-24-82	10.25	0.99	37.81	0.44	42.61	0.50	99-99-99	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
773	07-06-82	5.80	0.00	35.86	0.55	71.38	1.10	99-99-99	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
775	06-19-82	18.30	1.00	38.98	0.56	24.60	0.35	50-49-82	1	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0
777	99-99-99	8.70	1.00	89.40	0.97	40.00	0.57	99-99-99	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
778	02-27-82	14.43	1.00	30.40	0.41	24.34	0.33	99-99-99	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
779	05-05-82	12.30	0.97	37.70	0.75	35.37	0.71	99-99-99	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
780	05-05-82	11.40	0.99	36.00	0.45	36.32	0.46	99-99-99	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
781	05-05-82	12.60	0.94	59.90	0.67	54.84	0.61	99-99-99	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
783	06-04-82	14.90	0.00	33.49	0.56	25.40	0.43	99-99-99	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

NO.	DATE	T 1/2	CORR ELAT	VOL DI	V/KG	TOT B.	CL/KG	HISTOLOGY	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
<----------ANTIPYRINE---------->																									
784	02-12-82	8.25	0.99	40.22	0.50	56.30	0.70	99-99-99	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
785	06-11-82	10.56	0.99	50.04	0.85	54.72	0.93	99-99-99	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
786	05-19-82	10.33	0.99	39.20	0.52	43.85	0.59	99-99-99	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

REPORT 3

NO.	INDOCYANINE	T 1/2	CORR	VOL DI	VOL/ KG	TOT BODY CLEARANCE	CLEAR	WB CLEARANCE	WB CL/ KG
001	00-00-81	15.29	0.97	6.12	0.140	277.40	6.45	407.90	9.49
003	11-13-81	11.74	1.00	3.00	0.060	177.30	3.41	*282.70	4.42
011	99-99-99	0.00	0.00	0.00	0.000	0.00	0.00	0.00	0.00
019	99-99-99	0.00	0.00	0.00	0.000	0.00	0.00	0.00	0.00
028	04-11-82	4.46	1.00	2.97	0.050	461.40	7.01	831.30	12.78
035	04-29-82	7.10	1.00	1.36	0.020	134.50	2.01	226.40	3.38
045	99-99-99	0.00	0.00	0.00	0.000	0.00	0.00	0.00	0.00
047	05-05-82	7.43	0.99	1.69	0.030	157.00	3.04	239.60	4.52
048	12-22-82	3.79	1.00	4.55	0.050	740.30	9.87	1656.00	22.08
054	01-12-82	4.69	1.00	4.12	0.070	609.50	10.16	1078.00	17.96
055	11-26-82	4.13	1.00	4.05	0.090	681.10	14.49	987.10	21.00
057	11-10-82	3.90	0.99	2.67	0.060	473.70	10.30	757.90	16.47
058	99-99-99	0.00	0.00	0.00	0.000	0.00	0.00	0.00	0.00

NO.	INDOCYANINE	T 1/2	CORR	VOL DI	VOL/KG	TOT BODY CLEARANCE	CLEARANCE	WB CLEARANCE	WB CL/KG
062	11-24-82	6.51	0.92	3.90	0.030	416.00	6.71	661.50	10.66
068	10-25-82	4.89	1.00	2.90	0.050	410.80	6.52	622.50	9.88
071	09-11-82	7.97	0.99	3.19	0.070	277.00	5.65	439.70	6.37
072	12-14-82	3.65	0.99	2.31	0.040	439.40	7.09	757.50	12.21
079	11-27-82	4.57	1.00	2.69	0.040	408.20	5.59	649.90	8.90
130	04-28-83	15.57	0.96	3.67	0.070	163.10	3.25	298.70	5.97
133	99-99-99	0.00	0.00	0.00	0.000	0.00	0.00	0.00	0.00
134	09-05-84	3.60	1.00	2.41	0.040	462.50	7.13	722.70	10.32
138	10-26-84	5.36	1.00	2.79	0.040	360.80	5.16	591.50	8.45
153	08-23-83	7.52	0.99	3.32	0.060	305.50	5.27	436.50	7.53
154	20-11-84	4.72	1.00	2.80	0.050	411.00	7.09	687.30	11.85
228	07-27-83	3.75	0.99	3.98	0.050	736.70	9.69	1248.00	16.42
002	99-99-99	0.00	0.00	0.00	0.000	0.00	0.00	0.00	0.00
017	12-09-81	7.70	0.99	2.80	0.040	247.30	3.43	399.50	5.51
032	11-28-82	17.80	0.97	3.03	0.060	118.10	2.41	181.70	4.04

NO.	INDOCYANINE	T 1/2	CORR	VOL DI	VOL/KG	TOT BODY CLEARANCE	CLEARANCE	WB CLEARANCE	WB CL/KG
050	09-10-92	5.13	0.99	2.09	0.020	283.10	3.03	544.30	5.79
059	10-15-82	4.42	0.99	3.10	0.070	487.00	10.83	785.80	17.08
067	10-18-82	4.07	0.99	2.51	0.040	426.30	6.09	761.30	10.87
074	11-17-82	4.64	1.00	1.79	0.040	267.70	5.35	478.00	9.56
080	11-28-82	3.15	1.00	1.35	0.050	517.50	10.35	892.30	17.84
108	03-01-83	18.17	0.99	6.13	0.070	233.10	2.85	348.80	4.25
111	03-17-83	17.47	0.98	3.46	0.050	137.10	2.18	224.80	3.57
150	12-01-84	19.20	1.00	4.68	0.080	168.90	2.97	239.70	4.21
191	10-19-83	15.88	1.00	3.50	0.060	152.90	2.68	238.10	4.18
004	11-27-81	36.55	0.99	6.07	0.080	155.10	1.54	185.10	2.85
006	01-19-83	9.29	1.00	5.24	0.060	390.80	4.77	548.80	6.69
010	11-16-81	17.56	0.99	3.13	0.030	465.30	4.50	878.00	10.45
012	11-27-81	8.29	0.99	5.35	0.070	447.40	6.05	780.80	10.41
015	11-20-81	16.72	1.00	3.35	0.060	139.00	2.40	210.70	3.63
016	02-02-83	6.30	1.00	3.26	0.060	363.30	6.86	550.50	9.33

NO.	INDOCYANINE	T 1/2	CORR	VOL DI	VOL/KG	TOT BODY CLEARANCE	CLEARANCE	WB CLEARANCE	WB CL/KG
023	01-22-82	11.26	1.00	3.90	0.050	239.90	3.16	374.80	4.93
024	99-99-99	0.00	0.00	0.00	0.000	0.00	0.00	0.00	0.00
025	01-15-82	12.59	1.00	5.01	0.060	275.60	3.45	448.80	5.68
027	01-24-82	18.33	1.00	5.06	0.070	191.40	2.49	314.80	4.09
029	99-99-99	0.00	0.00	0.00	0.000	0.00	0.00	0.00	0.00
038	04-20-84	18.89	1.00	5.26	0.070	193.10	2.58	330.10	4.40
051	06-27-82	9.21	1.00	2.23	0.030	168.10	2.40	320.20	4.51
052	00-00-82	11.71	1.00	1.39	0.020	82.51	1.23	135.30	2.02
053	99-99-99	0.00	0.00	0.00	0.000	0.00	0.00	0.00	0.00
056	09-23-82	9.23	0.99	4.13	0.060	288.30	4.06	461.30	6.59
060	10-20-81	4.58	0.99	4.63	0.060	700.10	9.79	1372.00	19.60
061	10-25-82	18.41	1.00	1.82	0.040	68.46	1.49	106.90	2.32
063	10-11-82	15.60	1.00	4.61	0.060	204.90	2.89	322.60	4.54
070	10-21-82	4.05	0.99	2.39	0.030	409.50	5.85	724.80	10.20
073	08-12-82	3.40	1.00	3.34	0.040	681.80	8.97	1363.00	17.93

NO.	INDOCYANINE	T 1/2	CORR	VOL DI	VOL/KG	TOT BODY CLEARANCE	CLEAR	WB CLEARANCE	WB CL/KG
076	11-20-82	32.91	0.99	3.00	0.060	63.12	1.24	106.10	2.08
087	12-21-82	4.13	0.99	3.89	0.060	652.20	10.35	1043.00	16.55
094	02-04-83	21.26	0.99	5.36	0.070	172.40	2.21	294.70	3.78
098	02-20-83	6.32	0.99	5.24	0.090	575.30	1.00	927.90	15.21
100	01-11-82	5.62	0.99	2.34	0.040	288.40	4.73	515.10	8.59
112	03-16-83	10.77	1.00	4.94	0.060	317.90	3.61	512.80	5.83
123	04-13-83	17.44	0.99	3.05	0.070	121.10	2.75	179.40	4.08
127	03-23-83	38.01	0.97	5.89	0.070	107.10	1.26	179.10	1.83
128	04-27-83	4.84	0.99	4.94	0.050	707.10	7.56	1214.00	12.98
135	10-31-84	14.90	1.00	4.40	0.070	204.60	3.10	324.70	4.92
139	09-06-83	18.80	1.00	5.14	0.060	189.50	2.37	284.90	3.56
143	08-04-83	15.25	0.99	8.08	0.110	367.50	4.90	574.20	8.09
144	11-18-83	57.21	0.84	4.11	0.070	48.41	0.81	78.72	1.31
145	02-13-84	9.52	1.00	3.54	O.060	257.80	4.69	409.30	7.44
146	02-13-84	6.85	0.99	6.24	0.070	631.60	6.65	986.80	10.72

NO.	INDOCYANINE	T 1/2	CORR	VOL DI	VOL/KG	TOT BODY CLEARANCE	CLEARANCE	WB CLEARANCE	WB CL/KG
147	08-07-83	27.30	0.99	3.29	0.060	83.44	1.52	154.50	2.81
148	11-24-83	6.41	1.00	3.72	0.050	401.60	5.23	647.70	14.08
151	21-08-83	4.27	0.99	3.66	0.070	594.60	10.62	868.10	15.50
152	11-18-83	31.89	1.00	4.00	0.060	87.02	1.23	138.10	1.95
156	29-11-84	30.36	1.00	3.65	0.060	83.32	1.46	136.80	2.40
157	28-11-84	11.87	1.00	3.65	0.090	213.30	5.08	291.30	6.93
158	06-12-84	5.08	1.00	2.88	0.050	393.10	6.66	677.80	11.48
159	04-16-84	19.48	1.00	1.56	0.050	162.10	11.71	243.80	2.57
165	04-13-83	28.78	1.00	4.74	0.060	114.10	1.48	178.40	2.32
168	01-22-85	13.00	1.00	7.74	0.090	359.90	4.67	514.90	6.69
201	03-23-83	38.01	0.97	5.89	0.070	107.50	1.26	179.10	2.11
203	02-28-84	10.50	0.99	2.88	0.070	189.90	4.32	316.60	7.19
205	03-05-83	70.71	0.98	4.89	0.060	47.90	0.61	83.31	1.05
210	04-24-83	27.34	0.99	3.44	0.070	87.17	1.68	119.10	2.34
214	06-07-83	14.30	1.00	3.94	0.070	190.00	3.29	282.80	4.88

NO.	INDOCYANINE	T 1/2	CORR	VOL DI	VOL/KG	TOT BODY CLEARANCE	CLEAR	WB CLEARANCE	WB CL/KG
220	09-08-83	2.70	1.00	3.08	0.050	791.10	13.63	1400.00	24.13
221	09-08-83	5.66	1.00	2.86	0.050	350.40	5.74	519.00	7.75
222	01-10-83	2.17	1.00	2.64	0.040	845.80	12.61	1483.00	22.10
223	10-10-84	3.54	1.00	2.48	0.040	486.40	6.95	721.70	10.31
224	11-12-83	2.57	0.99	2.68	0.050	721.20	12.44	1222.00	21.06
225	09-10-83	13.23	1.00	5.82	0.080	304.90	4.36	438.80	6.27
227	11-28-83	3.47	1.00	2.90	0.050	580.00	9.70	1026.00	17.10
229	01-13-84	11.80	1.00	4.41	0.070	259.20	3.99	370.30	5.70
230	01-18-84	11.08	0.99	5.50	0.060	343.90	3.82	529.10	5.88
233	01-22-85	37.52	1.00	9.22	0.130	170.30	2.35	273.70	3.78
236	01-28-85	4.24	0.99	2.01	0.050	328.70	8.65	490.60	12.91
789	06-01-82	4.30	0.98	3.95	0.060	636.00	9.79	1087.00	15.52
798	04-21-82	3.84	1.00	4.08	0.050	735.90	9.81	1226.00	16.34
005	11-09-81	4.63	0.99	2.07	0.030	310.60	3.98	429.60	5.51
014	02-10-83	17.10	1.00	3.19	0.070	129.30	2.94	202.00	4.59

NO.	INDOCYANINE	T 1/2	CORR	VOL DI	VOL/KG	TOT BODY CLEARANCE	CLEAR	WB CLEARANCE	WB CL/KG
026	99-99-99	0.00	0.00	0.00	0.000	0.00	0.00	0.00	0.00
069	11-20-82	6.51	1.00	3.06	0.050	326.60	5.02	466.50	7.18
077	00-00-82	6.45	1.00	2.76	0.040	296.90	4.50	486.70	7.26
086	12-07-82	24.78	1.00	5.59	0.080	156.40	2.11	266.70	3.51
093	99-99-99	0.00	0.00	0.00	0.000	0.00	0.00	0.00	0.00
034	99-99-99	0.00	0.00	0.00	0.000	0.00	0.00	0.00	0.00
312	01-07-84	3.88	0.99	3.06	0.050	546.60	8.16	881.70	13.15
036	09-12-82	4.29	0.99	5.67	0.070	929.90	12.08	1537.00	19.21
037	99-99-99	0.00	0.00	0.00	0.000	0.00	0.00	0.00	0.00
075	11-19-82	4.60	0.99	3.48	0.060	522.70	9.17	823.20	14.44
101	02-25-82	4.00	0.99	5.63	0.100	975.80	16.83	1629.00	28.08
132	05-27-83	2.94	0.99	5.04	0.080	1189.00	19.18	1829.00	29.50
007	99-99-99	0.00	0.00	0.00	0.000	0.00	0.00	0.00	0.00
008	12-08-81	3.80	1.00	5.34	0.110	961.60	20.03	1500.00	28.30
013	02-08-83	3.52	0.99	2.06	0.060	406.40	11.61	738.90	21.11

NO.	INDOCYANINE	T 1/2	CORR	VOL DI	VOL/ KG	TOT BODY CLEARANCE	CLEAR	WB CLEARANCE	WB CL/ KG
018	99-99-99	0.00	0.00	0.00	0.000	0.00	0.00	0.00	0.00
020	01-24-82	4.79	0.99	3.66	0.040	529.50	5.88	920.90	10.23
030		0.00	0.00	0.00	0.000	0.00	0.00	0.00	0.00
041		0.00	0.00	0.00	0.000	0.00	0.00	0.00	0.00
043		0.00	0.00	0.00	0.000	0.00	0.00	0.00	0.00
082	12-01-82	4.82	1.00	2.78	0.050	400.80	6.68	709.20	11.82
114	03-23-83	2.56	0.99	1.93	0.030	521.10	6.86	904.70	12.06
115	05-08-84	4.48	1.00	4.03	0.050	596.00	7.22	1070.00	12.96
121	03-30-83	3.16	0.99	3.04	0.050	666.30	10.40	1129.00	17.64
141	29-11-83	3.81	1.00	3.27	0.040	594.00	8.13	950.40	13.07
141	01-12-83	4.02	1.00	3.03	0.040	522.40	7.19	924.70	12.71
169	30-03-83	3.16	0.00	3.04	0.050	666.20	10.41	1129.00	16.12
207	05-10-83	3.20	0.99	4.03	0.060	872.70	13.85	1646.00	26.12
208	05-19-83	3.98	1.00	6.15	0.110	1071.00	18.48	1864.00	32.13
209	05-26-83	4.08	0.99	3.17	0.090	538.50	14.83	899.00	24.76

NO.	INDOCYANINE	T 1/2	CORR	VOL DI	VOL/KG	TOT BODY CLEARANCE	CLEAR	WB CLEARANCE	WB CL/KG
211	05-31-83	4.19	1.00	3.23	0.050	534.60	7.98	1028.00	15.34
212	05-31-83	3.62	0.99	4.91	0.060	938.60	11.47	1722.00	21.00
215	06-16-83	2.89	1.00	4.66	0.070	1119.00	15.77	1865.00	26.26
216	06-16-83	4.74	0.99	3.47	0.060	506.80	8.97	913.20	16.16
226	10-28-83	3.05	0.99	3.69	0.060	839.90	12.54	1473.00	21.98
232	01-15-85	4.01	0.99	3.44	0.090	594.80	14.87	959.50	23.98
234		0.00	0.00	0.00	0.000	0.00	0.00	0.00	0.00
235	01-22-85	3.34	1.00	8.95	0.170	1858.00	6.08	2997.00	58.19
600	99-99-99	0.00	0.00	0.00	0.000	0.00	0.00	0.00	0.00
601	07-06-82	3.51	1.00	4.21	0.040	832.20	8.76	1734.00	18.25
722	08-24-82	4.87	0.99	3.55	0.040	504.90	5.94	801.50	9.43
773	07-06-82	3.30	0.96	2.44	0.040	506.90	7.80	965.60	14.85
775	02-19-82	3.61	0.99	5.36	0.080	1029.00	14.70	1584.00	22.62
777	06-04-82	2.70	1.00	4.01	0.060	1027.00	14.68	1938.00	27.68
778	04-27-82	3.28	0.99	3.72	0.050	786.00	10.48	1355.00	18.06

NO.	INDOCYANINE	T 1/2	CORR	VOL DI	VOL/KG	TOT BODY CLEARANCE	CLEARANCE	WB CLEARANCE	WB CL/KG
779	00-00-82	3.86	0.68	4.52	0.090	811.50	16.23	1424.00	28.48
780	05-05-82	2.72	0.99	2.17	0.030	553.10	6.91	1005.00	12.56
781	04-20-82	3.36	0.99	3.16	0.040	652.30	7.25	1219.00	13.54
783	04-06-82	4.18	0.99	3.41	0.060	565.00	9.74	991.30	17.09
784	04-20-82	3.98	0.99	3.53	0.040	613.70	7.67	1252.00	15.65
785	06-11-82	4.56	0.97	3.43	0.060	521.60	8.84	1043.00	17.67
786	04-21-82	4.56	0.98	5.18	0.070	786.80	10.49	1311.00	17.48

APPENDIX 4

METHODS OF DATA COLLECTION AND DATA HANDLING

The data and references used in this thesis have been collected and organised using microcomputers. Three file structures have been used:-

1. Liver Function Data File
2. Drug Data File
3. References

1. Liver Function Data File

The liver function data has been collected on an Apple IIE microcomputer using the DB Master Database version 4 published by Stoneware Incorporated of San Rafael, California. This database allows the storage of 100 fields or pieces of information in each record and the database was structured so that each time a patient was assessed they had a new record filled out. The data collected is discussed in Chapter 7. The data was edited and corrected on the Apple microcomputer and then written out of the database as a straight text file. This file was then directly transferred using an on line Apple IIE computer to the University main frame computer for analysis.

FILE DEFINITION - LIVER FUNCTION

Field No.	Field Label	Primary Key	Second Key	Read Protected	Field Type	Field Length
1	DIAGNOSIS	YES	NO	NO	0-255	3
2	STUDY NUMBER	YES	NO	NO	ALPHA	3
3	LAST NAME	YES	NO	NO	ALPHA	12
4	FIRST NAME	NO	NO	NO	ALPHA	12
5	HOSPITAL NUMBER	NO	NO	NO	NUMER	6
6	DATE OF BIRTH	NO	NO	NO	DATE	8
7	AGE	NO	NO	NO	0-255	3
8	SEX	NO	NO	NO	0-255	1
9	RACE	NO	NO	NO	0-255	1
10	HEIGHT	NO	NO	NO	NUMER	5
11	WEIGHT	NO	NO	NO	NUMER	4
12	OTHER DIAGNOSIS 1	NO	NO	NO	0-255	3
13	OTHER DIAGNOSIS 2	NO	NO	NO	0-255	3
14	OTHER DIAGNOSIS 3	NO	NO	NO	0-255	3
15	OTHER DIAGNOSIS 4	NO	NO	NO	0-255	3
16	MEAT CONSUMPTION	NO	NO	NO	0-255	1
17	VEG. CONSUMPTION	NO	NO	NO	0-255	1
18	BEER	NO	NO	NO	INTGR	3
19	SPIRITS	NO	NO	NO	INTGR	3
20	WINE	NO	NO	NO	INTGR	3
21	TOTAL ALCOHOL	NO	NO	NO	0-255	2
22	PIPE SMOKING	NO	NO	NO	0-255	1
23	CIGARETTES	NO	NO	NO	0-255	2
24	COFFEE	NO	NO	NO	0-255	2
25	TEA	NO	NO	NO	0-255	2
26	LIVER	NO	NO	NO	0-255	2
27	SPLEEN	NO	NO	NO	0-255	2
28	PORTAL H.T.	NO	NO	NO	INTGR	1
29	ASCITES	NO	NO	NO	0-255	1
30	ENCEPHALOPATHY	NO	NO	NO	0-255	1
31	HAEMOGLOBIN	NO	NO	NO	NUMER	4
32	PROTHROMBIN	NO	NO	NO	0-255	2
33	CONTROL	NO	NO	NO	NUMER	4
34	BILIRUBIN	NO	NO	NO	INTGR	3
35	SGOT	NO	NO	NO	INTGR	5
36	SGPT	NO	NO	NO	INTGR	5
37	ALKALINE PHOSPHATE	NO	NO	NO	INTGR	4
39	ALBUMIN	NO	NO	NO	INTGR	2
40	GLOBULIN	NO	NO	NO	INTGR	2
41	CREATININE	NO	NO	NO	0-255	3
42	LIVER VOLUME	NO	NO	NO	INTGR	6
43	CHILD'S	NO	NO	NO	0-255	1
44	DRUGS 1	NO	NO	NO	INTGR	3
45	2	NO	NO	NO	INTGR	3
46	3	NO	NO	NO	INTGR	3
47	4	NO	NO	NO	INTGR	3
48	5	NO	NO	NO	INTGR	3

49	6	NO	NO	NO	INTGR	3
50	7	NO	NO	NO	INTGR	3
51	8	NO	NO	NO	INTGR	3
52	9	NO	NO	NO	INTGR	3
53	10	NO	NO	NO	INTGR	3
54	ANTIPYRINE KINETICS	NO	NO	NO	DATE	8
55	HALF LIFE	NO	NO	NO	NUMER	5
56	CORRELATION COEF	NO	NO	NO	NUMER	3
57	VOLUME OF DIST.	NO	NO	NO	NUMER	5
58	VOLUME/KILOGRAM	NO	NO	NO	NUMER	3
59	TOTAL BODY CLEARANCE	NO	NO	NO	NUMER	5
60	CLEARANCE/KILOGRAM	NO	NO	NO	NUMER	5
61	K	NO	NO	NO	NUMER	3
62	CONCENTRATION AT 0	NO	NO	NO	NUMER	5
63	INDOCYANINE GREEN	NO	NO	NO	DATE	8
64	HALF LIFE	NO	NO	NO	NUMER	5
65	CORRELATION COEF	NO	NO	NO	NUMER	3
66	VOLUME OF DIST.	NO	NO	NO	NUMER	5
67	VOLUME/KILOGRAM	NO	NO	NO	NUMER	5
68	TOTAL BODY CLEARANCE	NO	NO	NO	NUMER	5
69	CLEARANCE/KILOGRAM	NO	NO	NO	NUMER	5
70	K	NO	NO	NO	NUMER	5
71	CONCENTRATION - 0	NO	NO	NO	NUMER	5
72	W.B. CLEARANCE	NO	NO	NO	NUMER	5
73	W.B. CLEARANCE/KG	NO	NO	NO	COMP.	5
74	ACID GLYCOPROTEIN	NO	NO	NO	NUMER	5
75	HISTOLOGY	NO	NO	NO	DATE	8
76	ARCH-NORMAL	NO	NO	NO	0-255	1
77	-DISSARAY	NO	NO	NO	0-255	1
78	-CIRRHOSIS (ACT)	NO	NO	NO	0-255	1
79	-CIRRHOSIS (INAC)	NO	NO	NO	0-255	1
80	NECROSIS-ABSENT	NO	NO	NO	0-255	1
81	-DIFFUSE	NO	NO	NO	0-255	1
83	-SPOTTY	NO	NO	NO	0-255	1
84	-PIECEMEAL	NO	NO	NO	0-255	1
85	-CONFLUENT	NO	NO	NO	0-255	1
86	GRADE 1	NO	NO	NO	0-255	1
87	2	NO	NO	NO	0-255	1
88	3	NO	NO	NO	0-255	1
89	4	NO	NO	NO	0-255	1
90	FATTY CHANGE	NO	NO	NO	0-255	1
91	PAREN IRON	NO	NO	NO	0-255	1
92	BALLOONING	NO	NO	NO	0-255	1
93	A1	NO	NO	NO	ALPHA	10
94	A2	NO	NO	NO	ALPHA	10
95	A3	NO	NO	NO	ALPHA	10
96	N1	NO	NO	NO	NUMER	5
97	N2	NO	NO	NO	NUMER	5
98	N3	NO	NO	NO	NUMER	5
99	N4	NO	NO	NO	NUMER	5
100	N5	NO	NO	NO	NUMER	5

The database can be searched rapidly on the fields in the primary key, i.e. fields 1-3. It will "find" any record within 5-10 seconds if given the information in the primary key. The data is stored in the file in the order of its first field. By making this field the diagnostic field, the reports will naturally group together patients with the same diagnosis. This database has the facility of translating a numerical code into text in the printed reports. The following fields were coded.

FIELD NO 1	CODE	1	=	PRIMARY BILIARY CIRRHOSIS
		2	=	CHRONIC ACTIVE HEPATITIS
		3	=	ALCOHOLIC LIVER DISEASE
		4	=	IDIOPATHIC PORTAL HYPERTENSION
		6	=	CRYPTOGENIC CIRRHOSIS
		7	=	PRIMARY SCLEROSING CHOLANGITIS
		8	=	HAEMACHROMATOSIS
		9	=	DIAGNOSIS OBSCURE
		100	=	CONTROL
		101	=	METHOTEXATE STUDY
FIELD NO 8	CODE	0	=	FEMALE
		1	=	MALE
FIELD NO 28	CODE	0	=	NO EVIDENCE OF PORTAL HYPERTENSION
		1	=	OESOPHAGEAL VARICES PRESENT
		2	=	BLEEDING OESOPHAGEAL VARICES
		3	=	PORTACAVAL SHUNT
FIELD NO 29	CODE	0	=	NO ASCITES
		1	=	ASCITES
FIELD NO 30	CODE	0	=	NO ENCEPHALOPATHY
		1	=	ENCEPHALOPATHY
FIELD NO 43	CODE	1	=	CHILD'S GRADE A
		2	=	CHILD'S GRADE B
		3	=	CHILD'S GRADE C
		4	=	CONTROL

FIELD NOS 44,45,46,47,48,49,50,51,52,53.

CODE	1	=	PENICILLAMINE	36	=	CEPHRADEINE
	2	=	KETOCONAZOLE	37	=	VITAMIN D
	3	=	CHLORPROPAMIDE	38	=	VITAMIN C
	4	=	CHOLESTYRAMINE	39	=	METFORMIN
	5	=	RANITIDINE	40	=	ISOSORBIDE
	6	=	KANAMYCIN	42	=	INDOMETHACIN
	7	=	BETNESOL	43	=	SULPHASALAZINE
	8	=	AZATHIOPRINE	44	=	ISPAGHULA
	9	=	NEOMYCIN	45	=	TEMAZEPAM
	10	=	BROMOCRYPTINE	46	=	PHENERGAN
	11	=	LACTULOSE	47	=	HYDROCORTISONE
	12	=	NITRAZEPAM	48	=	ATENOLOL
	13	=	SPIRONOLACTONE	49	=	CHLORTHALIDONE
	14	=	VITAMIN K	52	=	HALOPERIDOL
	15	=	CHLORMETHIAZOLE	53	=	GLIPIZIDE
	16	=	OROVITE	54	=	PARACETAMOL
	17	=	FERROUS SULPHATE	55	=	FENOPROFEN
	18	=	FOLIC ACID	56	=	TRIAMTERENE
	19	=	CIMETIDINE	57	=	ALLOPURINOL
	20	=	CHLORDIAZEPOXIDE	58	=	GIN
	21	=	DIAZEPAM	59	=	NADOLOL
	22	=	INSULIN	60	=	METHOTREXATE
	23	=	FRUSEMIDE	61	=	LORAZEPAM
	24	=	PROCHLORPERAZINE	63	=	PSORALENS
	25	=	AMILORIDE/HYDROCHLORTHIAZIDE	64	=	FLURAZEPAM
	26	=	IBUPROFEN	66	=	METOPROLOL
	27	=	POTASSIUM	67	=	AMITRIPTYLINE
	28	=	PREDNISOLONE	68	=	BENDROFLUAZIDE
	29	=	PARENTEROVITE	69	=	ORPHENEDRINE
	30	=	AMPICILLIN	70	=	PIROXICAM
	31	=	AMILORIDE	72	=	PROPRANOLOL
	32	=	THYROXINE	73	=	MEFANAMIC ACID
	33	=	MEBEVERINE			
	34	=	BC 500			
	35	=	QUININE			

FIELD NOS 76-92 CODE - HISTOLOGY FIELDS

These fields are marked with a 1 when the histological feature measured in the field is present and a 0 when that feature is absent.

FIELD NOS 93-100

In the original file definition these fields were designed as empty fields. The first three (93,94 and 95) are alpha-numeric fields and the other fields are numeric fields.

Field 93 has been used to include a clinical description of the type of liver disease present.

1 = Clinically non-cirrhotic
2 = Clinically cirrhotic
3 = Clinically hepatitic
4 = Control

Field 96 contains information about the survival of the patient.

1 = The patient still alive
2 = The patient died of liver disease
3 = Unrelated death

Field 95 contains the months of follow up since the antipyrine and indocyanine green appearances were estimated. This field is globally edited on patients still alive and the values were those current on 1st January 1985.

2. DRUG DATA FILE

The DB Master Database has also been used to extract information for the production of appendices 1 and 2. The database was structured to allow the entry of information from papers on drug metabolism in liver disease and using the report facility in DB Master the percentage changes between control and disease groups were calculated for each of the pharmacokinetic parameters entered.

The following file definition was used:

FILE DEFINITION - DRUGS

	FIELD LABEL	PRIMARY KEY	SECOND KEY	READ PROT	FIELD TYPE	FIELD LEN
1	DRUG NAME	YES	NO	NO	ALPHA	15
2	REF NUMBER	YES	NO	NO	NUMER	4
3	ENTRY NUMBER	YES	NO	NO	0-255	1
4	ROUTE OF ADMINISTRATION	NO	NO	NO	0-255	1
5	DOSE	NO	NO	NO	ALPHA	8
6	CONTROL NO	NO	NO	NO	0-255	3
7	CONTROL TYPE	NO	NO	NO	0-255	3
8	DISTRIBUTION HALF LIFE	NO	NO	NO	NUMER	5
9	UNITS	NO	NO	NO	0-255	2
10	ELIMINATION HALF LIFE	NO	NO	NO	NUMER	5
11	UNITS	NO	NO	NO	0-255	2
12	VOLUME OF DISTRIBUTION	NO	NO	NO	NUMER	5
13	UNITS	NO	NO	NO	0-255	2
14	STEADY STATE VD	NO	NO	NO	NUMER	5
15	UNITS	NO	NO	NO	0-255	2
16	CLEARANCE	NO	NO	NO	NUMER	5
17	UNITS	NO	NO	NO	0-255	2
18	CLEARANCE/KG	NO	NO	NO	NUMER	5
19	UNITS	NO	NO	NO	0-255	2
20	PATIENT NO.	NO	NO	NO	0-255	3
21	PATIENT TYPE	NO	NO	NO	0-255-3	
22	DISTRIBUTION HALF LIFE	NO	NO	NO	NUMER	5
23	ELIMINATION HALF LIFE	NO	NO	NO	NUMER	5
24	VOLUME OF DISTRIBUTION	NO	NO	NO	NUMER	5
25	STEADY STATE VD	NO	NO	NO	NUMER	5
26	CLEARANCE	NO	NO	NO	NUMER	5
27	CLEARANCE/K	NO	NO	NO	NUMER	5
28	P VALUE - T 1/2 DIS	NO	NO	NO	ALPHA	7
29	P VALUE - T 1/2 EL	NO	NO	NO	ALPHA	7
30	P VALUE - VD	NO	NO	NO	ALPHA	7
31	P VALUE - VD SS	NO	NO	NO	ALPHA	7
32	P VALUE - CL	NO	NO	NO	ALPHA	7
33	P VALUE - CL/KG	NO	NO	NO	ALPHA	7
34	CORRELATION WITH	NO	NO	NO	ALPHA	8
35	BILIRUBIN (R)	NO	NO	NO	ALPHA	5
36	P VALUE	NO	NO	NO	ALPHA	7

37	ALBUMIN (R)	NO	NO	NO	ALPHA	5
38	P VALUE	NO	NO	NO	ALPHA	7
39	SGOT (R)	NO	NO	NO	ALPHA	5
40	P VALUE	NO	NO	NO	ALPHA	7
41	SGPT (R)	NO	NO	NO	ALPHA	5
42	P VALUE	NO	NO	NO	ALPHA	7
43	GGT (R)	NO	NO	NO	ALPHA	5
44	P VALUE	NO	NO	NO	ALPHA	7
45	A.P. (R)	NO	NO	NO	ALPHA	5
46	P VALUE	NO	NO	NO	ALPHA	7
47	PT (R)	NO	NO	NO	ALPHA	5
48	P VALUE	NO	NO	NO	ALPHA	7
49	ANTIP (R)	NO	NO	NO	ALPHA	5
50	P VALUE	NO	NO	NO	ALPHA	7
51	ICG (R)	NO	NO	NO	ALPHA	5
52	P VALUE	NO	NO	NO	ALPHA	7
53	SPECIFY	NO	NO	NO	0-255	3
54	(R)	NO	NO	NO	ALPHA	5
55	P VALUE	NO	NO	NO	ALPHA	7
56	SPECIFY	NO	NO	NO	0-255	3
57	(R)	NO	NO	NO	ALPHA	5
58	P VALUE	NO	NO	NO	ALPHA	7
59	BIOAVAILABILITY	NO	NO	NO	NUMER	5
60	DIS	NO	NO	NO	NUMER	5
61	PROTEIN BINDING	NO	NO	NO	NUMER	7
62	DIS	NO	NO	NO	NUMER	7
63	EXTRACTION R/T	NO	NO	NO	NUMER	7
64	DIS	NO	NO	NO	NUMER	7
65	COMMENT	NO	NO	NO	ALPHA	80

FIELD NOS	EXPLANATION
1,4,5	Contain information of drug route of administration and dose used.
2,3	Contain reference number and entry number.
8-19	Contain pharmacokinetic parameters for control group together with the unit in which they are expressed.
22-27	Contain pharmacokinetic parameters for the disease group.
28-33	Contain the p values for the differences between the control and disease groups.
34-52	Contain the correlations between the stated pharmacokinetic parameters and standard liver function tests, antipyrine and indocyanine green and there are 2 blank fields at the end of this group (53 and 56) for specified parameters correlating pharmacokinetic parameters. The r values and p values are included.

CODES FOR DRUG/DISEASE TYPE FIELD 7 AND 21

1. CIRRHOSIS
2. CIRRHOSIS + PSE
3. CIRRHOSIS + PHT
4. ACUTE HEPATITIS
5. MIXED LIVER DISEASE
6. CHOLESTASIS
7. MILD ALD
8. MODERATE ALD
9. SEVERE ALD
10. CAH - HEP B
11. FATTY LIVER
12. HEPATITIS - ALD
13. CAH - LUPOID
14. PC ANASTOMOSIS
15. ASCITES
16. ABN LFT/NORMAL HIST
17. ABN LFT/MILD ABN HIST
18. ABN LFT/SEVERE ABN HIST
19. POLYCYSTIC LIVER DISEASE
20. HEPATIC NEOPLASM
21. EXTRAHEPATIC CHOLESTASIS
22. INTRAHEPATIC CHOLESTASIS
23. CIRRHOSIS - POST NECROTIC
24. IDIOPATHIC PORTAL HT
25. CIRRHOSIS - DECOMPENSATED
26. CIRRHOSIS - + PROPRANOLOL
27. CIRRHOSIS - ALD
28. CIRRHOSIS - PBC
29. PYREXIA
30. CIRRHOSIS + CIMETIDINE
31. LD + ENZYME INDUCERS
32. CIRRHOSIS + ALB < 35 G
33. ROTOR SYNDROME
34. PARACENTESIS
35. PORTAL VEIN THROMBOSIS
36. BUDD CHIARI SYNDROME
37. AMOEBIC LIVER DISEASE
38. GILBERTS SYNDROME
39. CPH
40. FHF - SURVIVORS
41. FHF - NON SURVIVORS
42. CAH + BRIDGING NECROSIS
43. CAH = CIRRHOSIS
44. PORPHYRIA
45. CIRRHOSIS - COMPENSATED
46. CIRRHOSIS - DECOMPENSATED
47. PSE
48. PSE ON RECOVERY
51. URAEMIA
52. URAEMIA + PHENOBARBITONE
53. MALNUTRITION
54. UNDERNOURISHED
55. IDIOPATHIC HYPOALBUMINAEMIA
56. CHRONIC HEPATITIS
57. LIVER FIBROSIS
58. HEPATORENAL SYNDROME
59. LIVER FAILURE
100. CONTROLS
101. CONTROL - SALIVA
102. MALES
103. FEMALES
104. NON SMOKERS
105. SMOKERS
106. NORMAL SMOKERS
107. YOUNG MALES
108. OLD MALES
109. YOUNG FEMALES
110. OLD FEMALES
111. SUDANESE IN ENGLAND
112. SUDANESE IN SUDAN
113. ORAL ADMINISTRATION
114. IV ADMINISTRATION
115. NOON
116. MIDNIGHT
117. GENERAL ANAESTHESIA
118. GAMBIANS
119. VEGETERIANS
120. NON-VEGETARIANS
121. SUMMER
122. WINTER
123. EXERCISE
124. ELDERLY
125, VIT C DEFICIENCY
126. < 70 YS OLD
127. EPILEPTICS
128. EPILEPTICS + ABN LIVER HISTOL
129. ANOREXIA NERVOSA
130. HIGH CHO DIET

131. HIGH FAT DIET
132. HIGH PROTEIN DIET
133. RAPID ACETYLATORS
134. SLOW ACETYLATORS
135. PARKINSONISM
136. TWINS
137. CHILDREN + CYSTIC FIBROSIS
138. HYPERTHRYOIDISM
139. HYPOTHYROIDISM
140. SPROUTS/CABBAGE DIET
141. 2/52 FAST
142. FLUID DEPRIVATION
143. FLUID DEPRIVATION/HEAT/EXERC.
144. HEAT
145. HEAT + EXERCISE
146. CRITICALLY ILL-SURVIVORS
147. CRITICALLY ILL-NON SURVIVORS
148. DEBRISOQUINE METAB +++
149. DEBRISOQUINE METAB +
150. L500 CALORIE DIET
151. L800 CALORIE DIET
152. 3000 CLAORIE DIET
153. 72 HR FAST
154. HYPERTROPHIC PYLORIC STENOSIS
155. H.P.S. AFTER SURGERY
156. CCF
157. BED REST
158. ALCOHOLICS
159. 18 - 39
160. 40 - 59
161. 60 - 92
162. NO COFFEE
163. < 5 CUPS COFFEE/D
164. > 5 CUPS COFFEE/D
165. NON SMOKER
166. MODERATE SMOKER
167. HEAVY SMOKER
168. 200G POTATO DIET
169. TPN - DEXTROSE
170. TPN - AMINOACIDS
171. VITAMIN A DEFICIENCY
172. SUPINE
173. STANDING
174. SITTING
175. EXERCISE
176. 500 ML MILK
200. PHENOARBITONE
201. MIXED ENZYME INDUCERS
202. INDUSTRIAL SOLVENTS
203. VITAMIN C
204. ANTIPYRINE
205. CANNABIS
206. ORAL CONTRACEPTIVE
207. PHENYTOIN
208. PHENYTOIN + CIMETIDINE
209. RANITIDINE
210. PROPRANOLOL
211. ATENOLOL
212. LABETOLOL
213. RIFAMPICIN
214. GLUTETHEMIDE
215. SULPHINPYRAZONE
216. CIMETIDINE
217. LOW DOSE COMBINED OC
218. PROGESTERONE ONLY OC
219. ANFLURANE
220. MEDROXYPROGESTERONE
221. VITAMIN SUPPL
222. ETHANOL
223. DEXAMETHASONE
224. ACTH
225. AMINOPYRINE
226. AMYLOBARBITONE
227. NITRAZEPAM
228. MANDRAX
229. METHAQUALONE
230. DIPHENHYDRAMINE
231. HYDROCORTISONE
232. DISULFIRAM
233. FENFLURAMINE
234. HALOFENATE
235. LEVODOPA
236. METHYLDOPA HYDRAZINE
237. LDOPA+MD HYDRAZINE
238. ALLOPURINOL
239. NORTRIPTYLINE
240. TESTOSTERONE
241. SPIRONOLACTONE
242. AZATHIOPRINE
243. FRUSEMIDE
244. CARBAMAZEPINE
245. ETHINYL OESTRADIOL
246. CHLORINATED HYDROCARBONS
247. PIRENZEPINE
248. ANTIPYRINE + PHENOBARB
249. ANTIPYRINE + RIFAMPICIN
250. ASTEMIZOLE
251. COCAINE
252. GIN
253. PHENOXYBENZAMINE
254. ISONIAZID

CODES FOR UNITS

FIELDS NO 9,11,13,15,17 and 19

1.	HRS	15.	ML/MIN/L LIVER
2.	ML/MIN	18.	L/HR/KG
3.	ML/MIN/KG	19.	% DOSE @ 2 HR
4.	LITRES	20.	% MIN
5.	MIN	21.	% @ 45 MIN
6.	L/KG	22.	L/MIN
7.	L/HR	23.	MG/KG/HR
8.	ML/KR/KG	24.	MG/100ML/HR
9.	ML/MIN/KG-WB	25.	UG/MIN
10.	ML/KG	26.	UMOL/MIN/KG
11.	ML/M-2	27.	MMOL/MIN/KG
12.	ML/MIN/M-2	28.	MG/MIN
13.	% DOSE/HR		
14.	% DOSE @ 1 HR		

CODES FOR FIELDS 53 and 56

1.	BSP	100.	CHOLESTEROL
2.	GALACTOSE	101.	APOPROTEIN
3.	PARACETAMOL	200.	AMINOPYRINE DEMETHYLA
4.	LIGNOCAINE	201.	ANILINE HYDROXYLASE
5.	OXAZEPAM	202.	NADPH CYTOCHROME C
6.	VIT C		REDUCTASE
7.	DIAZEPAM BT	203.	P450
8.	DIAZEPAM	204.	WEIGHT
9.	DESMETHYL DIAZEPAM	205.	AGE
10.	DESALKYLFLURAZEPAM	206.	IV VS ORAL
11.	LORAZEPAM	207.	PLASMA VS SALIVA
12.	TEMAZEPAM	208.	ARYL HYDROCARBON
13.	SERUM FLUORIDE		HYDROLASE
14.	ANTIPYRINE CL	209	BILIRUBIN CLEARANCE
15.	ANTIPYRINE T1/2	210.	ASCITES
50	LIVER VOLUME	211.	PSE
51.	LIVER VOL AFTER	212.	SERUM ZINC
	PHENOBARBITONE	213.	SERUM COPPER

SPECIMEN PRINT-OUT

DRUG NAME : THEOPHYLLINE

GROUP	NO.	Tl/2	DI UNITS/ %	Tl/2 EL UNITS / %	VOL DIS	UNITS / %	VD SS UNITS/%	CL	UNITS / %	CL.KG	UNITS / %	REF
CONTROLS	19	0.00	0	6.70 hrs	0.51	l/kg	0.25	0	0.06	l/hr/kg 0.00	0	329
CIRRHOSIS	9	0.00	0.0	25.60 -282.1	0.33	35.0	0.79	100.0	0.04	32.3	9.00 0.0	
CONTROLS	0	0.00	0	6.00 hrs	0.48	l/kg	0.00	0	0.00	0	63.00 ml/kg	386
CIRRHOSIS	0	0.00	0.0	28.80 -380.0	0.56	-16.8	0.00	0.0	0.00	0.0	0.00 70.2	
CONTROLS	8	0.00	0	6.00 hrs	0.49	l/kg	0.00	0	0.00	0	0.99 ml/min/kg	183
CARBOHYDRATE DIET	8	0.00	0.0	7.90 -31.	0.51	-4.1	0.00	0.0	0.00	0.0	8.00 23.2	
CONTROLS	8	0.	0	6.00 hrs	0.49	l/kg	0.00	0	0.00	0	0.99 ml/min	183
FAT DIET	8	0.00	0.0	7.90 -31.7	0.50	-2.0	0.00	0.0	0.00	0.0	8.00 25.3	
CONTROLS	8	0.00	0	6.00 hrs	0.49	l/kg	0.00	0	0.00	0	0.99 ml/min/kg	183
PROTEIN DIET	8	0.00	0.0	5.80 3.3	0.49	0.0	0.00	0.0	0.00	0.0	8.00 1.0	
CONTROLS	7	0.00	0	5.10 hrs	31.70	l/kg	0.00	0	71.20	ml/min 0.00	0	142
CIMETIDINE	7	0.00	0.0	8.10 -58.8	39.20	-23.7	0.00	0.0	56.00	21.3	7.00 0.0	

3. REFERENCES FILE

The references for this thesis were organised on an Apricot Microcomputer using the Comsoft Delta database. The file was originally created on an Apple IIE computer but was transferred to an Apricot because of the increase floppy disc storage space on this computer. The Apricot microcomputer with double density floppy disks has a storage capacity of 750k per disk drive compared to 110k per disk drive on the Apple microcomputer. This results in an increased capacity to store references from about 250-300 on the Apple up to over 1000 references on the Apricot. This capacity can be further increased by the addition of a hard disc. The database has a theoretical maximum of 7 megabite of data storage which should allow for the storage of approximately 10,000 references in a single file.

The original Apple file in the DB master database was written out as a straight text file. The floppy discs were converted to PRO-DOS discs. The Apple IIE and Apricot were linked together using a serial interface. Both computers were configured as terminals using the ASYNC program on the Apricot and Access on the Apple. The data was then transferred to the Apricot as a straight text file. The data was checked using the Wordstar word processing package. A file was configured using Comsoft delta and the data was taken into this file using the link and copy facility in comsoft delta.

FILE DEFINITION - REFERENCES

Delta file name: REF
File Title: REFERENCE INDEX.....
Date created: 16-JUL-85
Last Updated: 16-JUL-85
Number of Fields: 12
Record Length: 621
Transaction Groups: 0

Field No.	Field Name	Field Type	Field Length
1.	ref numb	C	4
2.	title	C	65
3.	title 1	C	65
4.	title 2	C	65
5.	title 3	C	65
6.	authors	C	65
7.	authors 1	C	65
8.	ref	C	65
9.	ref 1	C	65
10.	keywords	C	80
11.	def 1	O	4
12.	def 2	O	4

EXPLANATION

This file definition stores the references by reference number. The title is stored across three fields, the authors across two fields and the reference across two fields. There is then a single field for keywords. These are words which the computer can rapidly search for in order to extract groups of references with a common theme. There are two blank fields at the end of the file definitions - def 1 and def 2 - which are numerical fields. These allow groups of references to be numbered.

The following report formats were used from this file definition.

1. A numerical reference list.

2. A journal list. This report re-organises the references by the first line of the reference. This allows for the checking of anomalies in the journals and allows correction of the abbreviations for the journal titles.

3. Extract reports. Various extract reports were produced from this list by extracting records on the keyword e.g. a group of references were extracted where antipyrine was included as a keyword and another group where indocyanine green was included as a key word.

4. Alphebetical Reference list. For this report the references are extracted in alphabetical order from the main file. The DEF.1 field is then used with a process file to number the references.

```
297  FOR I = 1 TO X1
300  HOME : INVERSE : PRINT "ENTRY NO. ";I: NORMAL  : PRINT
310  INPUT "TIME AND CONCENTRATION (X,Y) ";X(I),Y(I)
315  IF X(I) > 48 THEN PRINT ">48 HRS"; GOTO 310
330  GOSUB 700
340  NEXT I
350  N = X1
355  PR£ 1
360  FOR I = 1 TO N: PRINT X(I), EXP (Y(I)): GOSUB 760
370  NEXT I
380  R1 = SQR (R / (R + G))
385  V = SQR (V / (N - 2))
390  PRINT " "
400  PRINT "              DATA SET NUMBER  ";JJ
410  PRINT " ----------------------------"
420  PRINT ""
425  GOSUB 845
430  PRINT "HALF LIFE.....................=";T2
440  PRINT "CORRELATION COEFFICIENT..=";R1; " FOR ";N;" OBSERVATIONS'
450  PRINT "APPARENT V.D.............=";GA;" LITRES "
460  PRINT "V.D./KG BODY WT..........=";HA
470  PRINT "TOTAL BODY CLEARANCE.....=";IA;"ML/MIN"
480  PRINT "CLEARANCE/KG BODY WT.....=";JA;"ML/MIN/KG"
490  PRINT "ESTIMATED VALUE OF K.....=";K
500  PRINT "CONCENTRATION AT TIME 0..=";CO;" MG "
520  PRINT "============================================================"
522  PR£ 0
525  PRINT "TO CONTINUE PRESS SPACE BAR";A$
526  GET A$
530  PRINT : PRINT : PRINT : PR£ 0
540  GOSUB 1000
550  I = 0:R = 0:S1 = 0:S3 = 0:S4 = 0:S5 = 0:V = 0:G = 0
580  HOME : PRINT "DO YOU WANT TO AMEND ANY INPUTS";: GET Y$
590  IF Y$ = "N" THEN PRINT : PRINT "RUNNING PROGRAM FROM THE
     BEGINNING": FOR I = 1 TO 1000: NEXT : HOME : GOTO 190
595  IF Y$ < > "Y" THEN PRINT G$: GOTO 580
597  HOME
600  PRINT : PRINT "TO DELETE DATA TYPE 'D'": PRINT "TO AMEND DATA
     TYPE 'A'"
602  VTAB 12: HTAB 10
605  PRINT "INPUT YOUR CHOICE ";: GET CH$
607  IF CH$ = "A" OR CH$ ' "D" THEN 609
608  IF CH$ < > "A" AND CH$ < > "D" THEN PRINT G$: GOTO 597
609  IF CH$ = "D" THEN 640
610  IF CH$ = "A" THEN PRINT : PRINT "THERE ARE ";X1;" ENTRIES": INPUT
     "WHICH ONE DO YOU WISH TO CHANGE?";I
615  FOR T = 1 TO X1:Y(T) = EXP (Y(T)): NEXT
620  PRINT : INPUT "INPUT YOUR NEW VALUES (X,Y) ";X(I),Y(I)
625  FOR I = 1 TO X1: GOSUB 700: NEXT
630  GOTO 350
640  PRINT : PRINT "THERE ARE ":X1;" ENTRIES": INPUT "WHICH ONE DO
     YOU WISH TO DELETE";T
648  FOR I = 1 TO T - 1:J = J +1:X(J) = X(I):Y(J) = Y(I):NEXT
650  FOR I = T + 1 TO X1:J = J + 1:X(J) = X(I):Y(J) = Y(I): NEXT
655  X1 = X1 - 1
```

```
660  FOR I = 1 TO X1:Y(I) = EXP (Y(I)): GOSUB 700: NEXT I
670  GOTO 350
680  PRE 0
690  END
700  Y(I) = LOG (Y(I))
710  S1 = S1 + Y(I)
720  S3 = S3 + X(I)
730  S5 = S5 + X(I)
740  S4 = S4 + X(I) * Y(I)
750  RETURN
760  S2 = N
770  M = S1 / S2
780  K = (S1 * S3 - S4 * S2) / (S5 * S2 - S3   2)
790  CO = EXP ((SI + S3 * K) / S2):T2 = LOG (2) / K
800  G = G + (Y(I) - LOG (CO) + K * X(I))   2
820  R = R + (M - LOG (CO) + K * X (I)) / K)   2
830  V = V + (X(I) - ( LOG (CO) - Y(I)) / K)   2
840  RETURN
845  RA = R1 * 1000:RA = INT (RA):RA$ = STR$ (RA):  IF RIGHT$ (RA$,1)
     = > "5" THEN RA = RA + 10:RA = RA / 10: RA = INT (RA): R1 = RA /
     100: GOTO 850
847  RA = RA / 10:RA = INT (RA):R1 = RA / 100
850  GA = (D / CO) * 1000:GA = INT (GA):GA$ = STR$ (GA): IF RIGHT$
     (GA$,1) = > "5" THEN GA = GA +10:GA = GA / 10:GA = INT (GA):GA =
     GA / 100: GOTO 860
855  GA = GA / 10:GA = INT (GA):GA = GA / 100
860  HA = ((D / CO) / BW) * 1000:HA = INT (HA):HA$ = STR$ (HA):
     IF RIGHT$ (HA$,1) = > "5" THEN HA = HA + 10: HA = HA / 10:HA =
     INT (HA):HA = HA / 100: GOTO 870
865  HA = HA / 10:HA = INT (HA): HA = HA / 100
870  IA = (((D / CO) * K) * 1000 / 60) * 1000:IA = INT (IA):IA$ = STR$
     (IA):  IF RIGHT$ (IA$,1) = > "5" THEN IA = IA + 10:IA = IA /
     10:IA = INT (IA):IA = IA / 100: GOTO 880
875  IA = IA / 10:IA = INT (IA):IA = IA / 100
880  JA = (((D / CO) * K / BW) * 1000 / 60) * 1000:JA = INT (JA):JA$ =
     STR$ (JA): IF RIGHT$ (JA$,1) = > "5" THEN JA = JA + 10:JA = JA /
     10:JA = INT (JA): JA = JA / 100: GOTO 890
885  JA = JA / 10:JA = INT (JA):JA = JA / 100
890  KA = K* 1000:KA = INT (KA):KA$ = STR$ (KA): IF RIGHT$ (KA$,1) = >
     "5" THEN KA = KA + 10:KA = KA / 10:KA = INT (KA):KA = KA / 100:
     GOTO 900
895  KA = KA / 10:KA = INT (KA):K = KA / 100
900  LA = CO * 1000:LA = INT (LA):LA$ = STR$ (LA): IF RIGHT$ (LA$,1) =
     > "5" THEN LA = LA + 10:LA = LA / 10:LA = INT (LA):CO = LA / 100:
     GOTO 910
905  LA = LA / 10:LA = INT (LA):CO = LA / 100
910  RETURN
1000 REM ********
1010 REM * PLOT *
1020 REM ********
1025 FOR I = 1 TO N
1026 IF X(I) > 48 OR X(I) < 0 OR EXP (Y(I)) > 150 OR EXP (Y(I)) < 0
     THEN HOME : X$ = "CANNOT PLOT AS DATA IS OUT OF BOUNDS"": GOSUB
     6000: RETURN
1027 NEXT I
```

```
1030 HGR : HCOLOR=3
1032 HPLOT 2,2 TO 2,157 TO 277,157
1034 FOR X = 2 TO 277 STEP 275 / 49: HPLOT  X,157 TO X,159: NEXT: FOR
     X = 157 TO 2 STEP - 10: HPLOT 2,X TO 0,X: NEXT X
1035 HPLOT 2,157
1037 HPLOT 2 + (5.612 * X(1)),157 - EXP (Y(I))
1040FOR I = 2 TO N: HPLOT TO 2 + (5.612 * X(I)),157 - EXP (Y(I)):
     NEXT I
1041 FOR I = 1 TO N: HPLOT 2 + (5.612 * X (I)),157 - EXP (Y(I)) TO 2 +
     (5.612 * X(I)),154 - EXP (Y(I)): NEXT I
1043 HPLOT 2,157
1045 YY = K * 0 + (157 - CO)
1046 YZ = K * 48 + (157 - CO): HPLOT 2,YY TO 271.388,YZ
1050 VTAB 24:X$ = "TIME (HRS)": GOSUB 6000
1100 VTAB 24: PRINT "RUN PROGRAM AGAIN?";: GET A$: IF A$ = "N" THEN
     TEXT : HOME : PRINT "PROGRAM IS FINISHED": END
1110 IF A$ < > "Y" THEN PRINT G$: GOTO 1100
2000 TEXT : HOME : RETURN
5999 REM * CENTRE STRING *
6000 HT = (40 - LEN (X$)) / 2: HTAB HT: PRINT X$: RETURN
```

PHARMACOKINETIC PROGRAM 2

```
10   REM PROGRAM FOR CARDIOGREEN ANALYSIS - ORIGINALLY WRITTEN IN
     MICROSOFT BASIC
40   DIM A(10),C(10,M(10),T(10)
50   HOME : VTAB 3
60   PRINT "CARDIOGREEN ANALYSIS"
70   PRINT "--------------------"
80   VTAB 5
130  INPUT "WHAT IS THE SUBJECTS NAME? - IF NO MORE SUBJECTS TYPE -
     DONE ";N$
140  IF N$ = "D;ONE" THEN 690
150  PRINT
160  INPUT "WHAT IS HIS/HER LABORATORY NO. ? ";M$
170  PRINT
180  INPUT "ENTER THE DATE OF ANALYSIS - ";D$
190  PRINT
200  INPUT "WHAT WAS THE DRUG DOSE (MGS) ? ";D
210  PRINT
220  INPUT " - THE BODY WEIGHT IN KGS ";BW
230  PRINT
240  INPUT " - AND THE PCV ";PC
250  PR£ 1
255  PRINT "NAME OF SUBJECT - "N$
257  PRINT "-----------------": PRINT
260  PRINT "LAB.NO: ";M$;"     DATE: ";D$
265  PRINT
300  PRINT "DOSE:  ";D;" MGS  WEIGHT:  ";BW;"  KG PCV:  ";PC
320  PR£ 0
330  INPUT "WHAT WAS THE ABSORBANCE OF THE 5MG/LITRE STANDARD ? ";Q9
335  PRINT
340  C9 = Q9 / 5
350  PR£ 1
355  PRINT : PRINT
360  PRINT "STANDARD 5MG/LITRE -- ABSORBANCE  ";Q9
370  PR£ 0
380  INPUT "HOW MANY SAMPLES DO YOU HAVE ? ";N9
390  HOME
395  PRINT "SAMPLE TIME (MINS) AND ABSORBANCE "
396  PRINT "~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~"
397  PRINT "CONCENTRATION (MG/L)"
398  PRINT "~~~~~~~~~~~~~~~~~~~~~"
400  PRINT "NOW INPUT THE TIME (MINS) AND ABSORBANCE FOR EACH SAMPLE,
     SEPARATING THE "PRINT "2 VARIABLES BY A COMMA"
420  PRINT
430  FOR I = 1 TO N9
440  PRINT "    SAMPLE ";I;"  -  ";
450  INPUT M(I),A(I)
460  C(I) = A(I) / C9
470  T(I) = M(I) / 60
480  NEXT I
490  PR£ 1
494  PRINT : PRINT
```

```
495  PRINT "SAMPLE TIME (HRS) ABSORBANCE CONCENTRATION (MG/ML)"
496  PRINT "--------    ----------    ----------    ----------
     ---------"
497  PRINT
500  FOR I = 1 TO N9
510  PRINT TAB ( 3)I TAB ( 13)M(I) TAB ( 24)A(I) TAB( 39)C(I)
520  NEXT I
525  PRINT : PRINT
530  PR£ 0
540  PRINT : PRINT : PRINT
550  PRINT "CALCULATION OF CORRELATION COEFFICIENTS"
552  PRINT "~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~"
554  PRINT "AND HALF LIFE DATA"
560  PRINT "~~~~~~~~~~~~~~~~~~"
575  PRINT : PRINT : PRINT
580  PRINT "HOW MANY POINTS DO YOU WANT TO USE TO CALCULATE
     CORRELATION COEFFICIENTS AND ";
590  PRINT "HALF-LIFE DATA ?"
595  PRINT
600  PRINT "-IF YOU DO NOT WISH TO CALCULATE FURTHER REGRESSION LINES
     TYPE - 0"
610  INPUT N
615  PRINT : PRINT
620  IF N = 0 THEN 648
630  GOSUB 999
640  GOTO 575
648  GOTO 130
690  END
999  FOR I = 1 TO N
1000 X(I) = T(I):Y(I) = C(I): GOSUB 1340
1010 NEXT I
1020 FOR I = 1 TO N: GOSUB 1400
1030 NEXT I
1040 R1 = SQR (R / (R + G)):V = SQR (V / (N - 2))
1050 GOSUB 2000
1060 PR£ 1
1070 PRINT "HALF LIFE IS  ";T2;
1080 PRINT " WITH CORRELATION COEFFICIENT ";R1;
1090 PRINT " FOR ";N;" OBSERVATIONS"
1150 PRINT "APPARENT VOLUME OF DISTRIBUTION,V.D.  ";DC;
1160 PRINT " LITRES, - V.D.PER KG ";CB
1200 PRINT "TOTAL BODY CLEARANCE, ML/MIN  ";CK;
1210 PRINT "  CLEARANCE PER KG ";CL
1250 PRINT "ESTIMATED VALUE OF K ";K;
1270 PRINT "  CONCENTRATION AT TIME 0  ";CO;" MG"
1285 PRINT "WHOLE BLOOD CLEARANCE  ";WBC;" MLS/MIN
1286 PRINT "-------------------------------------------"
1287 PR£ 0
1290 I = 0:R = 0:S1 = 0:S4 = 0:S5 = 0:V = 0:G = 0
1295 PRINT : PRINT
1300 RETURN
1340 Y(I) = LOG (Y(I))
1350 S1 = S1 + Y(I)
1360 S3 = S3 + X(I)
```

```
1370 S5 = S5 + X(I)^2
1380 S4 = S4 + X(I) * Y(I)
1390 RETURN
1400 S2 = N
1410 M = S1 / S2

1420 K = (S1 * S3 - S4 * S2) / (S5 * S2 - S3^2)
1430 CO = EXP ((S1 + S3 * K) / S2)
1440 T2 = LOG (2) / K
1441 T2 = (LOG (2) / K) * 60

1450 G = G + (Y(I) - LOG (CO) + K * X(I))^2

1460 R = R + (M - LOG (CO) + K * X(I))^2

1470 V = V + (X(I) - (LOG (CO) - Y(I)) / K)^2
1480 RETURN

2000 T2 = INT (10^3 * T2) / 10^3

2010 R1 = INT (10^3 * R1) / 10^3
2020 DC = D / CO

2030 DC = INT (10^2 * CB) / 10^3
2040 CB = (D / CO) / BW

2050 CB = INT (10^2 * CB) / 10^2
2060 CK = ((D / CO) * K) * 1000 / 60

2070 CK = INT (10^3 * CK) / 10^3
2080 CL = ((D / CO) * K / BW) * 1000 / 60

2090 CL = INT (10^3 * CL) / 10^3
3000 WBC = (100 * (((D / CO) * K) * 1000 / 60)) / (100 - PC)

3010 WBC = INT (10^2 * WBC) / 10^2

3020 K = INT (10^3 * K) / 10^3

3030 CO = INT (10^3 * CO) / 10^3
3040 RETURN
```

PHARMACOKINETIC PROGRAM 3

```
2    REM PROGRAM UPDATED APRIL 1985
5    REM MEPTAZINOL KINETICS.  ENTER FIRST 4 POINTS FROM INITIAL PART
     OF CURVE AND THREE POINTS FROM LAST PART OF CURVE.  THIS PROGRAM
     ASSUMES TWO COMPARTMENT MODEL
10   REM DATA INPUT
20   INPUT "DOSE ( IN MGS )";0
1010 FOR I = 1 TO 7
1020 PRINT "(":I")":"FOR BLOOD SAMPLE ":I:"INPUT TIME. DRUG CONC "
1030 INPUT T(I).I(I)
1032 PR£ 1
1033 PRINT T(I).I(I)
1034 PR£ 0
1035 A(I) = I(I):B(I) = C(I)
1040 NEXT I
6000 FOR S = 1 TO 7:Y(S) = LOG (I(S)): NEXT S
6010 J4 = T(5) + T(6) + T(7)
6020 K4 = Y(5) + Y(6) + Y(7)

6030 L4 = (T(5)^2) + (Y(6)^2) + (Y(7)^2)

6040 M4 = (Y(5)^2) + (Y(6)^2) + (Y(7)^2)
6050 R4 = (T(5) * Y(5)) + (T(6) * Y(6)) + (T(7) * Y(7))

6060 B4 = (3 * R4 - K4 * J4) / (3 * L4 - (J4^2))
6065 T2 = 0.693 / B4
6070 A4 = (K4 - B4 * J4) / 3
6080 A4 = EXP (A4)
6085 ARB = A4 / B4
6087 CL = D / ARB
6090 P4 = B4 * (R4 - J4 * K4 / 3)

6100 Q4 = M41 - (K4^2) / 3
6110 R4 = SQR (P4 / Q4)
6120 REM NOW PERFORM AN EXP STR IF
6130 K5 = 0:J5 = 0:L5 = 0:M5 = 0:R5 = 0
6140 FOR P = 1 TO 4
6150 S(F) = I(F) - (A4 * EXP (T(P) * B4))
6160 S(P) = LOC (S(P))
6170 J5 = J5 + T(P)
6180 K5 = K5 + S(P)

6190 L5 = L5 + (T(P)^2)

6200 M5 = M5 + (S(P)^2)
6210 R5 = R5 + (T(P) * S(P))
6215 NEXT P

6220 B5 = (4 * R5 - K5 * J5) / (4 * L5 - (J5^2))
6230 A5 = (K5 - B5 * J5) / 4
6240 A5 = EXP (A5)
6245 T1 = 0.693 / B5
6250 P5 = B5 * (R5 - J5 * K5 / 4)
```

```
6260 Q5 = M5 - (K5^2) / 4
6270 R5 = SQR (P5 / Q5)
6280 VP = D / (A5 + A4)
6270 K = ((A5 + A4) / ((A5 / B5) + (A4 / B4)))
6275 KE = K * 60
6297 K21 = ((B5 + B4) * 60) * (B4 * 60)) / KE
6299 K12 = (((B5 + B4) * 60) - K2 1) - KE
6302 VDSS = ((K12 + K21) / K21) * VP
6304 VD1 = CL / (B4 * 60)
6306 VD2 = C / A4
6310 REM PRINT OUT
6320 PR£ 1
6330 PRINT ""
6332 PRINT "DOSE=":D"MGS"
6350 PRINT "L1=":B5 * 60"HR-1"
6355 PRINT "ALPHA T1/2=":T1"HOURS"
6360 PRINT "A1=":A5"NG/ML"
6370 PRINT "L2=":B4 * 60"HR-1"
6375 PRINT "BETA T1/2=":T2"HR-1"
6377 PRINT "AREA BETA=":ARB"NG/ML/HR"
6378 PRINT "CLEARANCE BETA=":CL * 1000"LITRES/HOUR"
6380 PRINT "A2=":A4"NG/ML"
6390 PRINT "R1 = ":R5
6400 PRINT "R2 = ":R5
6400 PRINT "R2 = ":R4
6410 PRINT "VD1= ":VD1 * 1000"LITRES"
6420 PR£ 0
6430 END
```

PHARMACOKINETIC PROGRAM 4

```
10  REM ********************************
20  REM * APRICOT PHARMACOKINETICS******
30  REM *DR. G. BIRNIE*****************
40  REM ********************************
100 PRINT "WESTERN INFIRMARY, GLASGOW"
110 PRINT "PHARMACOKINETICS : INTRAVENOUS INJECTION"
120 PRINT "ADJUSTMENT OF PLOT TO 1,2 OR 3 EXPONENTIAL CURVES BY RESIDUALS
    METHOD"
130 PRINT:PRINT:PRINT"Enter title ..."
140 PRINT:PRINT:INPUT B$:GOSUB 2730:LPRINT B$:CLOSE£1
150 PRINT:PRINT:INPUT"Enter number of points : ";N
160 PRINT:PRINT:HPOS=14:PRINT"ENTER POINTS IN INCREASING ORDER    !!!!"
170 DIM X(N),Y(N),Y2(N),Y3(N),Z(N),Z2(N),Z3(N)
180 FOR I=1 TO N:PRINT
190 HPOS=4:PRINT"Point " ";I;",:INPUT"t=";X(I)
200 HPOS=4:PRINT,:INPUT"C=";Y(I)
210 NEXT I
220 PRINT:PRINT:PRINT"Point No","t(h)","C((UG/ML)":FOR I=1 TO
    N:PRINT I,X(I),Y(I):NEXT I
230 PRINT:INPUT"Error (O,N) ? ";JL$
240 IF JL$="N" THEN 300
250 INPUT"Error on point number : ";I
260 INPUT "Error on T or C (,C) ? ";FC$
270 IF FC$="T" THEN PRINT CHR$(7):INPUT"Enter real value of t for
    this point : ";X(I)
280 IF FC$="C" THEN PRINT CHR$(7):INPUT"Enter real value of C for
    this point : ";Y(I)
290 GOTO 220
300 FOR I=1 TO N:Z(I)=Y(I):NEXT I
310 PRINT:PRINT:GOSUB 2730:PRINT"t(h)","C(ug/ml)":FOR I=1 TO
    N:PRINT X(I),Y(I):NEXT I:PRINT:PRINT
320 GOSUB 2760
330 GOSUB 3320
340 X=X
380 FOR I=1 TO N:Y(I)=Z(I):NEXT I
390 LPRINT"t(h)","C(ug/ml)":FOR I=1 TO N:LPRINT X(I),Y(I):NEXT I
400 PRINT:PRINT "ATTENTION !!!":PRINT
410 PRINT "I WANT THREE EXPERIMENTAL POINTS FOR EACH REGRESSION."
    :PRINT
420 INPUT"Computing : 1,2 or 3 exp (0 to stop) ? ";A
430 IF A=0 THEN END
440 ON A GOSUB 450,870,1640
450 REM 1 EXP
460 PRINT:INPUT"Dose (ug) ? ";D1
470 M=1:P=N:Z=N:GOSUB 2470
480 T2=LOG(2)/ABS(B)
490 VD=D1/A
500 CL=ABS(B)*VD
510 SC=A/ABS(B)
520 PRINT:PRINT"Equation : C=A*EXP-(B*t)"
530 PRINT"A = ";A;" ug.ml-1"
540 PRINT"B = ";ABS(B);" h-1"
```

```
550 PRINT"R^2 = ";R2
560 PRINT"Biological half-time (t1/2) = ";T2;" h"
570 PRINT"Apparent volume of distribution (Vd) = ";VD;" ml"
580 PRINT"Plasma clearance (CLP) = ";CL;" ml.h-1"
590 PRINT"Area under curve (AUC) =";SC;" ug.h.ml-1"
600 GOSUB 2730
610 LPRINT:LPRINT"Dose = ";D1;" ug"
620 LPRINT:LPRINT"Equation :C=A*EXP-(B*t)"
630 LPRINT"A = ";A;" ug.ml-1"
640 LPRINT"B = ";ABS(B);" h-1"
650 LPRINT"R^2 = ";R2
660 LPRINT"Biological half-time (t1/2) = ";T2;" h"
670 LPRINT"Apparent volume of distribution (Vd) = ";VD;" ml"
680 LPRINT"Plasma clearance (CLP) = ";CL;" ml.h-1"
690 LPRINT"Area under curve (AUC) = ";SC;" ug.h.ml-1"
710 FOR I=1 TO N:Z2(I)=A*EXP(B*X(I)):NEXT I
720 FOR I=1 TO N:Z3(I)=((Z2(I)-Z(I))*100)/Z(I):NEXT I
730 GOSUB 2730:PRINT:PRINT"t(h)","Cobs(ug/ml)","Ccal(ug/ml)","Relative
    error(%)":FOR I=1 TO N:PRINT X(I),Z(I),Z2(I),Z3(I):NEXT
    I:PRINT:PRINT
740 PRINT
750 LPRINT"t(h)","Cobs(ug/ml)","Ccal(ug/ml)","Relative error(%)": FOR
    I=1 TO N:LPRINT X(I),Z(I),Z2(I),Z3(I):NEXT I:PRINT
760 PRINT:INPUT"Do you want computed predicted values (O for yes,
    N for another adjustment ) ? ";A$
770 IF A$="N" THEN 340
780 GOSUB 2730:PRINT:PRINT"Computed predicted Values:":PRINT:
    PRINT"t(h)","Ccal(ug/ml)":CLOSE 1
790 PRINT:INPUT"I compute C for wished r (O for begin, N for
    another adjustment";A$
800 IF A$="N" THEN 340
810 PRINT:HPOS=4:INPUT"t=";X
820 Y=A*EXP(B*X)
830 PRINT:HPOS=4:PRINT"C=";Y
840 GOSUB 2730:PRINT X,Y
850 GOTO 790
860 RETURN
870 REM 2 EXP
880 PRINT:INPUT"Dose (ug( ? ";D
890 PRINT:INPUT"Break time (h) = ";H:PRINT
900 PRINT:PRINT:Z=0
910 FOR I=1 TO N
920 IF X(I)>=H THEN PRINT X(I),Y(I):Z=Z+1
930 NEXT I
940 PRINT Z;" values with time higher or equal to   ";H:PRINT:M=N-Z+1:P=N
950 GOSUB 2470
960 FOR I=M TO P:Y(I)=EXP(Y(I)):NEXT I
970 PRINT:A2=A:B2=B:RA=R2
980 FOR I=1 TO N
990 Y2(I)=A*EXP(B*X(I))
1000 NEXT I
1010 PRINT:PRINT:Z=0
1020 FOR I=1 TO N
1030 IF X(I)<=H THEN PRINT X(I),Y(I):Z=Z+1
1040 NEXT I
```

```
1050 PRINT Z;" values with time lower or equal to ";H:PRINT
1060 M=1:P=Z:PRINT:PRINT"Resulting differences for these values
     :":FOR I=M TO P:Y(I)=Y(I)-Y2(I):PRINT X(I),Y(I):NEXT I:GOSUB
     2470
1070 A1=A:B1=B:RB=R2
1080 T2=LOG(2)/ABS(B2)
1090 K2=((A1*ABS(B2))+(A2*ABS(B1)))/(A1+A2)
1100 KE=(ABS(B1)*ABS(B2))/K2
1110 K1=ABS(B1)+ABS(B2)-K2-KE
1120 SC=(A1/ABS(B1))+(A2/ABS(B2))
1130 CL=D/SC
1140 VD=D/(ABS(A1)+ABS(A2))
1150 ZZ=D/A2
1160 PRINT:PRINT"Equation : C=A1*EXP-(B1*t)+A2*EXP-(B2*t)"
1170 PRINT"A1 = ";A1;" UG.ML-1"
1180 PRINT"B1 = ";ABS(B1);"h-1"
1190 PRINT"R^2(1)= ";RB
1200 PRINT"A2 = ";A2;" ug.ml-1"
1210 PRINT"B2 = ";ABS(B2);" h=1"
1220 PRINT"R^2(2)= ";RA
1230 PRINT"Biological half-time (t1/2) =;T2;" H"
1240 PRINT"Apparent volume of distribution (Vd) = ";ZZ;" ml"
1250 PRINT"Volume of central compartment (Vc) = ";VD;" ml"
1260 PRINT"Plasma clearance (CLP) = ";CL;" ml.h-1"
1270 PRINT"Area under curve (AUC) = ";SC;" ug.h.ml-1"
1280 PRINT"Rate constant for transfer between compartment 2 and
     1(k21) = ";K2;" h-1"
1290 PRINT"Elimination rate constant (kel) =;KE;" H-1"
1300 PRINT"Rate constant for transfer between compartment 1 and
     2(k12) = ";K1;" h-1"
1310 GOSUB 2730
1320 LPRINT:LPRINT"Dose = ";D;" ug"
1330 LPRINT"Break time = ";H;" h"
1340 LPRINT:LPRINT"Equation : C=A1*EXP-(B1*t)+A2*EXP-(B2*t)"
1350 LPRINT"A1 = ";A1;" ug.ml-1"
1360 LPRINT"B1 = ";ABS(B1);" h-1"
1370 LPRINT"R^2(1)= ";RB
1380 LPRINT"A2 = ";A2;" ug.ml-1"
1390 LPRINT" B2 = ";ABS(B2);" H-1"
1400 LPRINT"R^2(2)= ";RA
1410 LPRINT"Biological half-time (t1/2) = ";T2;" h"
1420 LPRINT"Apparent voume of distribution (Vd) = ";ZZ;" ml"
1430 LPRINT"Volume of central compartment (Vc) = ";VD;" ml"
1440 LPRINT"Plasma clearance (CLP) = ";CL;" ml.h-1"
1450 LPRINT"Area under curve (AUC) = ";SC;" ug.h.ml-1"
1460 LPRINT"Rate constant for transfer between compartment 2 and
     1 (k21) = ";K2;" h-1"
1470 LPRINT"Elimination rate constant (kel) = ";KE;" h-1"
1480 LPRINT"Rate constant for transfer between compartment 1 and
     2 (k12) =";K1;" h-1"
1490 X=X
1500 FOR I=1 TO N:Z2(I)=A1*EXP(B1*X(I))+A2*EXP(B2*X(I)):NEXT I
1510 FOR I=1 TO N:Z3(I)=((Z2(I)-Z(I))*100)/Z(I):NEXT I
1520 GOSUB 2730:PRINT:PRINT"t(h)","Cobs(ug/ml)","Ccal(ug/ml)",
     "Relative error(%)":FOR I=1 TO N:PRINT X(I),Z(I),Z2(I),Z3(I):
```

```
     NEXT I:PRINT:PRINT
1530 LPRINT:LPRINT"t(h)","Cobs(ug/ml)","Ccal(ug/ml)","Relative
     Error(%)":FOR I=1 TO N:LPRINT X(I),Z(I),Z2(I),Z3(I):NEXT I:LPRINT

1540 PRINT:INPUT"Do you want computed predicted values (O for yes,
     N for another adjustment ) ? ";A$
1550 IF A$="N" THEN 340
1560 GOSUB 2730:PRINT:PRINT"Computed predicted Values:":PRINT:
     PRINT"t(h)","Ccal(ug/ml)"
1570 PRINT:INPUT"I compute C for wised t (O for begin, N for another
     adjustment) ";A$
1580 IF A$="N" THEN 340
1590 PRINT:HPOS=4:INPUT"t=";X
1600 Y=A1*EXP(B1*X)+A2*EXP(B2*X)
1610 PRINT:HPOS=4:PRINT"C=";Y
1620 GOSUB 2730:PRINT X,Y
1630 GOTO 1570
1640 REM 3 EXP
1650 PRINT:INPUT"Dose (ug) ? ";D
1660 PRINT"BT2<BT1"
1670 PRINT:INPUT"Break time 2 (h) = ";H2
1680 PRINT:INPUT"Break time 1 (h) = ";H1
1690 PRINT:PRINT:Z1=0
1700 FOR I=1 TO N
1710 IF X(I)>=H1 THEN PRINT X(I),Y(I):Z1=Z1+1
1720 NEXT I
1730 PRINT Z1;" values with time higher or equal to  ";H1:PRINT:
     M=N-Z1+1:P=N:Z=Z1
1740 GOSUB 2470
1750 FOR I=M TO P:Y(I)=EXP(Y(I)):NEXT I
1760 PRINT:A3=A:B3=B:RA=R2
1770 FOR I=1 TO N
1780 Y3(I)=A*EXP(B*X(I))
1790 NEXT I
1800 PRINT:Z3=0:FOR I=1 TO N:IF X(I)<=H2 THEN PRINT
     X(I),Y(I):Z3=Z3+1:NEXT I
1810 PRINT Z3;" values with time lower or equal to ";H2
1820 PRINT:Z2=0
1830 FOR I=1 TO N
1840 IF X(I)<=H1 AND X(I)>=H2 THEN PRINT X(I),Y(I):Z2=Z2+1
1850 NEXT I
1860 PRINT Z2;" values with time between ";H2;" and ";H1
1870 M=Z3+1:P=Z2+Z3:PRINT:PRINT"Resulting differences for these values
     :":FOR I=M TO P:Y(I)=Y(I)-Y3(I):PRINT X(I),Y(I):NEXT
     I:Z=Z2:GOSUB 2470
1880 PRINT:A2=A:B2=B:RB=R2
1890 FOR I=1 TO N:Y2(I)=A*EXP(B*X(I))
1900 NEXT I
1910 PRINT Z3=0:FOR I=1 TO N:IF X(I)<=H2 THEN PRINT
     X(I),Y(I):Z3=Z3+1:NEXT I
1920 PRINT Z3;" values with time lower or equal to ";H2
1930 M=1:P=Z3:PRINT:PRINT"Resulting differences for these values
     :":FOR I=M TO P:Y(I)=Y(I)-Y3(I)-Y2(I):PRINT X(I),Y(I):NEXT
     I:Z=Z3:GOSUB 2470
1940 PRINT
```

```
1950 A1=A:B1=B:RC=R2
1960 T2=LOG(2)/ABS(B3)
1970 VD=D/(ABS(A1)+ABS(A2)+ABS(A3))
1980 SC=(ABS(A1)/ABS(B1))+(ABS(A2)/ABS(B2))+(ABS(A3)/ABS(B3))
1990 CL=D/SC
2000 PRINT:PRINT"Equation :
     C=A1*EXP-(B1*t)+A2*EXP-(B2*t)+A3*EXP-(B3*t)"
2010 PRINT"A1 = ";A1;" ug.ml-1"
2020 PRINT"B1 = ";ABS(B1);" h-1"
2030 PRINT"R^2(1)= ";RC
2040 PRINT"A2 = ";A2;" ug.ml-1"
2050 PRINT"B2 = ";ABS(B2);" h-1"
2060 PRINT"R^2(2)= ";RB
2070 PRINT"A3 = ";A3;" ug.ml-1"
2080 PRINT"B3 = ";ABS(B3);" h-1"
2090 PRINT"R^2(3)= ";RA
2100 PRINT"Biological half-time (t1/2) = ";T2;" h"
2110 PRINT"Volume of central compartment (Vc) = ";VD;" ml"
2120 PRINT"Plasma clearance (CLP) = ";CL;" ml.h-1"
2130 PRINT"Area under curve (AUC = ";SC;" ug.h.ml-1"
2140 GOSUB 2730
2150 LPRINT"Dose = ";D;" ug"
2160 LPRINT"Break time 2 = ";H2;" h"
2170 LPRINT"Break time 1 = ";H1;" h"
2180 LPRINT:LPRINT"EQUATION :
     C=A1*EXP-(B1*t)+A2*EXP-(B2*t)+A3*EXP-(B3*t)"
2190 LPRINT"A1 = ";A1;" ug.ml-1"
2200 LPRINT"B1 = ";ABS(B1);" h-1"
2210 LPRINT"R^2(1)= ";RC
2220 LPRINT"A2 = ";A2;" ug.ml-1"
2230 LPRINT"B2 = ";ABS(B2);" h-1"
2240 LPRINT"R^2(2)= ";RB
2250 LPRINT"A3 = ";A3;" ug.ml-1"
2260 LPRINT"B3 = ";ABS(B3);" h-1"
2270 LPRINT"R^2(3)= ";RA
2280 LPRINT"Biological half-time (t1/2) = ";T2;" h"
2290 LPRINT"Volume of central compartment (Vc) = ";VD;" ml"
2300 LPRINT"Plasma clearance (CLP) = ";CL;" ml.h-1"
2310 LPRINT"Area under curve (AUC) =";SC;" UG.H.ML-1"
2320 X=X
2330 FOR I=1 TO  N:
     Z2(I)=A1*EXP(B1*X(I))+A2*EXP(B2*X(I))+A3*EXP(B3*X(I)):
     NEXT I
2340 FOR I=1 TO N:Z3(I)=((Z2(I)-Z(I))*100)/Z(I):NEXT I
2350 GOSUB 2730:PRINT:PRINT"t(h)","Cobs(ug/ml)","Ccal(ug/ml)",
     "Relative error (%)":FOR I=1 TO N:PRINT
     X(I),Z(I),Z2(I),Z3(I):NEXT I:PRINT:PRINT
2360 LPRINT:LPRINT"t(h)","Cobs(ug/ml)","Ccal(ug/ml)","Relative error (%)":
     FOR I=1 TO N:LPRINT X(I),Z(I),Z2(I),Z3(I):NEXT I
2370 PRINT:INPUT"Do you want computed predicted values (O for   yes,
     N for another adjustment) ? ";A$
2380 IF A$="N" THEN 340
2390 GOSUB 2730:PRINT"Computed predicted
     values:":PRINT:PRINT"t(h)","Ccal(microg/ml)":CLOSE£1
2400 PRINT:INPUT"I compute C for wished t (O for begin, N for another
```

```
    adjustment) ";A$
2410 IF A$="N" THEN 340
2420 PRINT:HPOS=4:INPUT"t=";X
2430 Y=A1*EXP(B1*X)+A2*EXP(B2*X)+A3*EXP(B3*X)
2440 PRINT:HPOS=4:PRINT"C=";Y
2450 GOSUB 2730:PRINT X,Y:CLOSE£1
2460 GOTO 2400
2470 REM COMPUTING METHOD
2480 FOR I=M TO P
2490 Y(I)=LOG(ABS(Y(I)))
2500 NEXT I
2510 XM=0:YM=0:XY=0:X2=0
2520 SY=0:BX=0:BY=0
2530 FOR I=M TO P
2540 SY=SY+Y(I)
2550 BX=BX+(X(I)*Y(I))
2560 BY=BY+(Y(I)^2)
2570 XM=XM+X(I)
2580 YM=YM+Y(I)
2590 NEXT I
2600 XM=XM/Z
2610 YM=YM/Z
2620 FOR I=M TO P
2630 X2=X2+(X(I)-XM)^2
2640 XY=XY+(X(I)-XM)*Y(I)
2650 NEXT I
2660 B=XY/X2
2670 A=YM-B*XM
2680 A=EXP(A)
2690 Z1=(LOG(A)*SY)+(B*BX)-((SY^2)/Z)
2700 Z2=BY-((SY^2)/Z)
2710 R2=Z1/Z2
2720 RETURN
2730 X=X
2750 RETURN
2760 REM TRACING CURVE
2770 XMAX=X(N)
2780 YMAX=0
2790 YMIN=10000
2800 FOR T= 1 TO N
2810 IF Y(T)>YMAX THEN YMAX=Y(T)
2820 IF Y(T)<YMIN THEN YMIN=Y(T)
2830 NEXT T
2840 ECHX=INT(XMAX/2)
2850 IF XMAX/2><INT(XMAX/2) THEN ECHX=ECHX+1
2860 ECHY=INT(YMAX/.01)
2870 IF YMAX/.01><INT(YMAX/.01)THEN ECHY=ECHY+1
2920 C=0
2930 FOR T=150 TO 550 STEP 100
2960 C=C+.4
2990 NEXT T
3000 C=0
3010 FOR T=50 TO 170 STEP 30
3040 C=C+.002
3070 NEXT T
```

```
3170 FOR C=1 TO N
3180 V=50+(500/ECHX/2*X(C))
3190 W=20+(150/ECHY/.01*Y(C))
3240 NEXT C
3250 REM PLOTTING
3310 RETURN
3320 REM TRACING SEMI-LOG CURVE
3360 C=0
3530 IF YMAX>100 THEN:C=3:INC=5:GOTO 3560
3540 IF YMAX>10 THEN C=2:INC=.5:GOTO 3560
3550 C=1:INC=.05
3560 V=50:W=20
3580 AA=0
3590 FOR B2=1 TO 3
3600 AA=INC
3610 W=LOG(5)*.434295*50+((B2-1)*50)+20
3660 AA=AA+INC
3670 W=LOG(10)*.434295*50+((B2-1)*50)+20
3720 INC=INC*10
3730 NEXT B2
3740 FOR B2=1 TO N
3750 ON C GOSUB 3950,3990,4030
3760 IF ZZ=0 OR ZZ<1 THEN W=20:GOTO 3780
3770 W=LOG(ZZ)*.434295*50+((NBMM-1)*50)+20
3780 V=50+(500/ECHX/2*X(B2))
3830 NEXT B2
3850 REM PLOTTING
3890 FOR I=1 TO 2000:NEXT I
3940 RETURN
3950 IF Y(B2)<.1 THEN ZZ=Y(B2)*100:NBM=1:GOTO 3980
3960 IF Y(B2)<1 THEN ZZ=Y(B2)*10:NBM=2:GOTO 3980
3970 NBMM=3:ZZ=Y(B2)
3980 RETURN
3990 IF Y(B2)<1 THEN ZZ=Y(B2)*10:NBMM=1:GOTO 4020
4000 IF Y(B2)<10 THEN ZZ=Y(B2):NBMM=2:GOTO 4020
4010 NBMM=3:ZZ=Y(B2)*.1
4020 RETURN
4030 IF Y(B2)<10 THEN ZZ=Y(B2):NBMM=1:GOTO 4060
4040 IF Y(B2)<100 THEN ZZ=Y(B2)*.1:NBMM=2:GOTO 4060
4050 NBMM=3:ZZ=Y(B2)*.01
4060 RETURN
```

PHARMACOKINETIC PROGRAMS

Four pharmacokinetic programs have been developed to determine the pharmacokinetic parameters for the various drugs studied in this thesis.

Program 1 is for a one compartment analysis and was used for the antipyrine data.

Program 2 is for a one compartment analysis and is modified for indocyanine green.

Program 3 is for a two compartment analysis and was used for the Midazolam and Meptazinol data.

Program 4 is a program which has been developed to allow 1,2 or 3 compartment analysis of pharmacokinetic data.

PHARMACOKINETIC PROGRAM 1

```
90   G$ =  CHR$  (7)
100  PR£  1
106  PRINT  "============================================================"
110  PRINT "HALF LIFE PROGRAMME"
111  PRINT "============================================================"
112  PR£ 0
113  PRINT ""
114  DIM X (50), Y (50)
116  HOME
120  INPUT "TODAY'S DATE ?........";DA$
125  PRINT ""
130  INPUT "WHICH DRUG ?....";Z$
135  PRINT ""
190  INPUT "WHAT DOSE OF DRUG ?....";N$
191  PRINT ""
195  INPUT "SUBJECT'S NAME ?.......";N$
200  PRINT ""
210  INPUT "SUBJECT'S BODY WEIGHT ?";BW
215  PRINT ""
216  HOME
220  PRINT "ENTER DATA IN FORMAT, ELAPSED TIME IN HOURS-,
     CONCENTRATION-,"
230  PRINT
250  JJ = JJ + 1
272  PRINT
275  PR£ 1
280  PRINT N$ SPC( 2)DA$ SPC(02)Z$ SPC( 2)D"MGS" SPC( 2)"WEIGHT "BW"
     KGS"
290  PRINT "------------------------------------------------------------"
291  PR£ 0
293  HOME
295  INPUT "HOW MANY ENTRIES ? "; X1
```

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