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COMMENTARY

EFFECTS OF LIVER DISEASE ON DRUG DISPOSITION IN MAN

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Liver disease in man consists of an assortment of pathophysiological disturbances which, in addition to damage to the hepatic cells and architecture, may lead to a reduction in overall hepatic blood flow, shunting of blood around or within the diseased liver and an alteration of plasma protein synthesis. It is not surprising, therefore, that both acute and chronic liver disease can produce significant effects upon drug disposition, particularly hepatic drug removal. However, the determination, quantification and interpretation of any such alterations in the handling of drugs by patients with liver disease are quite difficult. First, damage to the organ and the degree of functional abnormality of the organ vary widely within any diagnosed disease process and, importantly, the clinical and laboratory criteria for rating the severity of any particular class of liver disease are relatively crude. As a result, any study population has the potential for considerable heterogeneity with respect to the magnitude of alterations in the various processes of drug disposition [1]. Regrettably, many reported studies have failed to provide suitable clinical information to permit adequate assessment of the disease-state. Additionally, it is not unusual for the patients under study to be receiving concomitant therapy with other drugs, with the attendant potential for drug–drug interactions. These may well obscure any disease-induced changes in the disposition of the drug of interest, as exemplified by the study of Levi *et al.* [2] with phenylbutazone. A similar situation is becoming increasingly apparent in normal individuals utilized as control subjects [3], and this drug interaction factor clearly causes a considerable problem in data interpretation. Many investigators have also limited their assessment of altered drug disposition to the determination of the elimination half-life. Unfortunately, this parameter alone may have limited usefulness in identifying such factors (*vide infra*). Because of the lack of recognition of these types of problems, many reported studies are difficult to interpret definitively and a generally confused, and sometimes conflicting, picture has developed of the effects of liver disease on drug disposition. In recent years, more carefully designed and considered studies have been undertaken and a clearer impression is now emerging, particularly with respect to viral hepatitis and cirrhosis. Less information is available concerning the effects of biliary obstruction, neoplastic diseases and drug-induced liver damage. Recent reviews have dealt with specific classes of disease and drugs [4–6]. Consequently, this article will predominantly concern itself with the underlying nature of alterations in the various physiological determinants which lead to the observed changes in drug disposition in patients with hepatic dysfunction.

MECHANISMS OF ALTERED DRUG DISPOSITION

Hepatic extraction and clearance

Intuitively it might be expected that liver dysfunction would lead to an impairment in the ability of this organ to remove drugs irreversibly by either metabolism and/or biliary excretion. A major problem arises, however, in selecting a parameter to express such a change. This is because drug removal actually reflects a number of different, independent, and potentially rate-limiting physiological processes, which all have the possibility for change in the patient with liver disease. Moreover, these parameters may interact to exaggerate or dampen any effect associated with damage to the function of the liver cell *per se*. The clearance concept is of particular value in this regard since it is a measure of the efficiency of drug removal from a biological fluid [7, 8].

From a practical standpoint, the clearance of drug from blood circulating through the liver, hepatic clearance, is the most useful assessment of the overall functional efficiency of the liver. This is because hepatic clearance, plus any contribution from other organs of elimination such as the kidney, i.e. systemic drug clearance, controls the circulating drug concentration at steady-state. This, in turn, is generally considered to be the major determinant of any elicited pharmacological effects. Most analytical methodologies for determining drug concentrations in blood or plasma do not distinguish between free or unbound drug and that which is bound to the various consitituents of blood such as the plasma proteins. Consequently, the hepatic clearance is frequently expressed in terms of total drug ($Cl_{H,\,total}$). However, since it is usually presumed that only the unbound drug can cross the various biological membranes and translocate to the receptor site(s), it is more appropriate to consider the clearance and steady-state concentration of free drug ($Cl_{H,\,free} = Cl_{H,\,total}/f_B$, where f_B is the fraction of drug present unbound in the blood). Liver disease can significantly affect the binding of drugs in the blood, and, if this change is overlooked, inappropriate interpretations and conclusions may be drawn from the experimental data. For example, the total systemic plasma clearance of tolbutamide in acute viral hepa-

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titis is increased by about 50 per cent [9, 10]. Since almost all of this drug is eliminated by biotransformation and presumably by the liver, it might be interpreted that hepatitis paradoxically increases the efficiency of the liver to metabolize tolbutamide. But, if the clearance is corrected for the change in drug binding, there is no significant difference between normal and diseased individuals. This would suggest that the change in $Cl_{H,\,\text{total}}$ may be attributed entirely to the associated alterations in plasma drug binding, and there is in fact no significant change in metabolic activity of the liver. A similar phenomenon has been observed with phenytoin in acute viral hepatitis [11]. Even when liver disease causes a significant reduction in total systemic clearance, this change may not accurately reflect the degree of functional impairment of the hepatic cells, if it is also accompanied by a change in binding. For example, the 2-fold decrease in the clearance of diazepam in cirrhosis underestimates the actual hepatic damage since the unbound fraction in the blood is also increased [12]. In fact $Cl_{H,\,\text{free}}$ is reduced by almost 4-fold. Consideration should also be given to the fact that alterations in plasma binding may also affect the distribution of the drug within the blood [13, 14]. Since drug in the erythrocyte usually equilibrates rapidly with that in the plasma, the blood acts as a single compartment with respect to mass transfer. Consequently, assessment of hepatic clearance should be based upon blood rather than plasma determinations.

Unfortunately, an alteration in drug clearance from the blood in patients with liver disease. even if expressed in terms of unbound drug, does not generally indicate the responsible mechanisms or the magnitude of any changes in the involved physiological determinants of hepatic function. This is because removal of drug from the blood by the liver depends on its rate of delivery to the organ, i.e. liver blood flow (Q), the binding of drug in the blood as reflected by f_B and the inherent ability of the liver to eliminate the drug by the processes of metabolism and/or biliary excretion. The latter can be conceived as the rate of clearance of drug from the liver water, and has been termed the free intrinsic clearance ($Cl'_{\text{intrinsic}}$). The relationship between these determinants is indicated in Equation 1 [8].

$$Cl_{H,\,\text{total}} = Q\left[\frac{f_B Cl'_{\text{intrinsic}}}{Q + f_B Cl'_{\text{intrinsic}}}\right] = Q\left[\frac{Cl_{\text{intrinsic}}}{Q + Cl_{\text{intrinsic}}}\right] = QE. \quad (1)$$

This equation also indicates that the free intrinsic clearance and binding in the blood may be combined into a term for the intrinsic clearance of total drug ($Cl_{\text{intrinsic}}$), which reflects the ability of the liver to clear the unbound plus bound drug in the absence of any flow limitations. Also, the parenthetic term in Equation 1 is equivalent to the hepatic extraction ratio (E). If $Cl'_{\text{intrinsic}}$ is considered with respect to the kinetic characteristics of the enzymes responsible for the metabolism of the drug, then, so long as the drug concentration in liver water is significantly below K_m i.e. first-order conditions, this parameter is equivalent to the ratio of $V_{\max}$ to K_m [15, 16]. This condition is apparently applicable to the vast majority of drugs as they are normally used in clinical practice. Hence, it is apparent that the hepatic biochemical changes due to the underlying pathophysiology of the disease-state are best quantified by the $Cl'_{\text{intrinsic}}$ parameter. The latter concept is relatively new and studies designed to explicitly estimate any such changes have not yet been reported. Equation 1 indicates that, in addition to knowledge of f_B, estimation of $Cl'_{\text{intrinsic}}$ requires information about the hepatic extraction ratio and the functional blood flow to the liver. The latter two parameters are not directly determined in routine drug disposition studies. However, in those situations where hepatic venous catheterization has been carried out, the extraction ratios of compounds such as galactose [17], bromosulfophthalein [18–20] and indocyanine green [21–23] were significantly reduced in chronic liver disease. From the knowledge of the concomitantly determined hepatic clearance, an estimated total liver blood flow may be determined, and from this the reduction in $Cl_{\text{intrinsic}}$ calculated. Such calculations indicate that, in patients with chronic liver disease, the $Cl_{\text{intrinsic}}$ of these compounds is reduced to about 50–87 per cent of the values in normal individuals [24]. Of less direct evidence, particularly relevant to drug metabolism, are the findings that where the formation and elimination of particular drug metabolite have been followed in patients with liver disease, the results are consistent with a reduction in $Cl'_{\text{intrinsic}}$. For example, reduced amounts of hydroxyamylobarbital [25], conjugated phenobarbital [26] and 3-ketohexobarbital [27] are excreted in the urine of patients with liver disease after administration of the parent drugs. Additionally, the accumulation of the metabolite of diazepam in the plasma [12] and the $^{14}CO_2$ expired in 24 hr after administration of [^{14}C-*N*-methyl]diazepam [28] are reduced in such patients. An alternative approach to obtaining quantitative information on possible changes in hepatic intrinsic clearance is that offered by administering the drug orally. After the drug is absorbed into the portal circulation, it passes through the liver one extra time relative to the same amount of drug administered directly into the systemic circulation by intravenous injection. This first-pass effect magnifies the effect of any impairment of drug metabolism on the systemic drug levels. In fact, in the absence of portacaval shunting [8],

$$Cl_{\text{intrinsic}} = \frac{D_0}{AUC_0} - \frac{fD_0}{AUC_0}, \quad (2)$$

where AUC_0 is the total area under the blood concentration/time curve produced by the dose of drug, D_0, which reaches the portal circulation and f is the fraction of the systemically available drug which is eliminated by extrahepatic processes, such as renal excretion. Consequently, $D_0/f_B \cdot AUC_0$ is a good reflection of $Cl'_{\text{intrinsic}}$, and if the drug is totally metabolized, it is a direct measure of this parameter. Again, direct studies utilizing this approach in liver disease have not been reported. However, it is clear that future investigations should be directed more specifically toward quantification of the disease-induced changes in the inherent capability of the hepatic cell to irreversibly remove an administered drug.

Because of its involvement in both the hepatic extraction ratio and clearance, it would also appear appropriate that additional investigations on the effects of liver disease upon hepatic hemodynamics be carried out. This is particularly so with respect to chronic liver disease, and the differentiation of functional vs total hepatic blood flow. Based on the early study of Caesar *et al.* [21], it is generally considered that the estimated hepatic blood flow is significantly decreased in patients with chronic liver disease. However, other investigators [17–20, 22, 23] have not confirmed this finding, and the majority of the presently available data suggests that total liver blood is not significantly reduced in these patients [24]. A similar situation appears to exist in acute viral hepatitis where normal [29] or even slightly elevated [30, 31] flows have been reported. The presence of a surgical portacaval anastomosis may decrease the blood flow to the liver which would be expected to lead to a reduction in the hepatic clearance of drugs whose hepatic removal is flow dependent. This appears to occur for indocyanine green [20] and *d*-propranolol [24, 32] at any given degree of hepatic cell function. In addition, the surgical procedure may affect the metabolizing/excretory capacity of the liver [24]. Intra- as well as extrahepatic anastomoses may also exist as a direct result of the disease-state and these may be quite significant. In alcoholic liver disease, up to 62 per cent of mesenteric and 80 per cent of splenic flow may undergo extrahepatic shunting [33], and intrahepatic anastomosis has been reported to range from 3 to 66 per cent [34] and 3 to 34 per cent [35]. The effect of such shunting is to reduce functional flow to the hepatic cells further than total flow estimates would indicate. The existence of portasystemic shunts may also affect the fraction of the absorbed oral dose which reaches the systemic circulation. Because of the potential for first-pass elimination, this is more significant for drugs with high values of $Cl_{\text{intrinsic}}$ than those with low values, i.e. small hepatic extraction ratios. In such situations, the increased bioavailability will lead to higher blood concentrations than in a normal individual and in addition these levels will decline more slowly because of the presence of decreased hepatic clearance of the drug. The magnitude of such changes has been demonstrated in both animals [36] and man [37], and such a phenomenon has been suggested to be responsible for the increased incidence of toxicity of niridazole in the hepatosplenic form of bilharziasis compared to the intestinal form of the disease [38].

Previous mention has been made of the potential for liver disease, particularly if severe and of a chronic nature, to alter the plasma binding of a drug. Abnormal drug binding is frequently considered to be a result of the reduced concentration of serum albumin but binding changes also occur when this factor is not altered, as in acute viral hepatitis, and also where albumin is not significantly involved in the binding phenomenon, e.g. *d*-propranolol [32]. Elevated circulating levels of unconjugated bilirubin have been suggested to account for the change in binding of some drugs based upon a mechanism involving competitive displacement. Addition of comparable concentrations of bilirubin *in vitro* has in fact been shown to decrease the binding of tolbutamide [9, 10], phenytoin [11] and warfarin [39]. However, in general, the degree of change after such additions was less than that observed in the plasma from patients with liver disease. This would suggest the presence of other displacing agents in the plasma of such patients or alternatively a change in binding by some other mechanism. The quantitative effect of altered drug binding in the blood on hepatic extraction and, therefore, clearance is indicated by Equation 1. In general, an increase in f_B will tend to increase the efficiency of the hepatic removal process; however, the relationship is not linear [8]. Accordingly, the extent of change depends on the relative values of binding in normal and diseased individuals, $Cl'_{\text{intrinsic}}$, and liver blood flow. For drugs which are poorly extracted an almost proportional increase in total drug clearance results from a decrease in binding. On the other hand, if the drug is well extracted, the effect of an increase in the free fraction is blunted and may be of little importance in determining hepatic extraction, e.g. propranolol in normal man [40]. Counteracting this trend toward increased extraction is the potential for the simultaneous presence in patients with liver disease of a reduced $Cl'_{\text{intrinsic}}$, and, therefore, an impaired ability to metabolize and/or excrete the drug into the bile. The net effect of these opposing changes on extraction/clearance will depend upon their relative magnitudes. If the increase in the unbound fraction is insufficient to override the reduced metabolic ability, then the hepatic removal of total drug will be impaired relative to normal subjects, as previously mentioned for diazepam in cirrhosis [12]. At the other extreme, a paradoxical increase or minimal change in total clearance would be expected if the effect of the alteration in binding was greater than the change in $Cl'_{\text{intrinsic}}$. The aforementioned studies with tolbutamide [9, 10], phenytoin [11] and also warfarin [39] serve as examples of this. Whether this mechanism is also involved, in addition to other factors, in the reported increase in the total metabolic clearance of ampicillin in patients with cirrhosis [41] is not clear, because plasma binding was not determined. Importantly, Equation 1 indicates that consideration of the free clearance, obtained from the ratio of total clearance to the unbound fraction, will not indicate the magnitude of $Cl'_{\text{intrinsic}}$ except in the limiting situation where the latter value is very small relative to liver blood flow, and, therefore, $Cl_{H,\text{ total}}$ approaches $f_B \cdot Cl'_{\text{intrinsic}}$.

Impaired drug elimination induced by liver disease is most critical for those drugs which are predominantly removed from the body by hepatic processes, and, hence, extrahepatic elimination is small. For those drugs which are eliminated by other organs, particularly the kidney, any hepatic dysfunction would be expected to be dampened out. However, this presumption neglects the possibility of altered renal function which may occur in advanced cirrhosis [42, 43]. With the exception of carbenicillin [44] and benzylpenicillin [45] few studies have specifically investigated this particular situation.

Drug distribution

In view of the potential for liver disease to alter drug binding in the blood, it is not surprising that changes in the quantitative fashion in which the drug

distributes within the body are not uncommon in patients with liver disease. Such alterations are frequently measured by reference to the pharmacokinetic term, volume of distribution, which is best assessed at steady-state ($Vd_{(ss)}$). In addition, the apparent volume into which the drug initially distributes after rapid intravenous administration (V_1) may be utilized. These parameters, however, provide little insight into the mechanism of any observed alteration. The physiological approach to distribution developed by Gillette [15] is somewhat more useful, at least from a conceptual standpoint, in that it indicates that distribution is a function of several biological determinants.

$$Vd_{\text{total}} = V_B + V_T \frac{f_B}{f_T}, \tag{3}$$

where V_B is the blood volume, V_T is the volume of the other tissues of the body and f_T and f_B are the fractions of unbound drug in the tissue and blood respectively [8]. As with drug clearance, it is also possible to consider unbound in contrast to total drug by correcting for f_B.

The volumes of distribution at steady-state of diazepam [12], ampicillin [41] and lidocaine [46] have been reported to be increased in cirrhosis. The mechanism of such differences is not clear since they could involve possible changes in f_B and/or f_T, and f_B was not measured except in the case of diazepam. With this drug the change in $Vd_{(ss)}$ is greater than would be expected on the basis of altered drug binding in the blood, thus suggesting an alteration in tissue binding of the drug. In addition, the general and regional circulatory alterations which accompany liver disease may be involved. These factors may also affect the distribution volume (V_1) into which the drug initially distributes after rapid intravenous administration. It is not unusual to observe greater intersubject variability in this parameter in patients with liver disease compared to normal individuals. Although statistical differences may not be present in the small patient populations that are often investigated, trends toward increased [12, 41] and decreased [47] values for V_1 have been reported. The presence of ascites may also affect drug distribution. Thus, with *d*-propranolol [32], despite similar plasma binding, patients with chronic liver disease and ascites had a 2-fold increase in the distribution volume of the drug compared to similar patients without ascites. Moreover, the ascitic fluid may behave pharmacokinetically quite differently from other body tissues [41], probably due to its relatively small turnover [48].

Elimination half-life

A large proportion of the reported studies on the effects of liver disease on drug disposition have used the elimination half-life ($T_{1/2}$) as the quantitative index of any changes, and have generally presumed that this parameter is a reflection of the drug-eliminating function of the liver. While this may indeed be a correct assumption for certain drugs with specific dispositional characteristics, it is not generally valid. This is because the half-life is dependent on both the total systemic clearance of the drug [hepatic ($Cl_{H,\text{ total}}$) plus extrahepatic ($Cl_{EH,\text{ total}}$) clearances] and its quantitative distribution within the body (Vd_{total}).

$$T_{1/2} = \frac{0.693 Vd_{\text{total}}}{Cl_{H,\text{total}} + Cl_{EH,\text{total}}}. \tag{4}$$

Even where elimination is solely by the liver, substitution of Equations 1 and 3 into Equation 4 indicates that the elimination half-life is a complex parameter dependent upon the inter-relationship of a number of physiological variables. Disease-induced changes in the latter may well act in opposite directions with respect to their effect on the half-life. Hence, it is not surprising that the reported studies on the effect of liver disease on $T_{1/2}$ indicate in some instances prolongation, in others shortening, and with some drugs no change in this parameter [4, 5]. When the disease-state only produces an alteration in $Cl'_{\text{intrinsic}}$ and/or liver blood flow will the half-life change directly reflect this. If alterations occur in the degree of drug binding in the blood or tissues, or the size of the pharmacokinetic body spaces into which the drug can distribute, then the half-life is a poor indicator of the alterations in hepatic function. Hopefully, future studies will recognize this limitation in the interpretation of half-life information.

CLINICAL SIGNIFICANCE OF ALTERED DRUG DISPOSITION

Although acute drug disposition studies in patients with liver disease may reveal basic information concerning alterations in the physiological determinants of the involved processes, a major purpose of this type of study is directed toward a more rational use of the drug in these patients. The general hypothesis is that the alterations in drug disposition will require modification of the usual dosage regimen of the drug. Whether this is indeed true depends largely on the drug in question, the manner of its use and the disease-state itself. Most concern is expressed for the situation where the drug is used over a prolonged period of time, and administration of the drug to the diseased patient according to some regimen suitable for a patient without hepatic dysfunction will potentially lead to unexpected drug accumulation with its attendant increase in the risk of untoward effects. Any increased accumulation due to an impairment in systemic drug clearance will be exaggerated if a greater availability of drug is present because of the decrease in the hepatic extraction ratio or portacaval shunting. If the drug is to be used acutely or for a short period of time relative to its half-life, then the dispositional changes alone are unlikely to affect its efficacy or toxicity. This probably accounts for the lack of any significant management problems in the use of diazepam to treat delirium tremens where it would be expected that impaired drug clearance would be present in some such patients due to concomitant liver disease [12, 49]. The risk of toxicity will clearly depend not only upon the therapeutic ratio of the drug, i.e. the range between therapeutic and undesirable drug levels, but also on the magnitude of the accumulation relative to the non-diseased individual. These factors will vary for each individual drug and hence studies should be directed towards the more important drugs

as they are typically used, and an evaluation of efficacy and safety in patients with liver disease. Critical to such studies is an understanding of the pharmacokinetic differences in these patients compared to normal individuals. The most important and practically useful information in this regard is the systemic clearance of unbound drug (Cl_s/f_B). As indicated previously, systemic clearance is the controlling factor of steady-state blood levels, and the circulating unbound drug concentration is generally considered to be better related to any pharmacological effects than the total drug concentration. Unless the clearance of unbound drug is significantly altered, presumably by impairment of the hepatic contribution to this term, it is unlikely that dosage modification will be required even though other changes in total drug clearance and other processes of disposition are present. Knowledge of the elimination half-life is of secondary value but does provide information useful in determining an appropriate dosage interval to minimize fluctuations in the blood levels during this period.

Despite the problems involved in definitively interpreting many of the reported studies, it is clear that the observed alterations have often been small, e.g. ampicillin [41], pentobarbital [47, 50], phenobarbital [26] and phenylbutazone [2, 51]. When major alterations do occur they are usually no greater on the average than 2- to 3-fold, although certain individuals may exhibit greater changes than this. In patients without liver dysfunction a much wider intersubject variability is frequently observed. The significance of the abnormal pharmacokinetics in the patient with liver disease is, therefore somewhat questionable. The application of the knowledge of any pharmacokinetic parameter changes must also be tempered by the realization that the inherent receptor sensitivity and response, especially for drugs affecting the central nervous system, may be affected in liver disease. Examples are diazepam [52], morphine [53], chlorpromazine [54, 55], barbiturates [56] and warfarin [39]. It is highly probable that both pharmacokinetic and pharmacodynamic alterations are involved in the incrimination of sedative and analgesic drugs as the second most common precipitant of hepatic coma [57]. Presence of the latter may indicate an even greater degree of impairment of hepatic clearance [58]. In patients with significant liver disease, it would appear reasonable to use drugs whose disposition is unaltered by hepatic dysfunction, e.g. oxazepam [59], so long as normal and predictable clinical responses are obtained. Where this is not possible, then prudence and individualization of therapy according to the clinical response are still, at the present time, the most appropriate manner in which to utilize drugs in patients with liver disease.

PREDICTIVE TESTS OF ALTERED DRUG DISPOSITION

Impairment of urinary drug excretion in renal failure is often predictable from knowledge of the serum creatinine value or the creatinine clearance [60]. Attempts have been made and continue to be made to develop an analogous approach for the impaired hepatic clearance in liver disease. Until recently, these attempts have been largely unsuccessful. Initially, correlations were attempted between an observed pharmacokinetic change and an alteration in one or more of the conventional biochemical "liver function" tests, e.g. serum albumin, prothrombin time, SGOT, serum total bilirubin, LDH, and alkaline phosphatase. These tests reflect widely different aspects of the multifaceted functions of the liver, hence, it is not surprising that few successful correlations with drug elimination have been established. Some relationships have been seen with either serum albumin and/or prothrombin time [1, 2, 25, 26, 32, 61, 62]; however, these results probably reflect a distribution of patients into sub-groups, severe versus mild or compensated liver damage, since continuous correlations have not been established. Also, it should be noted that most investigators have attempted to obtain a relationship with the elimination half-life which does not necessarily give a good indication of the efficiency of hepatic drug removal, *vide supra.*

Because of the lack of success of these "liver function" tests to predict alterations in drug elimination in liver disease, there has been increasing interest in developing specific tests for this purpose, utilizing model compounds which are subject to hepatic removal. Substrates examined to date include such diverse substances as galactose [51, 62–64], indocyanine green [32, 65, 66], antipyrine [32, 65] and [^{14}C]aminopyrine [67–69]. The latter two compounds are particularly attractive in that they utilize non-invasive procedures to assess hepatic function, i.e. measurement of salivary concentrations of antipyrine or the urinary excretion of the metabolite, 4-hydroxyantipyrine, and measurement of the expired $^{14}CO_2$ formed by demethylation of aminopyrine.

The initial results from the model drug approach are quite encouraging, at least in chronic liver disease. Thus, the impairments in the clearances of propranolol, indocyanine green and antipyrine are well correlated [24, 32, 65]. In a less definitive study, the half-life of either antipyrine, lidocaine or acetaminophen was always associated with a corresponding impairment in the elimination of the other drugs [61]. However, rigorous prospective evaluation of these "marker" compounds will be required before their practical utility and limitations as general predictors of drug-metabolizing ability in the presence of liver disease of varying etiology and severity are determined. A possible spin-off of these types of investigations may well be the development of a valuable liver function test *per se*, since there is preliminary evidence that the ability to metabolize certain drugs may be a much more sensitive indicator of general hepatic dysfunction than the presently available biochemical tests [68].

Perhaps the most intriguing aspect of the studies with one or more drugs in the same patient with chronic liver disease is the strong correlations that appear. This is despite the fact that some compounds, such as indocyanine green, are excreted by biliary excretion, whereas others undergo biotransformation and, more importantly, involve different types of drug-metabolizing enzymes. Moreover, in some instances hepatic clearance by the normal liver is reflective of the drug delivery rate, i.e. hepatic blood flow (indocyanine green and propanolol), whereas in other cases the metabolizing activity of the liver is rate-

limiting (antipyrine and aminopyrine). Such positive correlations could occur if both $Cl_{intrinsic}$ and liver blood were reduced in parallel. However, this would not alter the hepatic extraction ratio (Equation 1). Direct measurement of this parameter [13, 18–23] indicates though that chronic liver disease does lead to a reduction in E. Thus, the reduction in both hepatic clearance and extraction must indicate that $Cl_{intrinsic}$ is reduced to a greater extent than liver blood flow. The parallel and proportionate reduction of both high and low clearance drugs might then be due to a reduced ability of each liver cell to eliminate drugs while blood flow is maintained. This "sick cell" hypothesis [24], however, would mean that the intrinsic clearance of drugs with an initially high value of this term would have to be reduced to a greater extent than that of drugs with an initially low $Cl_{intrinsic}$. While this is possible, an alternative is that chronic liver disease is associated with a reduced mass of normally functioning and perfused cells; the "intact cell" hypothesis. The reduced clearance of high clearance drugs would then be due to the presence of intrahepatic shunts. These two hypotheses [24] may not be mutually exclusive and investigations are clearly required to test their validity. Certainly the observations [70–72] that the metabolic activity *in vitro* of biopsied liver specimens is not significantly altered except when the liver disease is quite severe may be supportive evidence for the "intact cell" concept.

Despite the possibility that the clearance of a marker drug, such an antipyrine, may be indicative of the metabolic capability of a patient with liver disease, even for drugs which are handled by the body by very different pathways and perhaps processes, the empiric relationship for each drug of interest will have to be determined. Exceptions to any generalization are almost certain to occur and will likely occupy the attention of investigators for some years to come.

PRESENT AND FUTURE PERSPECTIVES

Despite the occasional conflicting data, there seems to be little doubt that the hepatic drug elimination for many drugs is impaired in patients with liver disease, and that the changes are somewhat less dramatic in acute viral hepatitis than in cirrhosis. However, the concept that only the intrinsic metabolizing or excretory abilities are affected by liver disease is too simplistic. All of the major determinants of disposition may be altered to varying degrees dependent on the specific drug and disease-state. The use of the elimination half-life to assess the severity of hepatic damage provides little indication, in general, of the magnitude or inter-relationship of these processes. Future studies must be more rigorously designed than in the past, if definitive and useful information on the nature of the specific perturbations is to be obtained. Consideration must be given to elucidating and quantifying the alterations in the physiological determinants of the disposition processes, particularly as they affect the systemic and hepatic clearance of both total and unbound drug. Information on liver blood flow, hepatic extraction ratio and intrinsic clearance would reveal the more fundamental aspects of any change in hepatic clearance. It would also be valuable to develop a clearer understanding of the unequal effect that liver disease can have upon the hepatic elimination of different drugs and different pathways of metabolism [73]. Even when a common type of biotransformation is involved, e.g. mixed function oxygenation, the clearance of some drugs is affected more than that of others, despite in many instances the fact that the same overall process is apparently involved. For example, the elimination of antipyrine is invariably impaired in both cirrhosis and acute viral hepatitis [1, 32, 62–65] whereas that of phenytoin is not affected in the latter disease-state [11], even though hydroxylation is an important elimination pathway for both drugs. Quite clearly the various routes of drug metabolism exhibit profoundly different sensitivities to the consequences of liver disease [73]. If the reasons for this were appreciated, this might allow a more rational choice of drug in the treatment of such patients. In the interim, empiricism coupled with a good understanding of any pharmacokinetic changes, in drug disposition, will still have to be the basis for the usage of drugs in patients with liver disease.

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