Br. J. clin. Pharmac. (1979), **7**, 49–54

THE EFFECT OF AGEING ON THE HEPATIC CLEARANCE OF PROPRANOLOL

C.M. CASTLEDEN* & C.F. GEORGE
Faculty of Medicine, University of Southampton, Southampton

1 Plasma propranolol concentrations were measured in healthy old and young subjects following single oral doses of 40 mg, single i.v. infusions of 0.15 mg kg^{-1} and after nine 40 mg oral doses given four times daily.

2 In each of the three studies, the elderly had higher plasma propranolol concentrations than the young despite having similar apparent volumes of distribution.

3 The terminal half-life of propranolol was similar in the two groups after oral propranolol but significantly shorter in the young after intravenous dosing ($P < 0.05$).

4 The bioavailability assessed from the concentration-time curves after i.v. and oral dosing was greater in the elderly ($P < 0.05$).

5 The differences between peak concentrations observed in old and young subjects after single oral doses were maintained during chronic therapy and there was a correlation between the individual values obtained on multiple therapy with that after a single dose ($P < 0.05$).

6 Ageing appears to affect the pharmacokinetics of propranolol in two ways. Firstly, distribution to the tissues appears to be slowed. Secondly, the increased bioavailability following oral administration suggests diminished intrinsic clearance by metabolism.

Introduction

Although the duration and intensity of action of the majority of drugs is largely determined by the speed at which they are metabolized (Conney, 1967), there is comparatively little information on changes in liver function which may occur with ageing. However it has been shown that bromsulphthalein excretion is reduced in the elderly (West, Brown, Simons, Carter, Kumagai & Englert, 1961; Thompson & Williams, 1965) and that clearance of plasma antipyrine and hydrocortisone is slower in normal, elderly individuals (West *et al.*, 1961; O'Malley, Crooks, Duke & Stevenson, 1971; Vestal, Norris, Tobin, Cohen, Shock & Andres, 1975).

There are three mechanisms whereby decreased hepatic function in the elderly could lead to higher plasma concentrations of drugs and thus to toxicity. Firstly, all drugs entering the portal vein after absorption from the gut must pass through the liver before reaching the systemic circulation. If drugs are metabolized therein some will be removed during passage through this organ, the amount depending on liver function and its affinity for the drug (Harris & Riegelman, 1969; Rowland, 1972; Shand, 1974). This mechanism is referred to as extraction at the first-pass. Secondly, the clearance of drugs from the systemic circulation may depend on hepatic blood flow. This is particularly important for drugs such as propranolol which are avidly extracted and metabolized in the liver (Nies, Evans & Shand, 1973; George, Orme, Buranapong, Macerlean, Breckenridge and Dollery, 1976). Liver blood flow is known to decrease with ageing (Sherlock, Bearn, Billing & Patterson, 1950; Bender, 1965) and could lead to a reduction in the rate of drug elimination. Finally, the rate of metabolism in the liver is important: although there is little information on the effects of ageing on the latter in man, elderly rats have lower than normal hepatic drug metabolizing activities including cytochrome P450 and respond to enzyme-inducing agents relatively poorly (Kato & Takanaka, 1968a & b).

In this paper, an attempt has been made to differentiate between these three mechanisms and to assess their relative role by examining plasma propranolol concentrations in old and young subjects. Propranolol was selected as a model drug because it undergoes extensive first-pass extraction (Shand, Rangno & Evans, 1972), is commonly prescribed in medical practice, and estimation of its concentration in plasma is relatively simple.

*Present address and address for all correspondence: Department of Medicine, The General Hospital, Leicester, LE5 4PW

Methods

These studies received approval from the Southampton and South-West Hampshire Joint Ethical Sub-Committee and all subjects received a detailed explanation of the purposes and nature of the study in which they participated: all freely gave their consent.

Selection of subjects

The young were members of the hospital or university staff and were in apparently good health. Apart from three elderly subjects living at home, the old resided in long-stay geriatric wards usually awaiting discharge to a Part III home. All had stable clinical conditions such as amputations, cerebral infarctions and osteoarthritis. No subject had clinical or biochemical evidence of cardiac, pulmonary, hepatic, renal or mental disease. None had a history of allergy to drugs or regularly took drugs, and no other medication was taken for at least 24 h before or during the studies. Apart from one elderly subject, all were non-smokers. Clinical details for each group are summarized in Table 1.

Procedures

(a) *Single oral dose* Subjects fasted from midnight, only water being allowed at 08.00 h when 40 mg propranolol (Inderal) was taken with 150 ml water. Venous blood samples were taken prior to dosing and at timed intervals afterwards through a butterfly pattern cannula in a fore-arm vein, kept patent with heparinised saline. Blood samples were placed in Lithium heparin tubes and centrifuged within 2 h. Plasma was removed and stored at −20°C until estimation of the plasma concentration was made by the fluorometric method of Shand, Nuckolls & Oates (1970).

(b) *Intravenous dosing* Intravenous propranolol was given in doses of 0.15 mg kg^{-1} at a rate of 1 mg min^{-1}. Patients were not asked to fast prior to this study but collection of blood samples was made according to the method described above.

(c) *Multiple oral dosing* Subjects were given 40 mg propranolol (Inderal) orally four times a day for 2 days. On the third day a single 40 mg dose of propranolol was given orally and venous blood samples were collected immediately before dosing and at 2, 4 and 6 h after administration.

Pharmacokinetic analysis

The areas under the plasma propranolol concentration-time curves (AUC) were subjected to pharmacokinetic appraisal using modifications of the programme of Saunders & Natunen (1976). In addition, the following parameters were calculated. The plasma half-life ($T_{\frac{1}{2}}$) was calculated from the terminal monoexponential decline in plasma concentration which was derived from a regression of the log-plasma concentration on time using the method of least squares.

The apparent volume of distribution ($V_d$app) in 1 kg^{-1} was calculated from the equation:

$$V_d\text{app} = \frac{\text{Amount of drug in body}}{\text{Concentration of drug in plasma at zero time (Co)}}$$

Co was obtained by extrapolation back to zero time of the terminal monoexponential decline in plasma concentration.

Clearance (Cl) of drug from the body was calculated from the equation:

$$\text{Cl} = \frac{V_d\text{app} \times 0.693}{T_{\frac{1}{2}}}$$

Since propranolol absorption from the gastrointestinal tract is almost complete in normal subjects (Paterson, Conolly, Dollery, Hayes & Cooper, 1970), the percentage extraction at the first-pass (E) was estimated from the following equation:

$$E = \left[1 - \left(\frac{AUC_{oral}}{AUC_{i.v.}} \times \frac{\text{Dose}_{i.v.}}{\text{Dose}_{oral}}\right)\right] \times 100\%$$

Table 1 Age, sex, weight and plasma albumin concentrations of young and old subjects. (mean ± s.e. mean)

	Young subjects				*Old subjects*			
	No.	*Age (years)*	*Wt (kg)*	*Plasma albumin (g/l)*	*No.*	*Age (years)*	*Wt (kg)*	*Plasma albumin (g/l)*
Single dose	7 (6M 1F)	29 ± 2	67 ± 3	42.6 ± 0.8	8 (3M 5F)	78 ± 3	64 ± 4	40.8 ± 1.0
Multiple dose	4 (3M 1F)	30 ± 4	64 ± 7	42.8 ± 1.3	5 (1M 4F)	83 ± 3	59 ± 4	39.8 ± 1.9

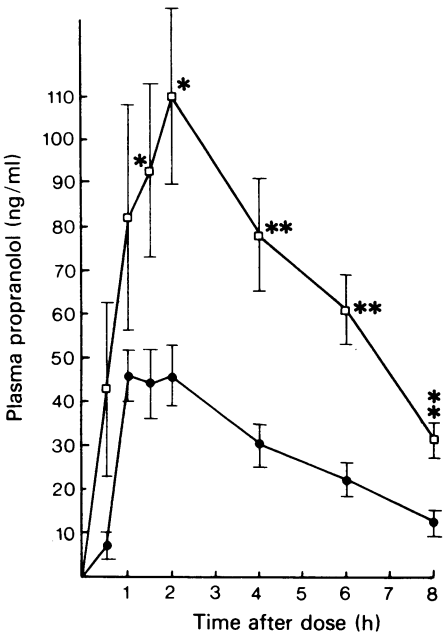

Figure 1 Mean ± s.e. mean plasma propranolol concentrations (ng/ml) of each age group (□ old $n=8$; ● young $n=7$) following a single oral dose of 40 mg (*denotes significant difference between the groups $P<0.05-P>0.01$, **denotes $P<0.01$).

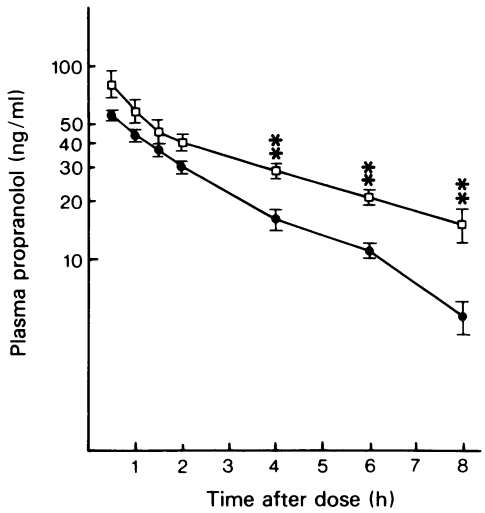

Figure 2 Mean ± s.e. mean log plasma propranolol concentrations for each age group (□ old $n=8$, ● young $n=7$) following a single i.v. dose of 0.15 mg/kg (**denotes significant difference between the groups $P<0.01$).

Statistical analysis

Data for the two groups were compared by means of Student's *t*-tests for unpaired data.

Results

(a) *Single oral dose of propranolol 40 mg*

Mean plasma concentrations of propranolol in the elderly were significantly higher at 1.5 h and thereafter compared with the corresponding concentrations in the young group (Figure 1). Peak plasma concentrations in the elderly (mean 110 ng ml^{-1}) were 2.3 times that of the young (mean 48 ng ml^{-1}): these occurred later at 2.4 ± 0.6 h compared with 1.6 ± 0.2 h but the difference was not statistically significant. Propranolol half-lives were similar in the two groups being 217 ± 13 min in the elderly and 215 ± 20 min in the young.

(b) *Single i.v. doses of 0.15 mg kg^{-1}* propranolol

The subjects studied were the same as in the single dose oral study, with the exception of one young man who did not participate. The mean plasma propranolol concentration of the elderly did not differ significantly from that of the younger age group until 4 h after dosing. Thereafter it remained significantly elevated (Figure 2). In addition, the distribution phase of the concentration-time curve appeared prolonged in the elderly; on average it lasted 75 min in the young compared to 108 min in the old. (A typical example of one old and young subject is shown in Figure 3).

The mean half-life of propranolol was longer in the elderly at 254 ± 51.9 min than in the young in whom it averaged 152 ± 10.3 min ($P<0.05$). However, the apparent volumes of distribution for the two groups were similar at 2.7 ± 0.41 l kg^{-1} and 3.0 ± 0.21 l kg^{-1} respectively. Thus, clearance in the elderly was significantly lower than in the young at 7.8 ± 1.3 ml kg^{-1} min^{-1} compared with 13.2 ± 1.4 ml kg^{-1} min^{-1} ($P<0.02$).

First-pass extraction and metabolism in the elderly amounted to 45.4 ± 8.0% which was significantly less than in the young (where it was 69.9 ± 4.5%; $P<0.05$). There was a good correlation between the percentage removed at the first-pass and peak plasma concentrations after a single dose (Figure 4).

(c) *Multiple oral dosing*

Mean plasma propranolol concentrations in the elderly were higher than in the young throughout the time studied (Figure 5). The difference between peak concentrations of the two groups noted on single oral

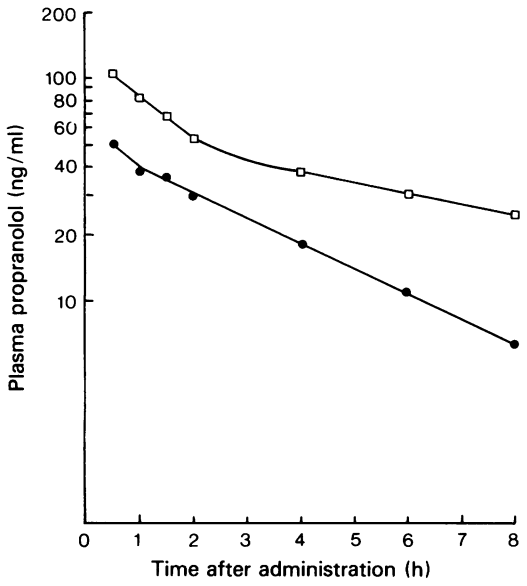

Figure 3 Log plasma propranolol concentrations in one old (□) and young (●) subject after a single i.v. dose of 0.15 mg/kg.

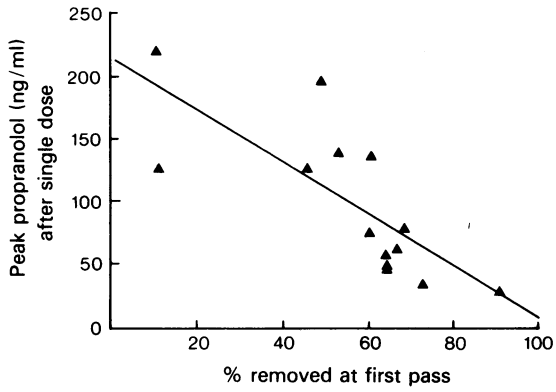

Figure 4 The relationship between the amount of propranolol removed during the 'first-pass' through the liver and the peak propranolol concentration (ng/ml) after a single oral 40 mg. dose in young and old subjects. The regression was calculated by the least squares method.

therapy was not only maintained but also slightly increased, that in the elderly being 3.1 times the value for the young. In both groups individual peak concentrations after a single dose correlated with those on multiple therapy ($P < 0.01$).

Discussion

The studies reported here were performed to assess the importance of ageing on the various factors which determine drug metabolism *in vivo*. In particular an attempt has been made to differentiate between the effects of ageing on first-pass extraction by the liver and on hepatic blood flow.

In the present studies, the elderly had substantially higher plasma propranolol concentrations than the young even though both groups were given similar oral doses. These results could be explained by a reduced volume of distribution in the elderly or alterations in the amount absorbed from their gastrointestinal tract after oral dosing. However, there was no difference in the apparent volume of distribution between the two groups and absorption from the gut is almost complete in normal subjects (Paterson *et al.*, 1970). Thus a more likely explanation for the observed differences between the groups is that the rate of hepatic elimination was decreased in the elderly. As the propranolol half-lives were similar in the two groups after oral therapy, but longer in the old after i.v. therapy, it is apparent that both hepatic blood flow and first-pass extraction fall with advancing age.

Several previous studies have shown that extraction of propranolol is virtually complete when this drug is presented to the liver in relatively low concentrations (Shand *et al.*, 1972; Evans & Shand, 1973). Under these circumstances which obtain when propranolol is given i.v., its rate of elimination is dependent upon delivery of the drug to the liver and hence on protein binding and hepatic blood flow (Nies *et al.*, 1973; Evans, Nies & Shand, 1973; George *et al.*, 1976). A change in either of these factors could explain our findings that the elderly eliminated propranolol more slowly than the young after an intravenous dose. There are two reasons for believing that protein binding was unaltered in the elderly. First, Hayes, Langman & Short (1975a & b) have shown that decreased protein binding in the elderly correlates with a fall in their plasma albumen concentrations but that there is no change in association constants. Hayes & Langman (1975), and Wallace, Whiting & Runcie (1976) found similar correlations between plasma binding and albumen concentrations for carbenoxolone and phenylbutazone. Thus, as plasma protein concentrations were similar in our two groups of subjects, plasma binding of propranolol was likely to be similar, especially as Evans *et al.* (1973) have shown that a linear relationship exists between the percentage bound and plasma protein concentrations. Secondly, the same authors found a correlation between the proportion of propranolol free in plasma water and its apparent volume of distribution: as the latter was similar in our two groups of subjects we eonclude the protein binding was similar.

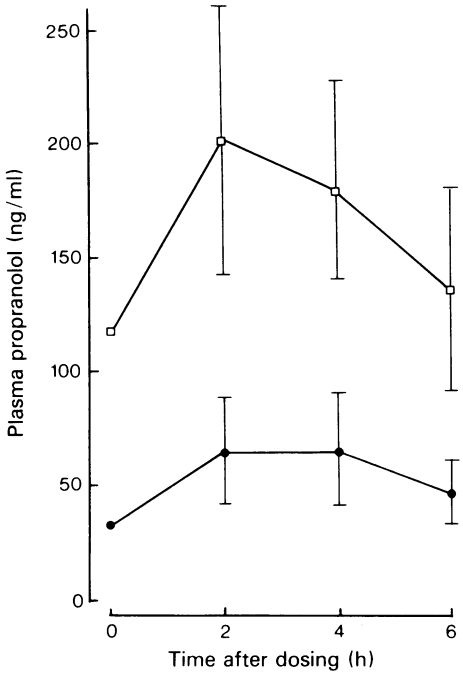

Figure 5 Mean ± s.e. mean plasma propranolol concentrations of each age group (□ old $n=5$; ● young $n=4$) following multiple oral doses (the last 40 mg dose was taken at 0 h).

The alternative explanation for our findings is that hepatic blood flow was diminished in the elderly. Bender (1965) reviewed published reports on the effects of increasing age on peripheral blood flow and concluded that regional blood flow was not uniformly affected. Where cardiac output was decreased, the cerebral coronary and skeletal blood flow tended to be maintained at the expense of supply to other organs including the liver. Brandfonbrener, Landowne & Shock (1955) measured cardiac output using an indicator dilution method in 67 males aged between 19 and 86 years. They found that cardiac output decreased by about 1% per year after the age of 30. Sherlock *et al.* (1950) estimated hepatic blood flow from the extraction of bromsulphthalein and concluded that it was reduced by 40–50% at the age of 60 when compared to that in individuals averaging 25 years. As the average age of elderly subjects was 78 years, the longer half-life after i.v. administration could be explained by a fall in their hepatic blood flow. There is further circumstantial evidence for this hypothesis in that the distribution of α phase following i.v. propranolol appeared to be more prolonged in the elderly which suggests an altered distribution due to decreased delivery to the tissues.

Once avid hepatic uptake is saturated, blood flow becomes less important and clearance of propranolol depends on the metabolic activity of the liver (Branch, Nies & Shand, 1973). However, the capacity to remove a drug completely is limited and once exceeded the proportion removed from plasma falls (Shand *et al.*, 1972; George *et al.*, 1976). Shand & Rangno (1972) showed a linear relationship between plasma propranolol concentrations and oral dose when the latter exceeded 30 mg. Below that only trace amounts of drug were detected in the systemic circulation, implying almost total extraction. For drugs like propranolol which undergo such avid hepatic extraction, the area under the concentration-time curve or bioavailability after oral administration is inversely proportional to intrinsic clearance by hepatic metabolism. Changes in the latter lead to pronounced alterations in the first-pass extraction but to minimal changes in the plasma clearance or half-life (Wilkinson & Shand, 1975). As some liver functions decline with ageing (Thompson & Williams, 1965; West *et al.*, 1971) a fall in intrinsic clearance of propranolol and a smaller percentage extraction at the first-pass would be expected. Our findings of higher plasma concentrations of propranolol in the elderly after single oral doses are explained most readily on this basis, especially as the half-lives were similar in the two age groups. Furthermore, calculation of the percentage removed at the first-pass showed that it was significantly reduced in the elderly.

It is interesting that a correlation existed between the peak plasma propranolol concentration after a single dose and that during multiple therapy. This suggests that although the percentage extracted at the first-pass decreases on chronic administration (Evans & Shand, 1973) it does so in a predictable manner, so that subjects with a small first-pass extraction after a single dose continued to have a small extraction following multiple doses. Thus, the differences between peak concentrations found between old and young after single doses are maintained following multiple doses. However in view of the relatively small numbers of subjects investigated, further studies are required to confirm these results, and in particular, the effect of ageing on other drugs undergoing first-pass extraction and metabolism needs to be investigated.

In summary, the results of our studies on the hepatic elimination of propranolol show that first-pass extraction is decreased in the elderly and suggest that both intrinsic clearance by hepatic metabolism and hepatic blood flow are reduced. Whether these changes with ageing influence the rate of adverse reactions in the elderly has not been answered by the present study. However, intensity of β-adrenoceptor blockade is proportional to plasma propranolol concentration (Coltart & Shand, 1970; George, Fenyvesi & Dollery, 1973; McDevitt, Frisk-Holmberg, Hollifield & Shand, 1976), and most life-threatening reactions occur within 4 h of starting therapy

(Greenblatt & Koch-Weser, 1973). Thus, the findings of higher concentrations of propranolol present in the systemic circulation of elderly patients would suggest that they are more susceptible to the effects of this drug and should lead to an appropriate reduction in dosage.

We wish to thank the British Heart Foundation for a grant to purchase a spectrophotofluorimeter.

References

BENDER, A.D. (1965). The effect of increasing age on the distribution of peripheral blood flow in man. *J. Am. ger. Soc.*, **13**, 192–198.

BRANCH, R.A., NIES, A.S. & SHAND, D.G. (1973). The disposition of propranolol VIII. General implications of the effects of liver blood flow on elimination from the perfused rat liver. *Drug Metab. Disposition*, **1**, 687–690.

BRANDFONBRENER, M., LANDOWNE, M. & SHOCK, N.W. (1955). Changes in cardiac output with age. *Circulation.*, **12**, 557–566.

CONNEY, A.H. (1967). Pharmacological implications of microsomal enzyme induction. *Pharmac. Rev.*, **19**, 317–366.

COLTART, D.J. & SHAND, D.G. (1970). Plasma propranolol levels in the quantitative assessment of β-adrenergic blockade in man. *Br. med. J.*, **3**, 731–734.

EVANS, G.H., NIES, A.S. & SHAND, D.G. (1973). The disposition of propranolol III. Decreased half life and volume of distribution as a result of plasma binding in man, monkey, dog and rat. *J. Pharmac. exp. Ther.*, **186**, 114–122.

EVANS, G.H. & SHAND, D.G. (1973). Disposition of propranolol. V. Drug accumulation and steady state concentration during chronic oral administration in man. *Clin. Pharmac. Ther.*, **14**, 487–493.

GEORGE, C.F., FENYVESI, T. & DOLLERY, C.T. (1973). In *Biological Effects of Drugs in Relation to their Plasma Concentrations*, Eds Davies, D.S. & Prichard, B.N.C. pp 123–133. London: Macmillan.

GEORGE, C.F., ORME, M.L'E., BURANAPONG, P., MACERLEAN, D., BRECKENRIDGE, A.M. & DOLLERY, C.T. (1976). Contribution of the liver to overall elimination of propranolol. *J. Pharmacokin. Biopharm.*, **4**, 17–27.

GREENBLATT, D.J. & KOCH-WESER, J. (1973). Adverse reactions to propranolol in hospitalised medical patients: A report from the Boston Collaborative Drug Surveillance Program. *Am. Heart J.*, **86**, 478–484.

HARRIS, P.A. & RIEGELMAN, S. (1969). Influence of the route of administration on the area under the plasma concentration time curve. *J. pharm. Sci.*, **58**, 71–75.

HAYES, M.J. & LANGMAN, M.J.S. (1975). An analysis of carbenoxolone plasma binding and clearance in young and elderly people. In *Proceedings of 4th Symposium on Carbenoxolone*, Eds Jones, F.A. & Parke, D.V. London: Butterworths.

HAYES, M.J., LANGMAN, M.J.S. & SHORT, A.H. (1975a). Changes in drug metabolism with increasing age: 1. Warfarin binding and plasma proteins. *Br. J. clin. Pharmac.*, **2**, 69–72.

HAYES, M.J., LANGMAN, M.J.S. & SHORT, A.H. (1975b). Changes in drug metabolism with increasing age: 2. phenytoin clearance and protein binding. *Br. J. clin. Pharmac.*, **2**, 73–79.

KATO, R. & TAKANAKA, A. (1968a). Metabolism of drugs in old rats (1) Activities of NADPH — linked electron transport and drug-metabolising enzyme systems in liver microsomes of old rats. *Jap. J. Pharmac.*, **18**, 387–388.

KATO, R. & TAKANAKA, A. (1968b). Effect of phenobarbital on electron transport system, oxidation and reduction of drugs in liver microsomes of rats of different age. *J. Biochem.*, **63**, 406–408.

McDEVITT, D.G., FRISK-HOLMBERG, M., HOLLIFIELD, J.W. & SHAND, D.G. (1976). Plasma binding and the affinity of propranolol for a beta receptor. *Clin. Pharmac. Ther.*, **20**, 152–157.

NIES, A.S., EVANS, G.H. & SHAND, D.G. (1973). The hemodynamic effects of beta adrenergic blockade on the flow-dependent hepatic clearance of propranolol. *J. Pharmac. exp. Ther.*, **184**, 716–720.

O'MALLEY, K., CROOKS, J., DUKE, E. & STEVENSON, I.H. (1971). Effect of age and sex on human drug metabolism. *Br. med. J.*, **3**, 607–609.

PATERSON, J.W., CONOLLY, M.E., DOLLERY, C.T., HAYES, A. & COOPER, R.G. (1970). The pharmacodynamics and metabolism of propranolol in man. *Eur. J. clin. Pharmac.*, **2**, 127–133.

ROWLAND, M. (1972). Influence of route of administration on drug availability. *J. pharm. Sci.*, **61**, 70–74.

SAUNDERS, L. & NATUNEN, T. (1976). A four parameter model for oral drug absorption. *J. Pharm. Pharmac.*, **28**, 572–579.

SHAND, D.G. (1974). Pharmacokinetic properties of the β-adrenergic and receptor blocking drugs. *Drugs*, **7**, 39–47.

SHAND, D.G., NUCKOLLS, E.M. & OATES, J.A. (1970). Plasma propranolol levels in adults with observations in four children. *Clin. Pharmac. Ther.*, **11**, 112–120.

SHAND, D.G. & RANGNO, R.E. (1972). The disposition of propranolol. 1. Elimination during oral absorption in man. *Pharmac.*, **7**, 159–168.

SHAND, D.G. & RANGNO, R.E. & EVANS, G.H. (1972). The disposition of propranolol. II. Hepatic elimination in the rat. *Pharmac.*, **8**, 344–352.

SHERLOCK, S., BEARN, A.G., BILLING, B.H. & PATERSON, J.C.S. (1970). Splanchnic blood flow in man by the bromosulfalein method: the relation of peripheral plasma bromosulfalein level to the calculated flow. *J. lab. clin. Med.*, **35**, 923–932.

THOMPSON, E.N. & WILLIAMS, R. (1965). Effect of age on liver function with particular reference to bromsulphalein excretion. *Gut*, **6**, 266–269.

VESTAL, R.E., NORRIS, A.H., TOBIN, J.D., COHEN, B.H., SHOCK, N.W. & ANDRES, R. (1975). Antipyrine metabolism in man: Influence of age, alcohol, caffeine and smoking. *Clin. Pharmac. Ther.*, **18**, 425–432.

WALLACE, S., WHITING, B. & RUNCIE, J. (1976). Factors affecting drug binding in plasma of elderly patients. *Br. J. clin. Pharmac.*, **3**, 327–330.

WEST, C.D., BROWN, H., SIMONS, E.L., CARTER, D.B., KUMAGAI, L.F. & ENGLERT, Jr. E. (1961). Adrenocortical function and cortisol metabolism in old age. *J. clin. Endocrinol. Metab.*, **21**, 1197–1207.

WILKINSON, G.R. & SHAND, D.G. (1975). A physiological approach to hepatic drug clearance. *Clin. Pharmac. Ther.*, **18**, 377–390.

(Received February 21, 1978)