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Age-Related Changes in Liver Size and Hepatic Blood Flow
The Influence on Drug Metabolism in the Elderly

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Summary

The propensity of elderly people to suffer from dose-dependent adverse drug reactions is well known. This may be largely related to reduced drug clearance. Changes in liver size and liver blood flow are probably the main reason for this decline in drug elimination with age. This review focuses on methods of measuring liver size and blood flow, on changes which have been reported in the elderly and on the clinical implications of these changes.

Most surveys indicate that the incidence of adverse drug reactions rises steadily with age (Hurwitz 1969). In many instances, this apparent increase can be accounted for by increased drug usage (Woodhouse et al. 1986). However, it does appear that the elderly are at increased risk of developing type A, dose-dependent adverse drug reactions. Part of the explanation for this phenomenon may be

increased sensitivity to drugs, but it has also been shown that the systemic elimination of many agents is decreased in the elderly population, leading to higher blood concentrations and hence adverse effects (Editorial 1984; Greenblatt et al. 1982a). When Kato et al. (1964) demonstrated that the activity of the most important drug metabolising enzymes (the hepatic microsomal mono-oxygenases) fell with advancing age in male rats, it appeared that a simple and easy explanation of reduced *in vivo* clearance of oxidised drugs in geriatric patients had been provided. However, subsequent studies have shown that no similar age-related decline in drug metabolising enzymes appears to occur either in humans (Woodhouse et al. 1984), or in non-human primates (Maloney et al. 1986). Furthermore, the affinity of the microsomal mono-oxygenases for their substrate appears not to decline either in rat or in human (Woodhouse et al. 1988; Wynne et al. 1987, 1988a).

If drug metabolising enzymes are indeed relatively normal in healthy elderly humans, it is likely that alterations in liver morphology and physiology are more important in explaining the decreased systemic drug elimination which has been repeatedly observed. It is upon these two factors that this review focuses.

1. Pharmacokinetic Principles

Most drugs are eliminated from the body by one of two main routes: renal excretion in the unchanged form, or hepatic metabolism prior to renal or biliary elimination.

The hepatic clearance (CL_H) of a drug can simply be described by the formula:

$$CL_H = \dot{Q} \cdot \frac{C_a - C_v}{C_a} = \dot{Q} \cdot E$$

where $\dot{Q}$ is organ blood flow, C_a and C_v are the arterial and venous concentrations of the compound, respectively, and E is the steady-state organ extraction ratio. From this equation it is clear that when E is small, CL_H will vary according to hepatic extraction and be relatively independent of flow. In contrast, as E approaches unity, CL_H will approach and be limited by liver blood flow. This has led to a classification of drugs and other foreign compounds into 2 types: those with a high hepatic extraction ratio whose elimination is *flow limited*, and those with a low hepatic extraction ratio whose elimination depends upon uptake and metabolism and which are described as *capacity limited* (Roberts et al. 1979). Liver size will, of course, influence both liver blood flow and hepatic extraction.

From these simple pharmacokinetic considerations it is clear that any age-related change which may occur either in liver size or in blood flow may have profound effects on systemic drug clearance.

2. Measuring Liver Size

2.1 Clinical Estimation

The clinical determination of liver volume by percussion and palpation is rough and inaccurate (Blendis et al. 1970). Hepatomegaly is not directly apparent until a 20% increase in size has occurred (Homeida et al. 1979).

Simple radiology is similarly unhelpful; it correlates poorly with clinical signs, and intra- and inter-observer variation is unacceptably large (Meyhoff et al. 1979).

2.2 Autopsy Studies

Direct measurement of liver weight is obviously accurate, and postmortem changes in liver size are thought to be relatively small if autopsy is performed soon after death (Walk 1983). Several studies have used autopsy data to investigate the effect of age on liver size (Boyd et al. 1933; Calloway 1965; Sato et al. 1970). However, all of these studies are limited by the fact that the deceased individuals may not represent the general population, even if death is accidental. For example, in the elderly, falls and injury often reflect physical illness.

2.3 Computerised Tomography

Images of parenchymal organs, including liver, are easily obtained by computerised tomography scanning. Because of its good density-resolution,

the organ can be delineated with little geometric distortion, allowing areas and volume to be precisely estimated from transverse sections. A good correlation has been obtained between liver volume measured by water displacement and by computerised tomography scanning (Fritschy et al. 1983; Van Thiel et al. 1985). Although accurate, computerised tomography is costly in time and manpower and involves radiation exposure. These factors limit its use as a research tool.

2.4 Ultrasound

Liver volume can be measured easily and accurately by ultrasound. It can be estimated on the basis of 3 maximum diameter measurements, namely anteroposterior, cranial-caudal and transverse (Zoli et al. 1986). However, it is more precisely calculated from the sum of several longitudinal images (Carr et al. 1976; Leung et al. 1986; Rasmussen 1972). The measurement of liver volume by ultrasound correlates well with both autopsy studies and computerised tomography (Fritschy et al. 1983; Raeth et al. 1984; Van Thiel et al. 1985). Because it is simple and non-invasive, ultrasound is a valuable tool, especially in volunteer studies and where serial measurements are required.

2.5 Radionucleotide Scanning

Hepatic imaging can be obtained using radioactive ligands which are taken up by the organ. Ligands such as technetium-99m galactosyl-neoglycoalbumin or technetium-99 sulphur colloid are used (Stadalnik et al. 1985).

Although radionucleotide methods may allow assessment of liver volume (Rollo & DeLand 1968), with results said to be reproducible (Kan & Hopkins 1979), the accuracy of these estimates has been questioned (Eikman et al. 1979). Furthermore, isotope techniques require expensive materials and equipment and involve exposure to ionising radiation, limiting their value for research purposes.

3. Liver Size and Ageing

3.1 Autopsy Studies

Perhaps the earliest, and one of the largest, studies of liver size in relation to age was undertaken by Boyd (1933). Data regarding liver weight were retrospectively collected in 1582 subjects between the ages of 20 and 80 years and dying within 24 hours of acute injury or accident. A fall in liver size of 24% in males and 18% in females was noted between the third and eighth decades. Changes were most marked after the sixth decade. Similarly, Calloway (1965) noted a 25% fall in liver weight between the ages of 20 and 70 years. A larger fall was noted in the very old, with a decline of 46% between the third and tenth decades. Racial differences have been seen, with Caucasians having larger livers and exhibiting earlier, but less marked, senile changes than Japanese (Sato et al. 1970). Although extremely valuable, postmortem studies suffer from the limitations described in section 2.2.

3.2 *In Vivo* Studies

Most studies investigating the effect of age on human liver size *in vivo* have used ultrasound. Swift et al. (1978) measured liver size using ultrasound in 15 volunteers in the third decade and 11 healthy volunteers aged 75 to 86 years. A reduction in estimated liver volume from a mean of 1303ml in the young group to 990ml in the aged group was noted – a fall of 24%. Similarly, Bach et al. (1981) noted a 17% fall in liver volume (measured by ultrasound) between the third and ninth decades. Our own studies (Wynne et al. 1988b) comprise one of the largest studies of liver size and age *in vivo*. 65 healthy volunteers between the ages of 24 and 91 years were studied, using an ultrasound technique modified from that of Carr et al. (1976). A significant negative correlation with age was observed, whether expressed in absolute terms or in relation to bodyweight. A 28% fall in liver volume was noted in those over 65 years of age compared with those under 40.

3.3 Clinical Significance

Several authors have demonstrated that liver size is an important determinant of the elimination of capacity-limited drugs [such as antipyrine (phenazone)], regardless of age. Pirttiaho et al. (1978) showed a significant correlation between liver volume (measured by technetium scanning) and antipyrine clearance, both in younger subjects and in patients with chronic liver disease. Correlations between antipyrine clearance and liver volume have subsequently been noted by other authors (Bach et al. 1981; Homeida et al. 1979; Spoelstra et al. 1986); similar associations between liver size and the elimination of other capacity-limited drugs such as phenytoin also exist (Bach et al. 1981).

Whether age-related reductions in liver size completely explain reduced elimination of capacity-limited agents in ageing humans remains open to debate. Liver shrinkage of between 17% (Bach et al. 1981) and 46% (Calloway 1965) with age is certainly of the same order as the reduction in drug elimination which has been reported, including a 20 to 45% decline in antipyrine clearance (Swift et al. 1978; Wood et al. 1979), and a 30 to 40% decline in clearance of imipramine (Abernethy et al. 1985) and theophylline (Antal et al. 1981).

However, in the study of Swift et al. (1978) already described, although liver size fell by 24%, antipyrine clearance fell by 42%. Interpretation of this study is rendered difficult by the fact that antipyrine clearance was higher in a group of hospitalised elderly than in the healthy aged volunteers and was, surprisingly, higher even than that in the young volunteers when corrections for liver size were made. These findings are at variance with other studies of the effect of frailty on drug metabolism (Williams et al. 1987).

Similarly, Bach et al. (1981) showed that while liver volume in their series fell by 17% between the third and ninth decades, free phenytoin clearance fell by 26%. Again, interpretation is a little difficult in that the patients in the study were hospitalised, more of the aged group were female, and while 6 of the 14 young patients smoked tobacco, none of the aged group did. It is accepted that smoking, drugs and hospitalisation influence drug elimination (Greenblatt et al. 1982b; Salem et al. 1978; Vestal et al. 1975; Williams et al. 1987; Wood et al. 1979), and such factors must be stringently controlled in studies of drug elimination in the elderly. Furthermore, the decrease in liver size noted in the Bach study was rather less than that described by other authors (referred to in section 3.2).

Studies of galactose elimination capacity in relation to age have shown a decrease of 25% from age 20 to 80 years (Schnegg & Lauterburg 1986). Galactose elimination, which is rate-limited by the cytosolic enzyme galactokinase, follows saturation (zero-order) kinetics, and its elimination is likely to be determined by functional hepatic mass. It is interesting that these authors found a good correlation between age-related changes in galactose elimination and that of antipyrine and caffeine, suggesting that changes in liver size are likely to be of greater importance than alterations in enzyme activity.

Of the few studies which have examined microsomal mono-oxygenase enzyme activity *in vitro* in primates, no reduction with age has been noted in either monkeys (Maloney et al. 1986; Sutter et al. 1985) or humans (Woodhouse et al. 1984; Wynne et al. 1988a).

In summary, it seems that changes in liver size may be the major factor determining decreased elimination of capacity-limited drugs with age. Changes in enzyme activity may be less important in the healthy elderly, but are probably very important in frail or hospitalised elderly (Woodhouse et al. 1988).

4. Measuring Liver Blood Flow

The afferent blood supply of the liver is from two sources, around 70% being blood from the splanchnic organs via the portal vein, the remainder being systemic arterial blood via the hepatic artery. Because of this dual supply, direct measurements of liver blood flow are difficult and are severely limited in humans by ethical constraints. Liver blood flow measurements have a number of surgical (Bircher et al. 1973) and pharmacokinetic

(George 1979) applications, and consequently a variety of methods of assessment have been developed.

4.1 Direct Methods

Electromagnetic Flowmeter: This device calculates liver blood flow by determining the electrical potential which the conductor, the blood, induces as it passes through a magnetic probe attached to the hepatic artery and portal vein. Current generated is proportional to the velocity of the stream (Kolin 1936).

Heat Exchange Method: This technique records the changes in conductivity of a thermocouple, which is implanted in the liver and cooled by blood flow. There is a linear correlation in the physiological range between thermal conductivity and blood flow (Grayson & Johnson 1953).

Use in Humans: Both of these methods have been used in humans (Grayson & Kinnear 1962; Schenk et al. 1962). However, both are extremely invasive and this fact, together with the availability of indirect methods, makes their use rare.

4.2 Indirect Methods

Several methods have been described and are reviewed by Ohnhaus (1979).

Doppler Effect: Although Doppler flowmeters allow estimation of portal blood flow (Moriyasu 1983), the dual hepatic blood supply, and difficulties in assessing cross-sectional areas and flow velocity (particularly in the phasic hepatic artery), make this method difficult to use. However, technical advances are expected to allow further studies along these lines in the future.

Clearance Techniques: Several different indicators have been used to estimate liver blood flow using clearance techniques. Bromosulphthalein (BSP) was first described in this context by Bradley et al. (1945), being considered suitable because of its high hepatic extraction. However, bromosulphthalein undergoes enterohepatic circulation (Lorber et al. 1953) and because of this another dye, indocyanine green, is used in preference. Indocyanine green is a carbocyanine dye which is solely eliminated by the liver, has an extraction ratio averaging 74% in normal volunteers (Grainger et al. 1983; Leevy et al. 1962; Weigand et al. 1960), and has no enterohepatic circulation.

Ideally, in order to calculate liver blood flow using these dyes, hepatic vein catheterisation is required. However, methods of estimating liver blood flow which avoid this invasive technique have been described for both bromosulphthalein (Clarkson et al. 1976) and indocyanine green (Grainger et al. 1983).

Single Injection Method: The uptake of colloidal substances such as ^{32}P-labelled chromic phosphate, ^{138}Au or ^{131}I human serum albumin by Kupffer cells after intravenous injection can be estimated by external counting with a scintillation collimeter, by gamma camera, or by peripheral venous sampling (Ohnhaus & Locher 1975; Vetter et al. 1954). Although extraction ratios are high (90%), some extrahepatic removal does occur and may introduce inaccuracies in liver blood flow calculations. Considerations of cost and radiation exposure limit the application of these methods in volunteer studies.

5. Liver Blood Flow in Ageing

5.1 Clearance Studies

For many years, hepatic blood flow has been said to fall with age, a statement based on the results of a study never intended for this purpose (Sherlock et al. 1950), and which estimated liver blood flow and bromosulphthalein clearance. Unfortunately, bromosulphthalein is not an ideal model, as age-related changes in the metabolism of the dye have been noted. Bromosulphthalein clearance is determined largely by relative storage capacity (S) and transport rate maximum (T_m). Initial studies in humans and female rats indicated an age-related decline in S, with little or no change in T_m (Thompson & Williams 1965). However, other authors, using different rat strains, have shown a fall in T_m with age, but no change in S (Kitani et al. 1981).

Indocyanine green is probably a better model

agent to use, because although the effect of age on its hepatic extraction ratio in humans is as yet unexamined, no change in the maximal rate of removal of the dye has been observed between young adulthood and senescence in ageing rodent livers (Kitani et al. 1978).

Indocyanine green clearance does fall with age in humans. Wood et al. (1979) noticed a significant negative correlation between the two ($p < 0.004$). Similarly, our own studies measuring indocyanine green clearance in 65 healthy volunteers aged 24 to 91 years (assuming a constant hepatic extraction ratio of 0.74) showed a decline in apparent liver blood flow of 35% in those over 65 years compared with those under 40 years, even after allowing for changes in bodyweight (Wynne et al. 1988b). Furthermore, liver perfusion (liver blood flow per unit of liver volume) also fell, by a factor of 11%.

5.2 Clinical Significance

Many studies have confirmed that there is a good relationship between elimination of many highly extracted drugs and liver blood flow. For example, reduced liver blood flow secondary to hypotension is associated with reduced clearance of morphine (Macnab et al. 1986) and lignocaine (lidocaine) [Feely et al. 1982]. Similarly, liver blood flow is increased in thyrotoxicosis (Wells et al. 1983) and after phenobarbitone treatment (Branch et al. 1974), and both situations are associated with increased clearance of the highly extracted drug propranolol. Changes in indocyanine green extraction can be a confounding factor. Thus, Feely et al. (1980) suggested that cimetidine decreased indocyanine green clearance and, by inference, liver blood flow. However, it now appears that these changes are due to a fall in hepatic indocyanine green extraction induced by H_2-receptor antagonists (Dunk et al. 1983; Lebrec et al. 1981).

The pharmacokinetic consequences of the age-related fall in liver blood flow have been examined by several groups. For example, an age-related decline in propranolol clearance has been noted in the rat, and this correlates well with a concurrent decrease in liver blood flow, measured using a hydrogen washout technique (Iwamoto et al. 1985). Similarly, a 41% fall in propranolol clearance with age has been noted in humans (Castelden & George 1979), a figure which is similar to our own observation of a 35% decline in liver blood flow, described in section 5.1. The hepatic clearance of chlormethiazole, which is also a highly extracted drug, has been found to be 30% lower in a group of 8 elderly volunteers (mean age 75 years) than in 6 young subjects (mean age 23 years) [Nation et al. 1976].

The relationship between clearance of high extraction drugs, liver blood flow and age is, however, complicated by concurrent age-related changes in intrinsic clearance of drugs. For example, the hepatic intrinsic clearance of propranolol falls with age in the rat (Iwamoto et al. 1985), and similar changes may occur in humans. However, in humans there is evidence that this may be due to the fact that smoking increases intrinsic clearance of propranolol, and there are fewer smokers among the elderly than among the young (Sellers et al. 1983). Furthermore, the effects of smoking on clearance may be less in the aged (Feely et al. 1981; Vestal et al. 1979). In contast, it has been suggested that, in the case of lignocaine, which is said to have similar systemic clearance in young and elderly, hepatic extraction actually increases with age to compensate for reduced hepatic blood flow (Nation et al. 1977).

6. Conclusions

There can be little doubt that both liver size and liver blood flow fall with age in humans. The reduced elimination of both capacity-limited and flow-limited drugs which is seen in the elderly, and which predisposes this group of people to type A adverse drug reactions, is likely to be due largely to these morphological and physiological changes. Alterations in activities of drug metabolising enzymes are probably of less significance in the healthy aged population, but are likely to assume greater importance in the presence of disease or frailty.

References

Abernethy DR, Greenblatt DJ, Shader RI. Imipramine and desipramine disposition in the elderly. Journal of Pharmacology and Experimental Therapeutics 232: 183-188, 1985

Antal EJ, Kramer PA, Mercik SA, Chapron DJ, Lawson IR. Theophylline pharmacokinetics in advanced age. British Journal of Clinical Pharmacology 12: 637-645, 1981

Bach B, Molholm Hansen J, Kampmann JP, Rasmussen SN, Skorsted L. Disposition of antipyrine and phenytoin correlated with age and liver volume in man. Clinical Pharmacokinetics 6: 389-396, 1981

Bircher J, Blankart R, Halpern A, Haecki W, Laisue J, et al. Criteria for assessment of functional impairment in patients with cirrhosis of the liver. European Journal of Clinical Investigation 3: 72-85, 1973

Blendis LM, McNeilly WJ, Shepperd L, Williams R, et al. Observer variation in the clinical and radiological assessment of hepatosplenomegaly. British Medical Journal 1: 727-730, 1970

Boyd E. Normal variability in weight of the adult human liver and spleen. Archives of Pathology 16: 350-372, 1983

Bradley SE, Ingelfinger FG, Bradley GP, Curry JJ. The estimation of hepatic blood flow in man. Journal of Clinical Investigation 24: 890-897, 1945

Branch RA, Shand DG, Wilkinson GR, Nies AS. Increased clearance of antipyrine and d-propanolol after phenobarbital treatment in the monkey. Journal of Clinical Investigations 53: 1101-1107, 1974

Calloway NO, Foley CF, Lagerbloom P. Uncertainties in geriatric data II: organ size. Journal of the American Geriatric Society 13: 20-28, 1965

Carr D, Duncan JG, Railton R, Smith CB. Liver volume determination by ultrasound: a feasibility study. British Journal of Radiology 49: 776-778, 1976

Castleden CM, George CF. The effect of ageing on the hepatic clearance of propranolol. British Journal of Clinical Pharmacology 7: 49-54, 1979

Clarkson MJ, Hardy-Smith A, Richards TG. Measurement of liver blood flow by means of a simple injection of bromosulphthalein without hepatic venous catheterisation. Clinical Science and Molecular Medicine 51: 141-150, 1976

Dunk AA, Jenkins WJ, Burroughs AK, Walt RP, Osuafor TOK, et al. The effect of ranitidine on the plasma clearance and hepatic extraction of indocyanine green in patients with chronic liver disease. British Journal of Clinical Pharmacology 16: 117-120, 1983

Editorial. Medication for the elderly. Journal of the Royal College of Physicians of London 18: 7-17, 1984

Eikman EA, Mack GA, Jain VK, Madden JA. Computer-assisted liver mass estimation from gamma-camera images. Journal of Nuclear Medicine 20: 144-148, 1979

Feely J, Crooks J, Stevenson IH. The influence of age, smoking and hyperthyroidism on plasma propranolol steady state concentration. British Journal of Clinical Pharmacology 12: 73-78, 1981

Feely J, Wade D, McAllister CB, Wilkinson GR, Robertson D. Effect of hypotension on liver blood flow and lidocaine disposition. New England Journal of Medicine 307: 866-869, 1982

Feely J, Wilkinson GR, Wood AJJ. Reduction of liver blood flow and propranolol metabolism by cimetidine. New England Journal of Medicine 304: 692-695, 1980

Fritschy P, Robotti G, Schneckloth G, Vock P. Measurement of liver volume by ultrasound and computed tomography. Journal of Clinical Ultrasound 11: 299-303, 1983

George CF. Drug kinetics and hepatic blood flow. Clinical Pharmacokinetics 4: 433-448, 1979

Grainger SL, Kealing PWN, Brown IMH, Marigold JH, Thompson RPH. Clearance and non-invasive determination of the hepatic extraction of indocyanine green in baboons and man. Clinical Science 64: 207-212, 1983

Grayson J, Johnson DH. The effect of adrenaline and noradrenaline on the liver blood flow. Journal of Physiology 120: 73-94, 1953

Grayson J, Kinnear T. Observations on temperature, blood flow and heat production in the human liver in relation to environment and to glucose and insulin administration. Clinical Science 22: 125-140, 1962

Greenblatt DJ, Divoll M, Abernethy DR, Harmatz JS, Shader RI. Antipyrine kinetics in the elderly: prediction of age related changes in benzodiazepine oxidising capacity. Journal of Pharmacology and Experimental Therapeutics 220: 120-126, 1982b

Greenblatt DJ, Sellers EM, Shader RI. Drug disposition in old age. New England Journal of Medicine 306: 1081-1088, 1982a

Homeida M, Roberts CJC, Halliwell M, Read AE, Branch RA. Antipyrine clearance per unit volume liver: an assessment of hepatic function in chronic liver disease. Gut 20: 596-601, 1979

Hurwitz N. Predisposing factors in adverse reactions to drugs. British Medical Journal 1: 536-539, 1969

Iwamoto K, Watanabe J, Araki K, Deguchi N, Sugiyama H. Effect of age on hepatic clearance of propranolol in rats. Journal of Pharmacy and Pharmacology 37: 466-470, 1985

Kan MK, Hopkins GB. Measurement of liver volume by emission computed tomography. Journal of Nuclear Medicine 20: 514-520, 1979

Kato R, Vassanelli P, Frontino G. Variation in the activity of liver microsomal drug metabolising enzymes in rats in relation to age. Biochemical Pharmacology 13: 1037-1051, 1964

Kitani K, Setsuko K, Miura R. Hepatic metabolism of sulfobromophthalein in ageing rats. In Kitani (Ed.) Liver and ageing, pp. 145-157, Elsevier Press, Amsterdam, 1978

Kitani K, Zurcher C, Van Bezooijen K. The effect of ageing on the hepatic metabolism of sulfobromophthalein in BN/Bi female and WAG/Rij male and female rats. Mechanisms of Ageing and Development 7: 381-393, 1981

Kolin A. An electromagnetic flowmeter: principle of the method and its application to blood flow measurements. Proceedings of the Society of Experimental and Biological Medicine 35: 43-56, 1936

Lebrec D, Goldfarb G, Benhamou JP. Reduction of liver blood flow by cimetidine. New England Journal of Medicine 305: 100, 1981

Leevy CM, Mendenhall CL, Lesko W, Howard MM. Estimation of hepatic blood flow with indocyanine green. Journal of Clinical Investigation 41: 1169-1180, 1962

Leung NWY, Farrant P, Peters TJ. Liver volume measurement by ultrasonography in normal subjects and alcoholic patients. Journal of Hepatology 2: 157-164, 1986

Lorber SH, Oppenheimer MJ, Shay H, Lynch P, Siplet H. Enterohepatic circulation of bromosulphthalein in intraduodenal, intraportal and intravenous dye administration in dogs. American Journal of Physiology 173: 259-264, 1953

Macnab MSP, Macrae DJ, Guy E, Grant IS, Feely J. Profound reduction in morphine clearance and liver blood flow in shock. Intensive Care Medicine 12: 366-369, 1986

Maloney AG, Schmucker DL, Vessey DS, Wang RK. The effects of ageing on the hepatic microsomal mixed-function oxidase system of male and female monkeys. Journal of Hepatology 6: 282-287, 1986

Meyhoff HH, Roder O, Andersen B. Palpatory estimation of liver size – within and between observer variation. Acta Chirurgica Scandinavica 145: 479-481, 1979

Moriyasu F. A new method of transcutaneous measurement of portal blood flow by an ultrasonic 'Duplex' system composed of a pulsed doppler flowmeter and a linear-type real-time B-mode electroscanner. Acta Hepatology (Japan) 24: 537, 1983

Nation RL, Learoyd B, Barber J, Triggs EJ. The pharmacokin-

etics of chlormethiazole following intravenous administration in the aged. European Journal of Clinical Pharmacology 10: 407-415, 1976
Nation RL, Triggs EG, Selig M. Lignocaine kinetics in cardiac patients and aged subjects. British Journal of Clinical Pharmacology 4: 439-448, 1977
Ohnhaus EE. Methods of assessment of the effect of drugs on liver blood flow in man. British Journal of Clinical Pharmacology 7: 223-229, 1979
Ohnhaus EE, Locher JTh. Liver blood flow and blood volume following chronic phenobarbitone administration. European Journal of Pharmacology 31: 161-165, 1975
Pirttiaho HI, Sotaniemi EA, Ahokas JT, Pirkanen U. Liver size indices of drug metabolism in epileptics. British Journal of Clinical Pharmacology 6: 273-278, 1978
Raeth U, Johnson PJ, Williams R. Ultrasound determination of liver size and assessment of patients with malignant liver disease. Liver 4: 287-293, 1984
Rasmussen SN. Liver volume determination by ultrasonic scanning. British Journal of Radiology 45: 579-585, 1972
Roberts RK, Branch RA, Desmond PV, Schenker S. The influence of liver disease on drug disposition. Clinics in Gastroenterology 8(1): 105-121, 1979
Rollo FD, DeLand FH. The determination of liver mass from radionuclide images. Radiology 91: 1191-1194, 1968
Salen SAM, Rajjayabu P, Sheperd AMM, Stevenson IH. Reduced induction of drug metabolism in the elderly. Age and Ageing 7: 68-73, 1978
Sato T, Miwa T, Tauchi H. Age changes in the human liver of different races. Gerontologia 16: 368-380, 1970
Schenk WG, McDonald JC, McDonald K, Drapanas T. Direct measurement of hepatic blood flow in experimental animals. Annals of Surgery 156: 463-471, 1962
Schnegg M, Lauterburg BH. Quantitative liver function in the elderly assessed by galactose elimination capacity, aminopyrine demethylation and caffeine clearance. Journal of Hepatology 3: 164-171, 1986
Sellers EM, Frecker RC, Romach MK. Drug metabolism in the elderly: confounding of age, smoking and ethanol effects. Drug Metabolism Reviews 14(2): 225-250, 1983
Sherlock S, Bearn AG, Billing BH, Paterson JCS. Splanchnic blood flow in man by the bromsulfalein method: the relation of peripheral plasma bromsulfalein level to the calculated flow. Journal of Laboratory and Clinical Medicine 35: 923-932, 1950
Spoelstra P, Teunissen MWE, Janssens AR, Weeda B, Van Duijn W. Antipyrine clearance and metabolite formation: the influence of liver volume and smoking. European Journal of Clinical Investigation 16: 321-327, 1986
Stadalnik RC, Vera DR, Woodle ES, Trudeau WL, Porter BA, et al. Technetium-99m NGA functional hepatic imaging preliminary clinical experience. Journal of Nuclear Medicine 26 (11): 1233-1242, 1985
Sutter MA, Wood G, Williamson LS, Strong R, Pickham K, et al. Comparison of the hepatic mixed function oxidase system of young, adult and old non-human primates (Macaca nemestrina). Biochemical Pharmacology 34: 2983-2987, 1985
Swift CG, Homeida M, Halliwell M, Roberts CJC. Antipyrine disposition and liver size in the elderly. European Journal of Clinical Pharmacology 14: 149-152, 1978
Thompson EN, Williams R. Effect of age on liver function with particular reference to bromsulphelein excretion. Gut 6: 266-269, 1965
Van Thiel DH, Hagler NG, Shade RR, Skolnick ML, Pollitt Heyl A, et al. *In vivo* hepatic volume determination using sonography and computed tomography. Gastroenterology 88: 1812-1817, 1985
Vestal RE, Norris AH, Tobin JD, Cohen DH, Shock MW, et al. Antipyrine metabolism in man: influence of age, alcohol, caffeine and smoking. Clinical Pharmacology and Therapeutics 18: 425-432, 1975
Vestal RE, Wood AJJ, Branch RA, Shand DG, Wilkinson GR. Effects of age and cigarette smoking on propranolol disposition. Clinical Pharmacology and Therapeutics 26 (1): 8-15, 1979
Vetter H, Falkner R, Neumayr A. The disappearance of colloidal radiogold from the circulation and its application to the estimation of liver blood flow in normal and cirrhotic subjects. Journal of Clinical Investigations 33: 1594-1602, 1954
Walk L. Liver size and its post-mortem changes. Radiologe 23: 189-191, 1983
Weigand BD, Ketterer SG, Rapaport E. The use of indocyanine green for the evaluation of hepatic function and blood flow in man. American Journal of Digestive Diseases 5: 427-436, 1960
Wells PG, Feely J, Wilkinson GR, Wood AJJ. Effect of thyrotoxicosis on liver blood flow and propranolol disposition after long-term dosing. Clinical Pharmacology and Therapeutics 33 (5): 603-608, 1983
Williams FM, Wynne HA, Woodhouse KW, Rawlins MD. Plasma aspirin esterase and cholinesterases in the elderly. British Journal of Clinical Pharmacology 24: 272P, 1987
Wood AJJ, Vestal RE, Wilkinson GR, Branch RA, Shand DG. Effect of ageing and cigarette smoking on antipyrine and indocyanine green elimination. Clinical Pharmacology and Therapeutics 26: 16-20, 1979
Woodhouse KW, Mortimer O, Wiholm BE. Hepatic adverse drug reactions: the effect of age. In Liver and ageing: liver and brain, pp. 75-80, Elsevier, Amsterdam, 1986
Woodhouse KW, Mutch E, Williams FM, James OFW. The effect of age on pathways of drug metabolism in human liver. Age and ageing 13: 328-334, 1984
Woodhouse KW, Williams F, Mutch E, Wynne H, Rawlins M, et al. Phase I drug metabolism in ageing. In Falk Symposium No. 47, Ageing and Gastrointestinal Tract, pp. 255-265, MTP Press, Lancaster, 1988
Wynne HA, Cope LH, Mutch E, Rawlins MD, Woodhouse KW, et al. The effect of age upon liver volume and apparent liver blood flow in healthy man. Hepatology, in press, 1988b
Wynne H, Mutch E, James OFW, Rawlins M, Woodhouse KW. Effect of age on monooxygenase enzyme kinetics in rat liver microsomes. Age and Ageing 16: 153-158, 1987
Wynne H, Mutch E, James OFW, Wright IP, Rawlins M, et al. The effect of age upon the affinity of microsomal monooxygenase enzymes for substrate in human liver. Age and Ageing, in press, 1988a
Zoli M, Marchesini G, Melli A, et al. Evaluation of liver volume and liver function following hepatic resection in man. Liver 6: 286-291, 1986

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