References

BARBER, H.E., HAWKSWORTH, G.M., PETRE, J.C., RIGBY, J.W., ROBB, O.J. & SCOTT, A.K. (1981). Pharmacokinetics of atenolol and propranolol in young and elderly subjects. *Br. J. clin. Pharmac.*, **11**, 118P–119P.

BEVINGTON, P.R. (1969). *Data reduction and error analysis for the physical sciences.* New York: McGraw Hill.

CASTLEDEN, C.M., KAYE, C.M. & PARSONS, R.L. (1975). The effect of age on plasma levels of propranolol and practolol in man. *Br. J. clin. Pharmac.*, **2**, 303–306.

CROOKS, J., O'MALLEY, K. & STEVENSON, I.H. (1976). Pharmacokinetics in the elderly. *Clin. Pharmacokin.*, **1**, 280–296.

FITZGERALD, J.D., RUFFIN, R., SMEDSTAD, K.G., ROBERTS, R. & McAINSH, J. (1978). Studies on the pharmacokinetics and pharmacodynamics of atenolol in man. *Eur. J. clin. Pharmac.*, **13**, 81–89.

JELLIFFE, R.W. & JELLIFFE, S.M. (1972). A computer program for estimation of creatinine clearance from unstable serum creatinine concentration. *Math. Biosci.*, **14**, 17–24.

KLOTZ, U., AVANT, G.R., HOYUMPA, A., SCHENKER, S & WILKINSON, G.R. (1975). The effects of age and liver disease on the disposition and elimination of diazepam in adult man. *J. clin. Invest.*, **55**, 347–359.

MASON, W.D., WINER, N., KOCHAK, G., COHEN, I. & BELL, R. (1979). Kinetics and absolute bioavailability of atenolol. *Clin. Pharmac. Ther.*, **25**, 408–415.

REEVES, P.R., McAINSH, J., McINTOSH, D.A.D. & WINROW, M.J. (1978). Metabolism of atenolol in man. *Xenobiotica*, **8**, 313–320.

RUBIN, P.C., SCOTT, P.J.W. & REID, J.L. (1981). Prazosin disposition in young and elderly subjects. *Br. J. clin. Pharmac.*, **12**, 401–404.

TRIGGS, E.J. (1979). Pharmacokinetics of lignocaine and chlormethiazole in the elderly; with some preliminary observations on other drugs. In *Drugs and the Elderly*, eds. Crooks J. & Stevenson, I. London: Macmillan.

WAN, S.H., KODA, R.T. & MARONDE, R.F. (1979). Pharmacokinetics, Pharmacology of atenolol and effect of renal disease. *Br. J. clin. Pharmac.*, **7**, 569–579.

WEBSTER, J., HAWKSWORTH, G.M., BARBER, H.E., JEFFERS, T.A. & PETRIE, J.C. (1981). Withdrawal of long-term therapy with atenolol in hypertensive patients. *Br. J. clin. Pharmac.*, **12**, 211–214.

YEE, Y-G., RUBIN, P. & BLASCHKE, T.F. (1979). Atenolol determination by high pressure liquid chromatography and fluorescence detection. *J. Chromatog.*, **171**, 357–362.

THE EFFECT OF AGE ON THE RESPONSES OF HUMAN ISOLATED ARTERIES TO NORADRENALINE

Increasing age is associated with a decreased cardiac response to the β-adrenoceptor agonist isoprenaline (Yin *et al.*, 1976; Vestal *et al.*, 1979; Bertel *et al.*, 1980). Schocken & Roth (1977) demonstrated an age-related reduction in the number of β-adrenoceptors on lymphocytic membranes; however a recent study did not confirm their findings (Abrass & Scarpace, 1981). The object of this study was to determine if there was an age-related change in α-adrenoceptor activity by an examination of the noradrenaline-induced contraction of human isolated arterial tissue.

Arteries, 2–3 mm external diameter, were obtained from surgical specimens either at gut resection or hysterectomy. Connective tissue was removed from around the vessel and a helical strip of muscle dissected. The vascular strip was then suspended in a medium of the following composition mmol/l: NaCl 118, $NaHCO_3$ 24.97, KH_2PO_4 1.25, KCl 4.75, $CaCl_2$ 2.54, $MgSO_4$ 1.19, glucose 1.11. Temperature was maintained at 37°C. Ninety-five percent O_2 and 5% CO_2 were passed through the solution, the resultant pH being 7.4. Muscle contractions were recorded under isometric conditions by a Grass FTO3 force displacement transducer and displayed by a Grass Polygraph pen recorder (Grass Instruments). After an initial rest period of 1 h the effect of increasing concentrations of noradrenaline (Sigma) was examined on several occasions with each artery to ensure reproducibility. At least 40 min rest was allowed between each dose series to permit tissue relaxation. The maximum contraction produced by potassium was also measured by the addition of 80 mmol/l KCl. Dose-response curves to noradrenaline were drawn and the concentration of noradrenaline which produced a 50% maximum response was calculated, the ED_{50}. The maximum noradrenaline response was also expressed as a percentage of the maximum potassium response.

This project was approved by the Stobhill General Hospital Research and Ethical Committee. Patients were excluded from the study if they had evidence of hypertension, treated or untreated thyroid disease, diabetes mellitus, ischaemic colitis or prior to surgery were receiving drugs known to modify sympathetic vascular activity. Results are shown as the mean with the standard deviation. All concentrations are expressed as final concentrations in the organ bath. Statistical analysis was by the Wilcoxon rank sum test.

Arteries were obtained from 20 patients whose ages ranged from 35 to 83 years and consisted of 7 uterine, 9 colonic and 4 gastric vessels. Pre-operative medication consisted of a narcotic analgesic with atropine and the anaesthesia was maintained by nitrous oxide and oxygen with or without halothane. All patients received muscle relaxants. Figure 1 shows the responses for three age groups: 30–49 years

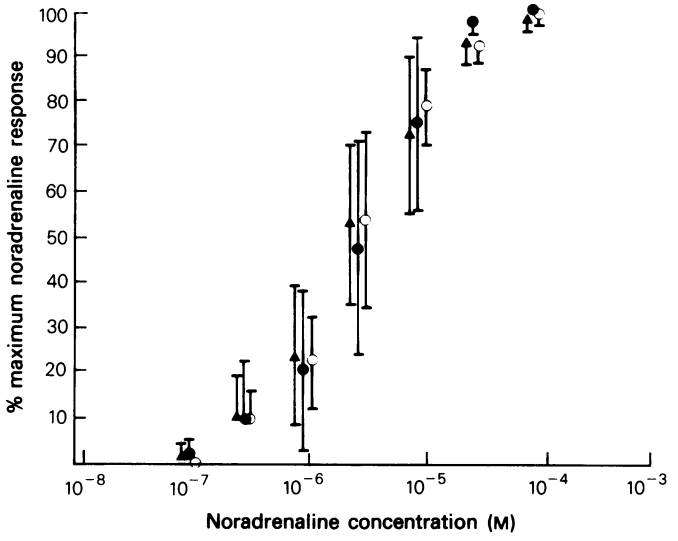

Figure 1 Contractile responses of arterial strips from patients of different ages. Vertical bars represent s.d. ▲ 30–49 years (mean 41 years, $n = 7$), ● 50–69 years (mean 62 years, $n = 5$), ○ 70+ years (mean 75 years, $n = 8$).

(mean 41, $n = 7$), 50–69 years (mean 62, $n = 5$) and 70+ years (mean 75, $n = 8$). As the individual arteries varied in size, comparisons are made between responses expressed as a percentage of the maximum noradrenaline response. There was no significant difference between the three groups. There was also no difference between the responses of gastric, colonic and uterine vessels. Table 1 shows the noradrenaline ED_{50} concentrations and the maximum noradrenaline response as a percentage of the maximum potassium response. Again there was no significant difference between the three groups.

Table 1 Noradrenaline ED_{50} ($M \times 10^{-6}$) and maximum noradrenaline response as percentage of maximum potassium response expressed as mean ± s.d.

Age range (years)	*ED_{50}*	*Maximum noradrenaline response as % maximum potassium response*
30–49 mean 41 $n = 7$	3.7 ± 2.5	122.3 ± 11.1
50–69 mean 62 $n = 5$	3.5 ± 2.1	105.5 ± 9.1
70+ mean 75 $n = 8$	5.3 ± 6.9	125.1 ± 53

Fleisch (1980) reviewed the literature concerning age related changes in the sensitivity of animal aortae to noradrenaline. The evidence is conflicting. Carrier *et al.* (1979) demonstrated a decrease in sensitivity with increasing age in the rat. Gray (1977) found an increase in sensitivity with age in the dog while Hayashi & Toda (1978) found no change with age in the rabbit. However these studies involved immature and mature animals as opposed to a comparison between mature and senescent. The present study involved mature and elderly subjects. There was no age related change in the sensitivity of human arterial muscle to noradrenaline. This is found when the noradrenaline response is considered alone or when it is compared with the non-receptor mediated contraction produced by potassium.

Although the arteries for these experiments had to be selected from subjects with an underlying disease, they were not, prior to surgery, receiving medication known to affect the adrenergic nervous system nor were known to have underlying arterial disease. Our findings are supported by recent studies *in vivo* with intact normal volunteers (Elliot *et al.*, 1981) and with forearm circulation in young and old subjects (Kiowski *et al.*, 1981).

In conclusion we can find no evidence *in vitro* that using noradrenaline vascular α-adrenoceptor sensitivity alters with increasing age. Further studies will be required to determine whether changes in β-adrenoceptors or in subtypes of α-adrenoceptors occur in the ageing cardiovascular system.

We gratefully acknowledge the co-operation of the surgical and gynaecological services of Stobhill General Hospital and Southern General Hospital, Glasgow.

PETER J.W. SCOTT
Department of Geriatric Medicine, Stobhill General Hospital, Glasgow G21 3UW

JOHN L. REID
Department of Materia Medica, University of Glasgow, Stobhill General Hospital, Glasgow G21 3UW

Received July 10, 1981

References

ABRASS, I.B. & SCARPACE, P.J. (1981). Human lymphocyte beta-adrenergic receptors are unaltered with age. *J. Gerontol.*, **36**, 298–301.

BERTEL, O., BÜHLER, F.R., KIOWSKI, W. & LÜTOLD, B.E. (1980). Decreased beta-adrenoreceptor responsiveness as related to age, blood pressure and plasma catecholamines in patients with essential hypertension. *Hypertension*, **2**, 130–138.

CARRIER, G.O., JACKSON, C.V. & OWEN, M.P. (1979). Influence of age on norepinephrine-induced vascular contractions as a function of extracellular calcium. *Res. Comm. Chem. Path. Pharmac.*, **26**, 433–446.

ELLIOT, H.L., RUBIN, P.C., SCOTT, P.J.W. & REID, J.L. (1981). Vascular alpha receptors and age. Studies with prazosin and phenylephrine. *Eur. J. clin. Invest.*, **11**, 9.

FLEISCH, J.H. (1980). Age related changes in the sensitivity of blood vessels to drugs. *Pharmac. Ther.*, **8**, 477–487.

GRAY, S.D. (1977). Reactivity of neonatal canine aortic strips. *Biol. Neonate*, **31**, 10–14.

HAYASHI, S. & TODA, N. (1978). Age related changes in the response of rabbit isolated aortae to vasoactive agents. *Br. J. Pharmac.*, **64**, 229–237.

KIOWSKI, W., BÜHLER, F.R., VAN BRUMMELEN, P. & AMANN, F.W. (1981). Plasma noradrenaline concentration and alpha-adrenoceptor mediated vasoconstriction in normotensive and hypertensive man. *Clin. Sci.*, **60**, 483–489.

SCHOCKEN, D.D. & ROTH, G.S. (1977). Reduced beta-adrenergic receptor concentrations in ageing man. *Nature*, **267**, 856–858.

VESTAL, R.E., WOOD, A.J.J. & SHAND, D.G. (1979). Reduced beta-adrenoceptor sensitivity in the elderly. *Clin. Pharmac. Ther.*, **26**, 181–186.

YIN, F.C., SPURGEON, H.A., RAIZES, G.S., GREEN, H.L., WEISFELDT, M.L. & SHOCK, N.W. (1976). Age associated decrease in chronotropic response to isoproterenol. *Circulation*, **54**, Suppl. II, 167.

BIOAVAILABILITY OF SUBLINGUAL ERGOTAMINE

Sublingual ergotamine has been used for years in the treatment of migraine attacks without any proof of its effectiveness. In a double-blind clinical trial no difference in relief was found between sublingual ergotamine and placebo (Crooks *et al.*, 1964). Similarly, a study on the buccal absorption of ergotamine indicated that it is unlikely for therapeutically useful amounts of drug to be absorbed across the buccal membrane (Sutherland *et al.*, 1974).

In contrast, Winsor (1981) in a nonblind cross-over study with finger-plethysmography found that the peripheral vasoconstrictory effect of ergotamine was equal after 0.25 mg intramuscularly or 2 mg sublingually, and significantly different from sublingual placebo. The two forms at those doses should thus be equally effective in migraine. With a high performance liquid chromatographic (h.p.l.c.) assay for ergotamine, with a detection level of 0.1 ng/ml in plasma (Edlund, 1981), we have investigated several administration forms of the drug. The results for sublingual ergotamine are reported as they cast serious doubt on the equipotency of sublingual and intramuscular forms of ergotamine.

Four volunteers (medical personnel, non-migraineurs) kept a sublingual tablet of 2 mg ergotamine tartrate (Lingraine®, Winthrop) under the tongue until dissolved. Blood was drawn after 5, 10, 20, 30, 60, 90 and 120 min. The samples were immediately centrifuged and kept deep frozen until analysed by the h.p.l.c. method. Ergotamine above the detection level was not found in any of the samples. Then the procedure was repeated in the same volunteers with another batch of Lingraine®. Again no ergotamine could be detected. The manufacturer informed us that both batches of Lingraine® were more than 2 years before their expiry date. For comparison we selected 4 migraine patients, who during the same period had their plasma levels of ergotamine determined with h.p.l.c. after 0.5 mg ergotamine tartrate/70 kg body weight intramuscularly. The mean and range of ergotamine levels in ng/ml plasma were after 30 min: 0.96 (0.48–1.41), after 60 min: 0.80 (0.57–1.07) and after 120 min: 0.57 (0.43–0.71). Even corrected to a dose of 0.25 mg the plasma levels of ergotamine are clearly above the detection level of 0.1 ng/ml.

These results were not obtained in a regular cross-over study. However, the discrepancy in plasma