percentage in four of six patients. The percentage fall in steady state plasma warfarin concentration varied between 27 and 64%. In the other two patients, who showed no significant change in the plasma warfarin concentration, warfarin half-life or thrombotest percentage, the nightly dose of quinalbarbitone was increased on a subsequent occasion to 200 mg. This caused a significant fall in the steady state plasma warfarin concentration of 33·3% in one patient and 40·5% in the second patient. These changes were accompanied by significant increases in the thrombotest percentage. The plasma warfarin half-life decreased during the administration of quinalbarbitone 200 mg nightly in both, there being a fall of 59% in the first patient and of 28% in the second patient. On a further occasion the nightly dose of quinalbarbitone to the first patient was increased to 300 mg for a 33 day period. The changes produced were not significantly different from those produced by 200 mg of quinalbarbitone at night. Measurements of the plasma concentration of quinalbarbitone showed inter-individual differences with steady state concentrations varying from 0·38 to 1·21 μg/ml but the degree of induction produced by quinalbarbitone in the various subjects correlated poorly with both the plasma concentration of quinalbarbitone ($r=0·2$) and with the initial rate of warfarin metabolism ($r=0·18$).

The response to varying doses of four enzyme inducing agents—phenobarbitone, amylobarbitone, quinalbarbitone and antipyrine were studied in rats using the changes in pentobarbitone sleeping time and in the V_{max} for the N-demethylation of ethylmorphine by rat liver microsomes. The drugs were given by intraperitoneal injection to groups of rats at least 6 dose levels. Different dose response curves were obtained for the four inducing agents and phenobarbitone was shown to be at least twenty times more potent an inducing agent than the other drugs. This difference in potency is partly explained by a longer plasma half-life of phenobarbitone (241 min) than of amylobarbitone (34 min) and quinalbarbitone (45 min), and partly by a higher liver to plasma ratio for phenobarbitone (3·5 : 1) compared to amylobarbitone (1·6 : 1) and quinalbarbitone (2·0 : 1).

Effects of metformin on glucose uptake by isolated human skeletal muscle

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The hypoglycaemic effect of the biguanide antidiabetic drugs is seen only in diabetic patients (Madison & Unger, 1960). It has been suggested that these drugs act by increasing uptake of glucose into skeletal muscle (Butterfield, 1968). *In vitro* studies using the isolated rat diaphragm preparation have shown that metformin in a therapeutic concentration is without effect on glucose uptake by diaphragm muscle from normal rats, but increases uptake by muscle from alloxan-diabetic rats (Adnitt & Frayn, 1972). The effect is also seen in normal diaphragm muscle incubated in a medium containing n-butyrate (2·27 mM) which induces a metabolic pattern similar to that seen in diabetes. These results suggest that, in rat muscle, metformin increases intracellular utilization of glucose 6-phosphate rather than acting at the level of membrane transport (Frayn & Adnitt, 1972).

Confirmation of these effects in man is important in view of the between-species differences in response to the biguanides. Direct measurement of peripheral glucose uptake in man is, however, difficult. Studies were therefore carried out on the effects of metformin on glucose uptake by human skeletal muscle *in vitro*.

Pieces of human skeletal muscle removed at surgery (from the rectus abdominis or gluteus maximus muscles) were dissected along the fibres into pieces weighing from 100 to 250 mg. Subsequent treatment of the tissue and measurement of glucose uptake followed the method used with the isolated rat diaphragm (Vallance-Owen & Hurlock, 1954). Glucose uptake by such muscle pieces is stimulated by a physiological concentration of insulin (100 μU/ml), and impaired by incubation with n-butyrate (2·27 mM) (Frayn, Adnitt & Turner, 1972).

The effects of metformin on this preparation were tested using a within-patients design and studying tissue from ten patients for each comparison. None of the patients had known diabetes. Metformin in a therapeutic concentration (10 μg/ml) was without effect on glucose uptake when tested both in the absence and presence of exogenous insulin (100 μU/ml). In the presence of insulin (100 μU/ml) together with n-butyrate (2·27 mM), however, metformin (10 μg/ml) caused a significant increase in glucose uptake ($t_9=3{\cdot}6$, $0{\cdot}01>P>0{\cdot}002$).

It is concluded that the action of metformin in isolated human skeletal muscle is similar to its action in isolated rat diaphragm. Glucose uptake by normal muscle is unaffected by a therapeutic concentration of metformin, but in tissue incubated with an inhibitory concentration of free fatty acids this drug causes a significant stimulation of uptake. These observations may explain the antidiabetic action of the biguanide drugs in diabetic patients as compared with their lack of effect in normal subjects.

We thank Rona Laboratories Ltd. for supplying metformin and financial support.

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Some aspects of the clinical pharmacology of bumetanide, a new, potent oral diuretic

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Bumetanide (PF-1593, 3-n-butylamino-4-phenoxy-5-sulphamoyl benzoic acid) is a new, potent, oral diuretic bearing some structural and pharmacological resemblance to frusemide but with greater potency weight for weight (Feit, 1971 ; Asbury, Gatenby, O'Sullivan & Bourke, 1972). In the rat, 6 metabolites of bumetanide have been detected but none have been found in man.

Oral administration of a 1 mg tablet of bumetanide to 13 normal, fasting volunteers produced increases in urinary volume and sodium and potassium excretion maximal within 2 h and complete by 4 h. Increases in urinary sodium excretion in the same subjects over the first 4 h after 0·25 mg, 0·5 mg and 1·0 mg bumetanide were paralleled by increases in urinary calcium ($r=0{\cdot}97$) and magnesium ($r=0{\cdot}99$) excretion. Uric acid excretion was unaffected during the period of maximum natriuresis (0–2 h) after the same three doses but was significantly reduced from the 3rd to 6th hour. The effect was dose-dependent and most marked in the 3rd hour.

An oral dose-response curve in 6 volunteers showed little increase in total natriuresis above a 2 mg dose although the duration of response was prolonged with increasing doses.

Intravenous injection of 2 mg bumetanide to normal subjects produced a maximal natriuresis not exceeding 16% of the calculated filtered sodium load in the first 30 min. Over 25% of the injected drug was recovered from the urine in this period and approximately 50% within 6 h. The increase above control in urinary sodium loss paralleled drug excretion except at peak diuresis when bumetanide/sodium ratios were much increased. The calculated volume of distribution of bumetanide was small and