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.

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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

despite rapid renal clearance of the drug, the overall rate of elimination suggests that a substantial proportion of the injected dose leaves the body by alternative pathways.

The factor limiting the natriuretic effect of bumetanide in normal subjects appears to be the renal response rather than the availability of the compound at its site of action.

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Atropine sulphate absorption from an intramuscular injection of a mixture of the oxime, P2S, and atropine in exercising humans

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The accepted therapy for poisoning by some anticholinesterase compounds is atropine and pralidoxime mesylate (P2S). Holland & White (1971) have already shown that the absorption of atropine from an intramuscular injection was not significantly affected by mixing it with P2S. The subjects of their investigation were, however, at rest, whereas, in practical circumstances it is most likely that the therapeutic mixture would have to be injected in men undertaking heavy physical activity. The present study was, therefore, conducted with men exercising on a bicycle ergometer. The investigation was arranged to disclose the effects of atropine uptake on heart rate, rectal and epigastric skin temperature, and sweat loss in the following experimental conditions for each of nine healthy male volunteers following a set work/rest routine of 150 min:

(a) control i.e. no injection;
(b) 2·0 mg atropine in 2·5 ml water for injection B.P.;
(c) 750 mg P2S mixed with 2·0 mg atropine;
(d) 750 mg P2S in 2·5 ml water for injection B.P.

The work component of the routine was such that men attained heart rates between 110–130 beats/min in the control condition and was determined during the training period. The injection was given either into the buttock (5 men) or the outer thigh (4 men). At least four days separated any two tests with any one subject.

Tests were held in a room with an air temperature of 25° C and a relative humidity 65–75%. The men wore shorts, pants, socks and army boots.

No significant differences were found between the data obtained from the men following injections of either the atropine alone or the atropine/P2S mixture. Both sets of data were higher than the corresponding control values, becoming significant at 10 min post-injection for the heart rate ($P<0·02$), 32 min for skin temperature ($P<0·05$), and 60 min for rectal temperature ($P<0·01$). Maximum mean heart rates were 164 beats/min compared to the 122 in the control tests.

The mean total sweat loss of 620 ± 156 g (mean $\pm$ S.E.) following atropine alone, and 648 ± 170 g following atropine/P2S were not significantly different; both were, however, significantly less than the value of 992 ± 246 g obtained in the control tests ($P<0·01$).

Time to maximal effect on heart rate is difficult to measure as other factors, such as changes in body temperature, also influence the rate. Examination of the change in heart rate increase would suggest that this may occur 40 to 50 min after the injection.

All men experienced a dry mouth between 10 and 25 min following either injection. This symptom had almost disappeared by 130 min.

One man complained of fatigue for a short time 70 min after both injections.

The data for P2S alone were the same as that for the control. Its rate of absorption was not altered by mixing it with atropine.

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