Figure 2 Effect of hCG administration on testosterone levels before (□) and after (■) ranitidine treatment (mean $\pm$ s.e. mean).

Our results stress the fact that ranitidine is not associated with changes in hypothalamic-pituitary-gonadal function in male as evidenced by its lack of influence on basal or stimulated plasma concentrations of testosterone during chronic treatment. These data are in full agreement with those of other authors (Peden *et al.*, 1981; Boyd *et al.*, 1981; Walt *et al.*, 1981; Bohnet & Riley, 1982).

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Received December 1, 1982,
accepted January 27, 1983

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ATENOLOL REDUCES PLASMA MELATONIN CONCENTRATION IN MAN

The production of melatonin by the pineal gland is dependent on the stimulation of post-synaptic pineal β -adrenoceptors (Axelrod, 1974). A number of studies have shown that pineal β -adrenoceptors in the rat are of the β_1 -subtype (Zatz *et al.*, 1976; Backström, 1977) and lie outside the blood-brain barrier (Arendt *et al.*, 1981; Cowen *et al.*, 1983). In both rat and man the synthesis of melatonin by the pineal gland and its

concentration in plasma show a marked diurnal variation, with the bulk of synthesis and release of melatonin occurring during the dark phase (see Arendt, 1978). In animals, melatonin has important effects on gonadal function (Reiter *et al.*, 1978). In man the physiological role of the pineal is unknown, although recent hypotheses implicate disturbances of melatonin secretion in certain psychiatric disorders,

particularly those associated with alterations in circadian rhythm (Lewy *et al.*, 1981).

Previous studies have indicated that propranolol reduces the nocturnal elevation of plasma melatonin in man (Vaughan *et al.*, 1976; Hanssen *et al.*, 1977). Propranolol, besides being a non-selective β -adrenoceptor antagonist, enters the brain with ease (Cruickshank *et al.*, 1980) where it may also act as a 5-HT antagonist (see Weinstock, 1980). To investigate more fully the neuropharmacological control of melatonin production in man, we have tested the effect on midnight plasma melatonin levels of the selective β_1 -adrenoceptor antagonist, atenolol, a drug which crosses the blood-brain barrier poorly (Cruickshank *et al.*, 1980).

Plasma melatonin was measured using a previously described radioimmunoassay (Fraser *et al.*, 1983). Blood samples were obtained from normal volunteers (four male, two female, age-range 23–28 years) at 14.00 h and 24.00 h on each of 2 days separated by an interval of 1 week. The investigation was carried out double-blind, but the order of tablet administration was not randomised, the subjects receiving placebo atenolol at 18.00 h on the first day and atenolol, 100 mg, at 18.00 h on the second. The subjects kept to the same routine on each of the two test days and avoided all other drugs and alcohol. They were, in addition, required at night to use subdued lighting; only light of high intensity (> 500 lux) affects nocturnal plasma melatonin levels in normal subjects (Lewy *et al.*, 1980).

Plasma melatonin was undetectable at 14.00 h in all subjects (limit of sensitivity of assay 11 pg/ml). There was a wide inter-subject variation in midnight plasma melatonin values (Figure 1) as has been reported previously (Arendt, 1978), although intra-subject variation has been found to be small (Arendt, 1978; Cowen, unpublished observations).

Administration of atenolol almost totally abolished the normal night-time rise in plasma melatonin (Figure 1). Indeed, in three of the subjects the plasma melatonin concentration was below the detection limit of the assay. Allocating these latter subjects a value of 11 pg/ml, the reduction in midnight melatonin concentration following atenolol was statistically significant ($P < 0.01$, paired *t*-test). These data suggest that human pineal β -adrenoceptors are of the β_1 -subtype.

The use of atenolol provides a relatively simple pharmacological means of modifying melatonin production and thus may aid investigation into the role of

Figure 1 The effect of atenolol on midnight plasma melatonin concentration.

The pair of points represent the midnight melatonin concentrations of individual subjects. Each subject was tested on two separate occasions, once after placebo administration and once after atenolol, as indicated. Atenolol significantly reduced the midnight elevation of plasma melatonin ($P < 0.01$, paired *t*-test).

the hormone in man. The effects observed occurred with the usual clinical dose of atenolol and it will be of interest to see whether the suppression of melatonin levels persists during long-term administration of β -adrenoceptor antagonists.

We thank Professors M.G. Gelder and D.G. Grahame-Smith for advice and encouragement. Atenolol and placebo were gifts of Stuart Pharmaceuticals.

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Received October 21, 1982,
accepted February 4, 1983

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β -ADRENOCEPTOR BLOCKERS REDUCE BLOOD PRESSURE IN NORMAL SUBJECTS

We would like to reply to the comments by Professor Turner (Turner, 1983) on our recent paper reporting the hypotensive action of atenolol in healthy volunteers (Fuller & Vallance, 1982). Before undertaking the study we made a search of the literature but found no mention of the paper quoted by Professor Turner (Ogle & Turner, 1974) which was published in a journal not listed in the Indexus Medicus or The National Lending Library's Index nor stocked in any leading medical lending library in London. Furthermore the title of the paper may well not have drawn our attention as it refers to CNS rather than CVS actions of the drugs. However had we found the article we would have still undertaken our study because their work, although they used a placebo,

was not *properly* controlled; it was not fully blind as they manually measured pulse rate before taking the blood pressure using a standard sphygmomanometer, and the huge fall in heart rate on the active therapy would have been obvious to the observer. In addition it was not a cross-over design.

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Received and accepted February 8, 1983

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