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Adrenaline and nocturnal asthma

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Abstract

***Objective*—To determine whether the nocturnal fall in plasma adrenaline is a cause of nocturnal asthma.**

***Design*—Double blind placebo controlled crossover study. In the first experiment the nocturnal fall in plasma adrenaline at 4 am was corrected in 10 asthmatic subjects with an infusion of adrenaline after parasympathetic blockade with 30 μg/kg intravenous atropine. In the second experiment 11 asthmatic subjects showing similar variations in peak expiratory flow rate had the nocturnal fall in plasma adrenaline corrected by infusion before atropine was given.**

***Patients*—Asthmatic subjects with a diurnal variation in home peak expiratory flow rate of >20% for at least 75% of the time in the two weeks before the study.**

***Main outcome measures*—Peak expiratory flow rate and plasma adrenaline.**

***Results*—Correction of the nocturnal fall in plasma adrenaline at 4 am to resting 4 pm levels did not alter peak expiratory flow rate either before or after parasympathetic blockade with atropine.**

***Conclusion*—A nighttime fall in plasma adrenaline is not a cause of nocturnal asthma.**

Introduction

Measurements of airway calibre vary more from day to night in patients with asthma than in normal subjects, probably as a result of biological day-night rhythms superimposed in the airway inflammation and bronchial hyperresponsiveness that are characteristic of the disease.[1,2] A large day-night variation in pulmonary function occurs during unstable asthma and may lead to severe nocturnal wheezing or even death. In a previous study we showed that when parasympathetic efferent nerves are blocked with atropine at the time of nocturnal asthma brochodilatation occurs such that the fall in respiratory function at night is almost completely reversed, implying that increased parasympathetic efferent activity is an important cause of nocturnal asthma.[3] This also implies, however, that other factors act in addition. These may include circadian rhythms of plasma adrenaline and cortisol,[4] body temperature,[5] sleep,[6] α sympathetic nerves, or even dysfunction of non-adrenergic non-cholinergic bronchodilator nerves containing vasoinhibitory peptide.[7] Circadian changes in airway oedema may also be important.

The role of plasma adrenaline in nocturnal asthma has been studied with two infusion rates of adrenaline at night in five asthmatic subjects. This study showed a reversal of the nocturnal fall in peak expiratory flow rate,[4] but the infusion rates that were used produce a plasma adrenaline concentration at the upper end of the resting daytime physiological range[8] and therefore the effect of adrenaline was almost certainly overestimated.

We investigated the role of plasma adrenaline in nocturnal asthma. In vitro studies have shown that, in addition to having a direct action on bronchial smooth muscle, adrenaline may modulate parasympathetic nervous activity through prejunctional β_2 receptors,[9] may influence the release of inflammatory mediators from mast cells,[4] or may alter microvascular leak from blood vessels:[10]

We measured the effect on peak expiratory flow rate of correcting the nocturnal fall in plasma adrenaline within the resting day/night range both before and after blocking parasympathetic efferent activity with atropine.[3]

Method

In this double blind placebo controlled crossover study we performed two experiments. In the first, 10 asthmatic subjects were studied, each with a diurnal

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Physical characteristics of patients (all non-smokers)

Case No	Age	Sex	Duration of asthma (years)	Atopy	Drugs	Peak expiratory flow rate (% predicted)
					First experiment	
1*	44	F	35	+	β_2 Agonists, anticholinergic drugs, inhaled steroids	70
2*	58	F	16	−	β_2 Agonists, anticholinergic drugs, inhaled steroids, theophyllines	65
3*	45	F	10	−	β_2 Agonists, anticholinergic drugs, inhaled steroids	54
4*	51	F	25	−	β_2 Agonists, inhaled steroids, theophyllines	71
5*	39	M	25	+	β_2 Agonists, inhaled steroids, theophyllines	85
6	50	F	20	+	β_2 Agonists, inhaled steroids, theophyllines	80
7	54	M	15	−	β_2 Agonists, anticholinergic drugs, inhaled steroids, theophyllines	56
8	23	F	8	+	β_2 Agonists, inhaled steroids	90
9	30	M	12	+	β_2 Agonists, inhaled steroids	75
10	60	F	40	+	β_2 Agonists, anticholinergic drugs, inhaled steroids	60
					Second experiment	
1	48	M	35	−	β_2 Agonists, anticholinergic drugs, theophyllines, inhaled steroids	49
2	57	M	9	−	β_2 Agonists, anticholinergic drugs, theophyllines, inhaled steroids	39
3	43	F	30	−	β_2 Agonists, inhaled steroids	37
4	54	M	5	−	β_2 Agonists, anticholinergic drugs, theophyllines, inhaled steroids	33
5	47	F	7	−	β_2 Agonists, anticholinergic drugs, theophyllines, inhaled steroids	33
6	64	F	2	−	β_2 Agonists, anticholinergic drugs, theophyllines, inhaled steroids	38

*Included in second experiment.

variation in peak expiratory flow rate of >20% for more than 75% of the time on home monitoring in the two weeks before the study. They were admitted to hospital for one day's acclimatisation to the ward routine followed by two successive study days. Oral theophyllines were omitted for two days before admission, and coffee and tea were not allowed throughout the study period. Inhaled steroids were continued and inhaled β_2 agonists and anticholinergic drugs excluded for 10 hours before each study session.

On study day 1 two cannulas were inserted before the patient went to sleep. The patient was woken at 4 am, the pulse rate recorded, and blood taken for measuring plasma adrenaline concentration. The best of three peak flow manoeuvres was noted. The patient then received, under double blind conditions, either intravenous atropine 30 μg/kg followed by adrenaline infusions or an equal volume of intravenous saline and saline infusions as a placebo. The pulse rate, plasma adrenaline concentration, and peak flow were checked five to 15 minutes after the intravenous injection and at the end of each infusion rate. The starting infusion rate for adrenaline was 1 ng/kg/min, which was infused for 20 minutes to reach equilibrium.[7] This was increased at 20 minute intervals to 2, 4, 8, 16, and 32 ng/kg/min. The same flow rates on the infusion pump were used for the placebo study.

At 4 pm on day 1 the patient's pulse rate, plasma adrenaline concentration, and peak expiratory flow rate were checked after he or she had rested supine for one hour. An intravenous injection of either atropine 30 μg/kg or saline was then given, followed by adrenaline or placebo infusions as above. The pulse rate and peak expiratory flow rate were recorded and blood taken for plasma adrenaline assay. The procedure was repeated on day 2 so that each patient received both the active drugs and placebo at 4 am and 4 pm. A washout period was not considered necessary due to the short plasma half life of adrenaline of several minutes and also because intravenous atropine has a bronchodilator effect for only two to three hours.[11]

In the second experiment 11 patients (five from the first experiment and a further six showing similar diurnal variations in peak expiratory flow rate) received an infusion of 3·5 ng/kg/min of adrenaline at 4 am for 20 minutes (after baseline measurements of peak flow rate) followed by intravenous atropine 30 μg/kg. This infusion rate was chosen on the basis of a pilot study and proved to be slightly higher than the infusion rate of 2·5 ng/kg/min that was found to correct the nocturnal fall in plasma adrenaline in the full series of experiments. At 4 pm the procedure was similar to that in the first experiment.

Adrenaline concentrations were determined radioenzymatically using a modification by McKechnie and colleagues[12] of the procedure described by DaPrada and Zurcher.[13] This method has a lower limit of sensitivity of 0·05-0·1 nmol/l depending on blank values. The intra-assay coefficient of variation was 11% and the interassay coefficient of variation was 16%.

Statistical analysis of dose-response studies were performed using the Statgraphics program (STSC Inc, Maryland, United States). A linear regression line best fitted the dose-response data. Paired comparisons were made with Student's t test and multiple comparisons by analysis of variance with Neumann-Keuls post hoc testing.

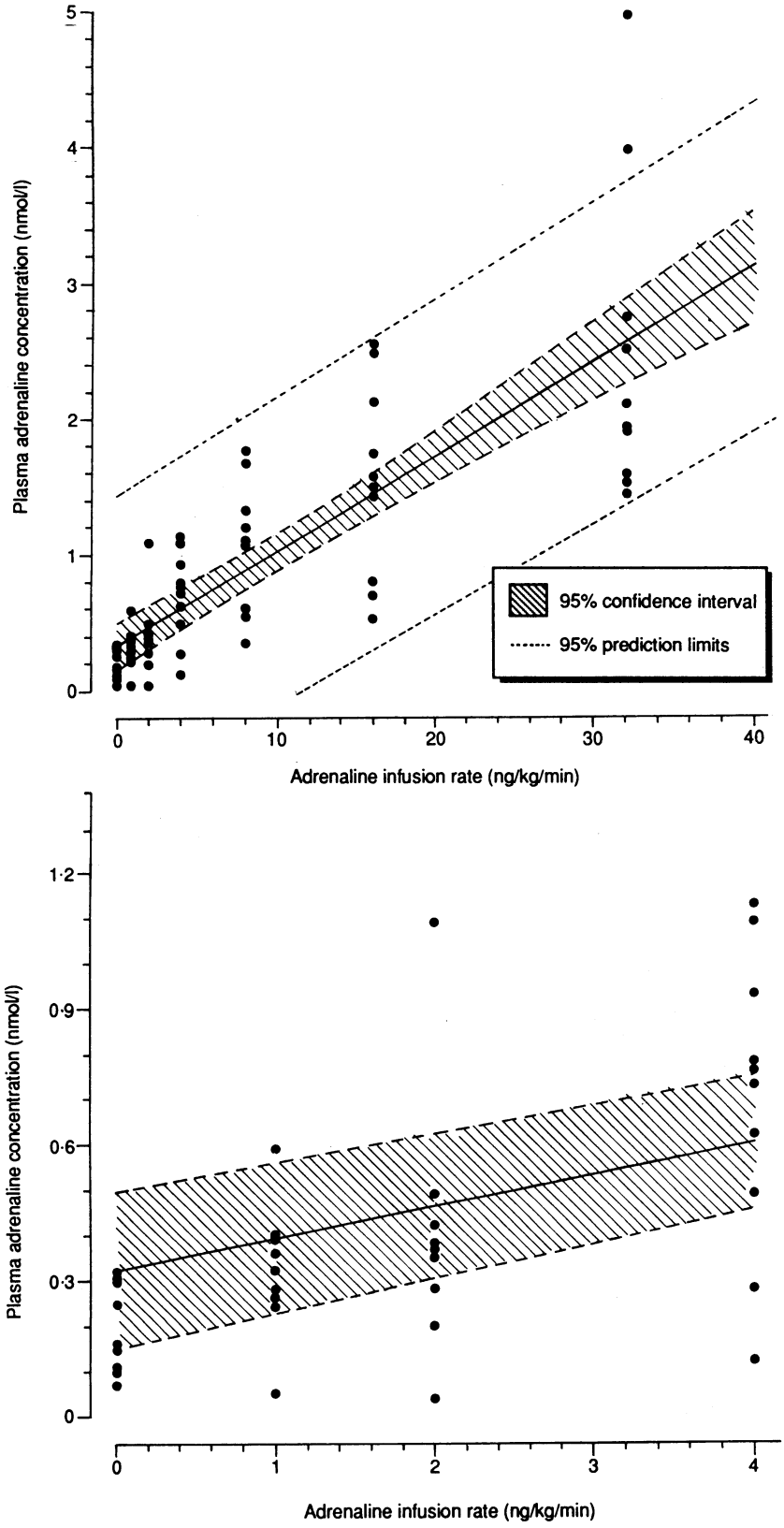

FIG 1—*(Top) Comparison of mean plasma adrenaline concentrations achieved at 4 am with incremental infusions of adrenaline in 10 patients (first experiment). (Bottom) Detail of range in which correction of the nocturnal fall in plasma adrenaline occurs*

Results

The table shows details of the subjects, and figure 1 shows the relation between infusion rates of adrenaline and mean plasma adrenaline concentrations based on the data from the 11 patients in the first arm of the study at 4 am. Infused adrenaline produced a dose related increase in peak flow rate after atropine at 4 am (fig 2).

In the first experiment there was a significant diurnal variation of peak flow rate between the mean 4 am placebo value and the 4 pm placebo value (160 l/min (95% confidence interval 115 to 204 l/min) *v* 256 (218 to 294) l/min; t=6·23, df=3, p=0·003; fig 3). Similarly, plasma adrenaline showed a significant

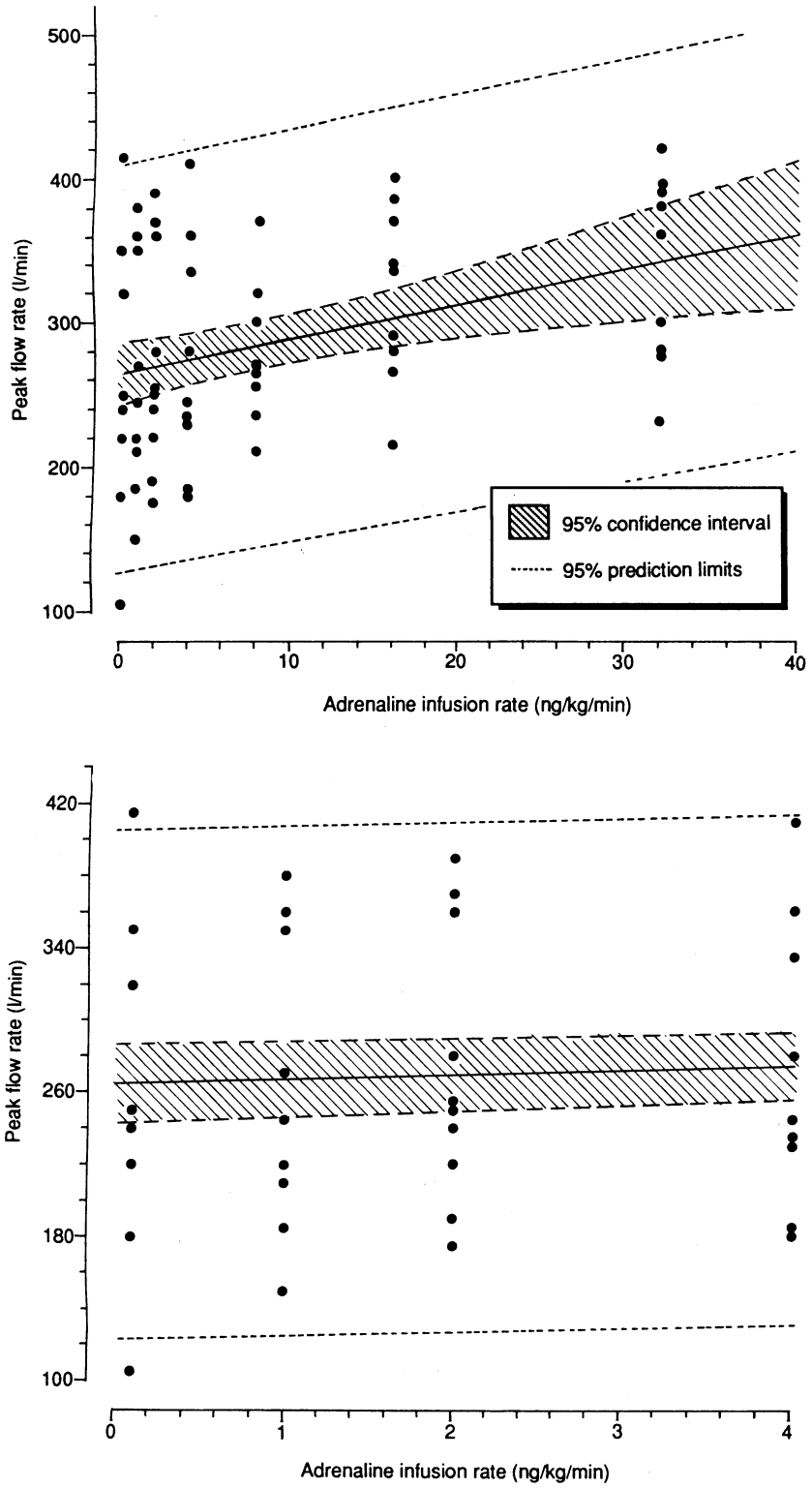

FIG 2—*(Top) Comparison of effect on mean peak flow rate of incremental infusions of adrenaline at 4 am after 30 μg/kg intravenous atropine. Values are means from 10 patients (first experiment). (Bottom) Detail of effect in range in which nocturnal fall in plasma adrenaline is corrected*

diurnal variation from the 4 am placebo value to the 4 pm placebo value (0·19 (−0·17 to 0·55) nmol/l *v* 0·51 (0·17 to 0·85) nmol/l; $t=8·17$, df=9, p=0·05). Figure 3 also shows the effect on peak flow rate of atropine at 4 am and 4 pm. The mean peak flow rate at 4 am after atropine rose significantly from 160 (115 to 204) l/min to 258 (214, 302) l/min; $t=4·05$, df=9, p=0·003). This value was not significantly different from the 4 pm placebo value of 256 (218 to 294) l/min, or the peak flow at 4 pm after atropine of 301 (262 to 339) l/min ($t=1·78$, df=9, p=0·10).

Placebo infusions had no effect on either plasma adrenaline concentration, pulse rate, or peak flow rate. The infusion rate of adrenaline required to raise plasma levels from 4 am placebo values (0·19 nmol/l) to 4 pm placebo values (0·51 nmol/l) was 2·5 ng/kg/min (fig 1). The nearest infusion rate to this value, of 2 ng/kg/min, produced a mean rise in peak flow rate after atropine of 15 l/min, which was not significantly different from the mean value for atropine at 4 am (fig 4).

In the second experiment the mean peak flow rate at 4 am was 167 (115 to 219) l/min, and at 4 pm 205 (153 to 257) l/min, which showed a significant diurnal variation ($t=2·97$, df=10, p<0·02). At 4 am infusions of adrenaline were given at a rate of 3·5 ng/kg/min; the peak flow rate was unchanged at 166 (114 to 218) l/min (fig 5). Subsequent administration of atropine produced an increase of 66 l/min to 232 (181 to 284) l/min (df=10, $t=4·9$, p<0·0001). This value at 4 am after both adrenaline and atropine was significantly below the 4

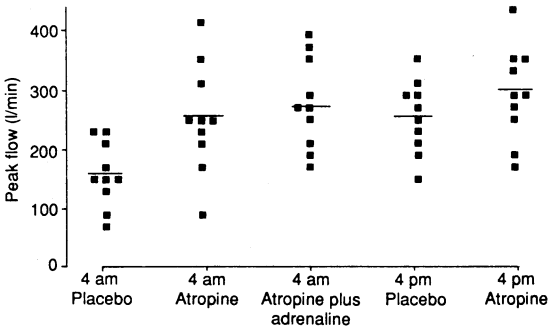

FIG 3—*Effect of 30 μg/kg of atropine on peak flow rate at 4 am and 4 pm (first experiment) and combined effect of atropine and infusion of adrenaline (2·0 ng/kg/min) at 4 am. Horizontal bars are mean values*

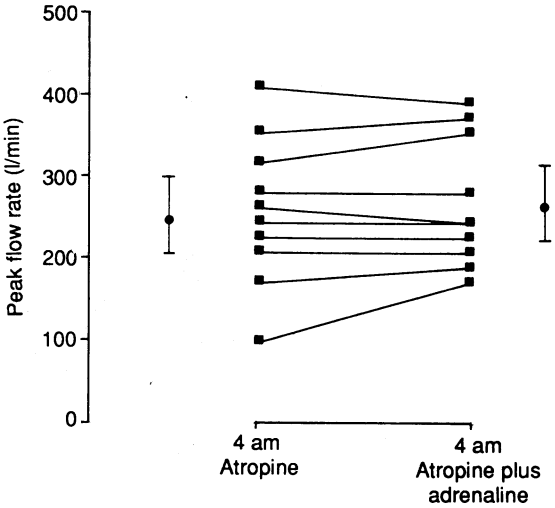

FIG 4—*Effect on peak flow rate of infusion of adrenaline (2·0 ng/kg/min) after atropine in 10 patients (first experiment). Vertical bars show means (95% confidence intervals)*

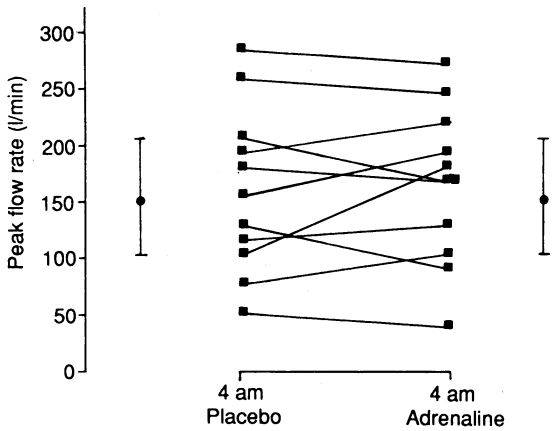

FIG 5—*Effect of infusion of adrenaline (3·5 ng/kg/min) on peak flow rate in 11 patients (second experiment). Vertical bars show means (95% confidence intervals)*

pm atropine value of 257 (205 to 309) l/min ($t=2{\cdot}4$, df=10, $p<0{\cdot}05$) but not different from the 4 pm placebo values.

Discussion

This study had investigated the dual role of parasympathetic efferent activity and plasma adrenaline in the pathogenesis of nocturnal asthma. Parasympathetic blockade in this study caused a significant reversal of the nocturnal fall in peak flow rate as shown in our previous work.[3] In the first arm of the study parasympathetic blockade reversed completely the nocturnal fall in peak flow rate, but the effect was not complete in the second arm.

Infusions of adrenaline in a dose more than sufficient to reverse the nocturnal fall in plasma adrenaline both before and after parasympathetic blockade produced no significant increase in the peak flow rate at 4 am. Thus, although infusions of adrenaline in higher concentrations can cause bronchodilatation in both normal and asthmatic subjects (fig 2),[14,15] alterations of plasma adrenaline within the concentrations seen on a diurnal basis do not have any significant physiological effect on expiratory airflow limitation either by direct action on bronchial smooth muscle, modulation of vagal neurotransmission,[8] mediator release from inflammatory cells,[4,16] or by increasing microvascular leakage.[9]

Our results agree with the earlier observation that a diurnal variation in pulmonary function can occur after adrenalectomy,[17] again confirming a lack of a primary role for adrenaline in nocturnal asthma. These observations do not detract from the therapeutic benefit of oral or inhaled β_2 agonists in nocturnal asthma, when (as in this situation) pharmacological concentrations of the agonist are achieved at the receptor.

We conclude that the nocturnal fall in plasma adrenaline does not account for the other factor(s) that act with parasympathetic nervous activity to increase airflow limitation at night in asthma. The effect of the α sympathetic and non-adrenergic non-cholinergic nerves and also the study of diurnal variation of airway oedema and inflammatory mediators in nocturnal asthma may be of relevance for future research.

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Effect of erythropoietin on anaemia in patients with myeloma receiving haemodialysis

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Sustained renal impairment in multiple myeloma is usually a consequence of glomerular and tubulointerstitial deposition of M component and of amyloidosis.[1] As peritubular endothelial cells are thought to be the site of production of erythropoietin[2] anaemia in patients with myeloma who are dependent on dialysis may be partly due to a lack of production of erythropoietin. In vitro experiments have shown that marrow cells from patients with myeloma respond to erythropoietin.[3] We report the successful use of erythropoietin in two patients with myeloma who were dependent on transfusions and were receiving haemodialysis.

Case reports

CASE 1

A 55 year old woman presented in May 1988 with end stage renal failure. She had myelomatosis with a serum M component band of IgA λ light chain (15 g/l) and Bence Jones proteinuria (1·53 g/24 h). Abnormal plasma cells made up between 10% and 90% of the marrow, which had an increased iron content. She was normotensive and normocalcaemic and did not have any lytic lesions or evidence of hyperparathyroidism on skeletal examination. Renal ultrasound scanning showed slightly small kidneys with normal outlines. Renal biopsy was not done. Between November 1988 and March 1989 she received two courses of melphalan and prednisolone and three courses of carmustine, vincristine, and adriamycin; her serum concentration and urinary excretion of M component fell to 6 g/l and 1·02 g/24 h respectively. She was given 14 units of blood between January and November 1989.

In November 1989, when her haemoglobin concentration was 51 g/l, recombinant human erythropoietin was started at a dosage of 120 IU/kg/week intravenously in divided doses after dialysis. After five weeks the dosage was increased to 240 IU/kg/week with an improved response. Her haemoglobin concentration had risen from 51 g/l to 97 g/l after 14 weeks of treatment (figure).

CASE 2

A 53 year old man presented in August 1988 with end stage renal failure and myeloma with a serum M component band of IgG κ light chain (2 g/l) and Bence Jones proteinuria (1·5 g/24 h). Abnormal plasma cells made up about 10% of his marrow, which contained adequate but not excess iron. He was normotensive and normocalcaemic and had lytic lesions but no evidence of hyperparathyroidism on skeletal examination. His kidneys appeared normal on ultrasound scanning. Renal biopsy showed tubular