

Though the urinary hydroxyproline to creatinine ratio has been proposed as a useful indicator of bone breakdown in malignancy,<sup>11</sup> we found no significant fall in this variable in patients whose rate of bone mineral resorption had clearly been decreased. The explanation is possibly that tissue other than bone continues to be broken down at a greatly increased rate, masking any fall produced from the decreased bone turnover.

Of additional interest was the finding of quite profound hypomagnesaemia in some patients (as low as 0.3 mmol/l). This may simply result from an inability of the renal tubules to differentiate between divalent cations as the filtration of calcium increases. Though no patient had symptoms directly related to hypomagnesaemia, its role in the neuromuscular symptoms in concert with hypercalcaemia warrants further investigation.

All patients obtained much relief of their distressing symptoms, and in a setting which is often preterminal the value of an effective agent which is free of side effects is self evident. We therefore now use APD 60 mg as a single infusion over eight hours along with adequate saline rehydration as the sole initial management of the hypercalcaemia of malignancy and give further APD when hypercalcaemia recurs or at regular intervals of three weeks to maintain normocalcaemia. Evidently other factors including the response to chemotherapy determine the eventual outcome.

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# Raised plasma intact parathyroid hormone concentrations in young people with mildly raised blood pressure

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## Abstract

To study the role of parathyroid gland activity in early primary hypertension plasma concentrations of intact parathyroid hormone were measured in 90 untreated young subjects, aged 16-29, with stable mildly raised blood pressure and in 40 normotensive control subjects selected from the same population in Zoetermeer, The Netherlands. Intact parathyroid hormone concentration was significantly higher in the hypertensive than the normotensive group (2.34 (SE 0.11) pmol/l v 1.47 (0.13) pmol/l, respectively; difference 0.87 pmol/l; 95% confidence interval 0.55 to 1.21;  $p < 0.0001$ ). Serum total calcium concentration was 2.36 (0.01) mmol/l in the hypertensive group and 2.42 (0.01) mmol/l in the normotensive group (difference 0.06 mmol/l; 95% confidence interval 0.02 to 0.09;  $p = 0.02$ ). Urinary calcium excretion over 24 hours did not differ significantly between the two groups (4.17 (0.28) mmol/24 h in the hypertensive group and

3.89 (0.39) mmol/24 h in the normotensive group; difference 0.28 mmol/24 h; 95% confidence interval -0.66 to 1.22). In the hypertensive group both systolic and diastolic blood pressures increased slightly though significantly with intact parathyroid hormone concentrations. No obvious associations between serum calcium concentration and blood pressure were observed.

These findings support the view that enhanced activity of the parathyroid gland may play a part in the early stage of primary hypertension.

## Introduction

An association between activity of the parathyroid gland and blood pressure was first suggested by Hellstrom *et al*, who reported an increased prevalence of hypertension in primary hyperparathyroidism.<sup>1</sup> Furthermore, the prevalence of hyperparathyroidism in subjects with primary hypertension is considerably higher than that in the general population.<sup>2</sup> The raised blood pressure seems not to be secondary to renal damage resulting from hypercalcaemia in hyperparathyroidism,<sup>3,4</sup> and whether blood pressure falls after parathyroidectomy in patients with primary hyperparathyroidism is still uncertain.<sup>4,5</sup>

Two studies have shown increased concentrations of circulating total immunoreactive parathyroid hormone in middle aged patients with hypertension,<sup>6,7</sup> and preliminary findings suggest that concentrations of circulating intact parathyroid hormone (1-84) may be raised in younger subjects with hypertension.<sup>8</sup> In addition, oral calcium supplementation seems to lower blood pressure in subjects with mild hypertension who have higher than average serum intact

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parathyroid hormone concentrations.<sup>9</sup> Intact parathyroid hormone concentration may be a more accurate index of activity of the parathyroid gland than total immunoreactive parathyroid hormone concentration because it is not affected by the changes in renal clearance of the metabolites of parathyroid hormone that are seen in chronic hypertension.<sup>10,11</sup> We measured plasma concentrations of intact parathyroid hormone in a group of young subjects whose blood pressure was persistently in the upper range of the distribution for their age and in a group of normotensive control subjects selected from the same population.

TABLE I—Characteristics of subjects studied

Variable	Hypertensive group (n=90)			Normotensive group (n=40)		
	Mean	Standard deviation	Interquartile range*	Mean	Standard deviation	Interquartile range*
Age (years)	24.3	2.8	5.3	24.4	3.1	5.8
Blood pressure (mm Hg):						
Systolic	143.2	10.5	14	125.0	11.0	12
Diastolic	83.0	10.1	15	74.3	7.3	7
Body weight (kg)	77.9	12.3	18	73.5	9.4	12

\*Q3 minus Q1.

TABLE II—Comparison of mean (SE) concentrations of plasma intact parathyroid hormone, serum calcium and creatinine, and urinary calcium excretion between two study groups

	Hypertensive group	Normotensive group	Mean difference (95% confidence interval)	p Value
Plasma intact parathyroid hormone	2.34 (0.11)	1.47 (0.13)	0.87 (0.55 to 1.21)	<0.0001
Serum calcium (mmol/l)	2.36 (0.01)	2.42 (0.01)	0.06 (0.02 to 0.09)	0.02
Serum creatinine (μmol/l)	73.8 (1.5)	74.0 (1.7)	0.2 (-4.3 to 4.7)	NS
Urinary calcium (mmol/l/24 h)	4.17 (0.28)	3.89 (0.39)	0.28 (-0.66 to 1.22)	NS

observations with pooled variances were used. The data are presented as means and standard error with mean differences and 95% confidence intervals. To assess interrelations between variables simple linear regression analysis was performed separately for hypertensive and normotensive subjects. The p values correspond to a two tailed test of significance.

## Results

Table I shows the characteristics of the subjects studied. Table II shows the mean concentrations of the variables measured—the groups. The distribution of intact parathyroid hormone concentrations as a whole was shifted to higher values in the hypertensive than the normotensive subjects (fig 1). Serum total calcium concentration was lower in hypertensive than normotensive subjects. There were no differences in 24 hour urinary calcium excretion or in serum creatinine concentration between the two groups. In the hypertensive group both systolic and diastolic blood pressure increased slightly though significantly with plasma intact parathyroid hormone concentration; the slope was 2.3 (SE 1.1) mm Hg/pmol/l ( $p=0.05$ ) for systolic pressure (fig 2) and 2.2 (1.1) mm Hg/pmol/l ( $p=0.05$ ) for diastolic pressure. Similar associations were found in the normotensive group, the slope being 4.6 (2.9) mm Hg for systolic pressure (fig 2) and 2.5 (1.9) mm Hg/pmol/l for diastolic pressure; in this group, however, the values for the slope failed to reach significance. No direct relation between serum calcium concentration and blood pressure was observed. Moreover, intact parathyroid hormone concentration was not significantly associated with serum total calcium concentration in either of the two groups or in the

## Subjects and methods

From 1975 to 1979 all residents of two districts of the Dutch town of Zoetermeer aged 5-19 years were invited to take part in a survey of risk factors for cardiovascular disease, and 4649 participated (82%). Of the children and young adults examined initially, 1597 were selected for yearly follow up as described previously.<sup>12</sup> None of the subjects received any specific intervention during the follow up. From this cohort the participants in the present study were selected. Stable mild hypertension was defined as at least three measurements of blood pressure of 140 mm Hg systolic or 90 or more mm Hg diastolic, or both, at the yearly examinations during seven to 10 years of follow up without identified secondary hypertension. Of 130 eligible subjects, 90 (77 male, 13 female) agreed to participate in the study, which was part of a subsequent intervention study.<sup>9</sup> Forty normotensive control subjects were randomly selected from the remainder of the subjects followed up. None of the participants used any drug known to affect blood pressure or calcium metabolism.

Blood pressure was measured with a random zero sphygmomanometer by two trained paramedical observers between 4 and 8 pm after the subjects had rested for 10 minutes and before a blood sample was taken. Three readings were taken alternately with taking the pulse rate while the subject was sitting; the mean was used in the analysis.

A plasma sample was obtained from each subject and placed in chilled tubes coated with edetic acid, which were frozen at  $-70^{\circ}\text{C}$  until assayed. All subjects collected one 24 hour urine sample. Urinary calcium excretion and serum total calcium and creatinine concentrations were measured by standard methods. Plasma intact parathyroid hormone concentration was determined by a recently developed two step immunochemical method.<sup>11</sup> The first step entails extracting and concentrating intact parathyroid hormone (1-84) on a solid phase with antibiotics to parathyroid hormone (1-34). Then after separation of the adsorbed hormone from the excess of mid-molecular and C terminal fragments intact parathyroid hormone (1-84) is eluted with hydrochloric acid and analysed with a mid-molecular antibody, bovine parathyroid hormone (1-84) as tracer, and human intact parathyroid hormone (1-84) as standard.

*Analysis of data*—For group mean comparisons *t* tests for unpaired

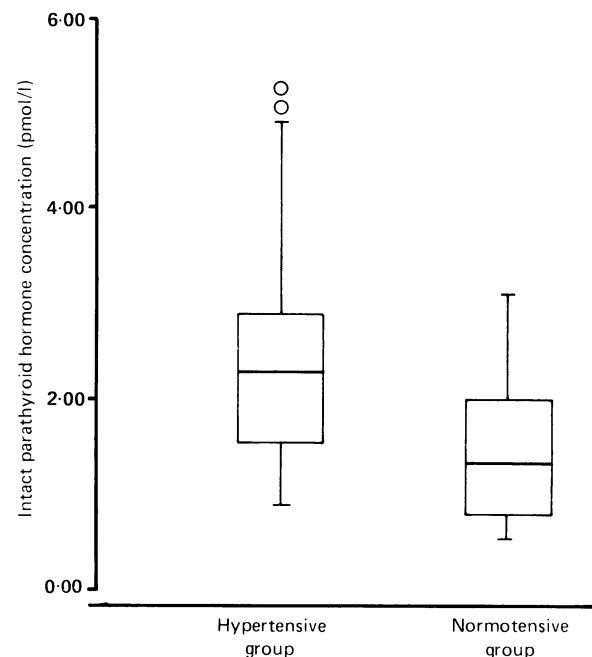


FIG 1—Box plot of plasma intact parathyroid hormone concentration in young hypertensive and normotensive subjects. Top and bottom lines of each box show 75th and 25th centiles, and middle line shows 50th centile (median value). Vertical bars extend to upper and lower adjacent values, points outside this range being indicated by open circles (hypertensive group only). Adjacent values are equivalent to the outlier cut off values. Outliers are defined as larger than  $Q3 + 2/3(Q3 - Q1)$  and smaller than  $Q1 - 2/3(Q3 - Q1)$ . For a Gaussian distribution 0.7% of the population is outside the outlier cut off values. Thus the population outlier cut off values contain  $\pm 99.3\%$  of the distribution.<sup>29</sup>

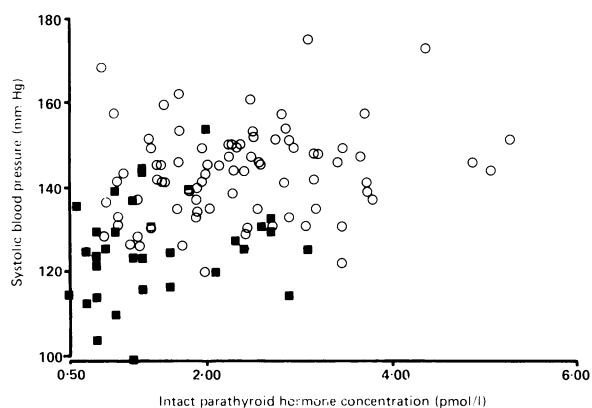


FIG 2—Scattergram of systolic blood pressure by plasma concentration of intact parathyroid hormone for hypertensive (○) and normotensive (■) subjects.

two groups combined, nor was it related to body weight in contrast with previous findings.<sup>8</sup>

### Discussion

Our findings of raised plasma concentrations of intact parathyroid hormone in young subjects with mildly raised blood pressure provide evidence that circulating intact parathyroid hormone may be increased in the early stage of primary hypertension. Furthermore, in subjects with hypertension both systolic and diastolic blood pressures seem to be positively associated with the plasma concentration of intact parathyroid hormone. It should be noted that the blood pressure in these young subjects was not high according to clinical standards. The participants were, however, selected because their blood pressure was raised on several occasions when measured in a way to which they had become accustomed. Therefore they represent a select group likely to develop overt hypertension in future years. These observations support the hypothesis that enhanced parathyroid gland activity is implicated in the development of primary hypertension.

Increased activity of the parathyroid gland may result from autonomous hyperfunction of parathyroid tissue or from other causes.<sup>13</sup> These include increased renal calcium loss or reduced dietary intake of calcium, and both have been reported in subjects with hypertension.<sup>6,7,14</sup> The effects on the activity of the parathyroid gland may be mediated by a slight reduction in serum calcium concentrations as observed in this and previous studies.<sup>15,16</sup> We did not observe differences in urinary calcium excretion. It is, however, difficult, if not impossible, to characterise the calcium excretion of a subject from a single urine specimen.

Basal parathyroid gland activity is also influenced by the sympathetic nervous system.<sup>17</sup> In a similar group of young subjects with hypertension selected from the same population increased plasma concentrations of noradrenaline, adrenaline, and dopamine were observed.<sup>18</sup> The question remains whether parathyroid hormone itself raises blood pressure or whether increased parathyroid gland activity merely results from other changes in calcium metabolism associated with hypertension.<sup>19</sup> Data on effects of exogenous parathyroid hormone on blood pressure are conflicting.<sup>20</sup> Long term administration of parathyroid hormone seems to increase blood pressure in humans and rats,<sup>21,22</sup> and it may raise calcium concentrations in smooth muscle, thereby increasing contractility and consequently peripheral resistance.<sup>23,24</sup> Alternatively, parathyroid hormone may relate to blood pressure by an intermediate action on the renin-angiotensin system.<sup>25</sup> Raised concentrations of parathyroid hormone may result from a higher sodium intake, although data on this are equivocal.<sup>26,27</sup> Studies in spontaneously hypertensive rats suggest that activity of the parathyroid gland may affect blood pressure predominantly during the early phase of the development of hypertension.<sup>28</sup> In humans studies on the role of calcium metabolism in the onset of primary

hypertension are clearly indicated, in particular the role of the parathyroid gland.

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### ONE HUNDRED YEARS AGO

MR. EDWIN CHADWICK, C.B., speaking at the annual dinner of the Association of Public Sanitary Inspectors on Saturday last, observed that it was important that time should be given to the Boundary Commissioners to make their examinations full and complete, as much of the reform needed would only come from larger areas than the present small administrative ones being provided for poor-law and sanitary purposes. He also urged that the scattered and weakened functions now spread over several Government departments should be consolidated under a Minister of Health. In conclusion he referred to the fact that the Lancashire manufacturers had an offer now made to them to work their engines by gas at two-thirds the price of working them by the flame of coal. This plan was proposed by the speaker thirty years ago; and there was no doubt that this might be done, and, when done, down would fall the big chimney which befouled all around with its smoke and dirt. (*British Medical Journal* 1888;i:310)