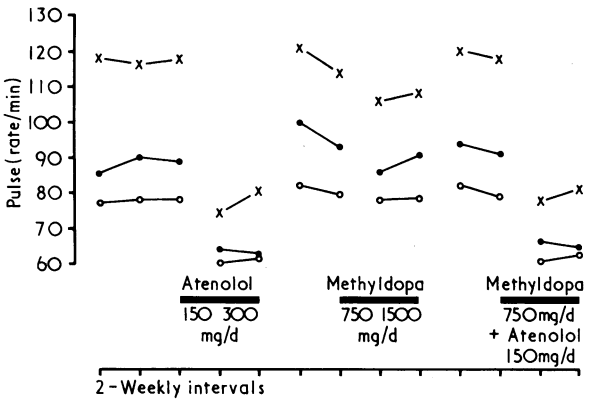

FIG 2—Mean pulse rate during run-in and treatment periods. ○ = Lying. ● = Standing. × = Post exercise.

The pulse rates during the atenolol treatment were all significantly lower than those during the methyldopa or non-atenolol periods ($P < 0.001$).

Analysis of the questionnaire on side effects showed that the periods of treatment that incorporated methyldopa could be identified. More patients complained of dreams, increased sleeping, increased tiredness, and reduced energy after four weeks of treatment with methyldopa than during the three periods of treatment with chlorthalidone alone or the one period on atenolol alone.

Discussion

In patients with moderate hypertension on continuous treatment with chlorthalidone the addition of atenolol, methyldopa, or low doses of atenolol and methyldopa in combination is effective in reducing blood pressure. The fall in blood pressure with the addition of atenolol 150 mg/day was greater than that with methyldopa 750 mg/day.

The doses of atenolol chosen for study were adequate. In other studies we have shown that atenolol 50, 100, and 200 mg once daily[2] or atenolol 200-400 mg/day, or in combination with bendrofluazide in twice daily doses,[3] reduces raised blood pressures. In both these studies an increase in dose above the lowest dose did not further reduce mean blood pressure levels. This finding has been confirmed in the present study. Doubling the dose of methyldopa from 750 to 1500 mg/day did not increase the hypotensive effect significantly. This confirms the findings of Barritt *et al*[4] and of Scott *et al* (personal communication).

The design of the study incorporated a run-in period and washout periods on chlorthalidone. The diuretic was included because in a previous study in a similar group of patients a period of treatment with placebo alone was included[1] and the mean levels of lying blood pressure during that placebo period were high—183/114 mm Hg (phase-4). Although we took the precaution of using a background diuretic we now believe that a lower initial dose of atenolol or methyldopa should have been used, because two patients on chlorthalidone had to be withdrawn from the study because of severe and symptomatic hypotension when the lower dose of each drug was added.

We thank all who helped in this study, particularly Mrs B Reid and Mrs M C Smith, and Dr W T Simpson and Mr J A Lewis of Imperial Chemical Industries Limited.

References

[1] Petrie, J C, *et al*, *British Medical Journal*, 1976, **2**, 137.
[2] Jeffers, T A, *et al*, *British Journal of Clinical Pharmacology*, 1977. In press.
[3] Petrie, J C, *et al*, *British Medical Journal*, 1975, **4**, 133.
[4] Barritt, D W, Marshall, A J, and Heaton, S, *Lancet*, 1976, **1**, 503.

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Rate of reversal of hypercalcaemia and hypercalciuria induced by vitamin D and its 1α-hydroxylated derivatives

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Summary

The rate of reversal of hypercalcaemia or hypercalciuria induced by calciferol, dihydrotachysterol, 1-α-hydroxycholecalciferol (1-α-OHD_3), or 1-α, 25-dihydroxycholecalciferol (1-α, 25-$(OH)_2D_3$) was measured in three normal subjects, two patients with osteoporosis, and 14 patients with disorders resistant to vitamin D. The half time for reversal after stopping 1-α, 25 $(OH)_2D_3$ was less than that after stopping 1-α-OHD_3, calciferol, or dihydrotachysterol. The differences observed were independent of the dose given or length of treatment. When 1-α-OHD_3 or 1-α-25-$(OH)_2D_3$ was stopped patients with vitamin D resistant states (hypoparathyroidism, renal tubular hypophosphataemia, or chronic renal failure) showed less rapid reversal of hypercalcaemia and hypercalciuria than did normal subjects. These studies show one potential advantage of 1-α-25-$(OH)_2D_3$ over vitamin D, and possibly over 1-α-OHD_3, in the management of vitamin D resistant states.

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Introduction

Since the discovery that vitamin D_3 (cholecalciferol) is converted in the kidney to 1-α, 25-dihydroxycholecalciferol (1-α-25-$(OH)_2D_3$) before exerting its biological effects,[1] there has been considerable interest in the potential advantages of using 1-α, 25-$(OH)_2D_3$ or its synthetic analogue, 1-α-hydroxycholecalciferol (1-α-OHD_3), for treating disorders resistant to

vitamin D. These vitamin D derivatives may overcome any block in the metabolic conversion of vitamin D in disorders such as bone disease secondary to chronic renal failure,[2-7] hypoparathyroidism,[8 9] and vitamin D dependent rickets.[5 10] The commonest complication of vitamin D treatment is hypercalcaemia. It may be easier to reverse hypercalcaemia if the 1-α-hydroxylated derivatives are used, but this assumption has not been tested in detail. We therefore measured the rate of return to normal of the increased plasma and urinary calcium levels induced by these compounds in various clinical conditions.

Patients and methods

Thirty studies were done on 16 patients and three normal subjects (see table) who had received vitamin D_2 (calciferol), dihydrotachysterol, 1-α-OHD_3, or 1-α, 25-$(OH)_2D_3$. The plasma concentration or urinary excretion rate of calcium was measured during and after treatment. The studies on normal subjects and patients with hypoparathyroidism[9] and vitamin D resistant rickets,[11] formed part of an investigation of the physiological and pharmacological effects of these compounds. In chronic renal failure the reversal of the biochemical changes was studied in those patients in whom hypercalcaemia had been induced accidentally during long-term use of these agents. In patients on maintenance haemodialysis blood samples were always taken immediately before dialysis. The osteoporotic patients treated with calciferol were referred for investigation from elsewhere because of toxic symptoms.

Plasma and urinary calcium were measured by atomic absorption spectrophotometry. The significance of differences between means was calculated by Student's *t* test for unpaired data. Half times of disappearance were judged by eye rather than by linear regression to give higher values on the exponential scale more significance than lower values.

Results

After the subjects had stopped taking vitamin D or its derivatives the rate of decrease in the plasma concentration and urinary excretion rate of calcium was monoexponential (figs 1 and 2). The calculated half times of decrease (see table; figs 1-3) after stopping 1-α, 25-$(OH)_2D_3$ were shorter than after stopping 1-α-OHD_3 (mean (±SE of mean) 1·5±0·2 days *v* 3·4±0·4 days; $P<0.001$). The longest half times were seen after calciferol (mean±SE of mean, 29·5±9·1 days; $P<0.001$) or dihydrotachysterol (44 days).

The half time did not depend on the daily dose given (see table). For example, the rates of reversal were similar in case 11 (fig 1) after the patient became hypercalcaemic to a similar degree on two different doses of 1-α-OHD_3. Although patients who had received calciferol had usually been treated for longer than those on 1-α-OHD_3 or 1-α, 25-$(OH)_2D_3$, the time courses of reversal seemed independent of

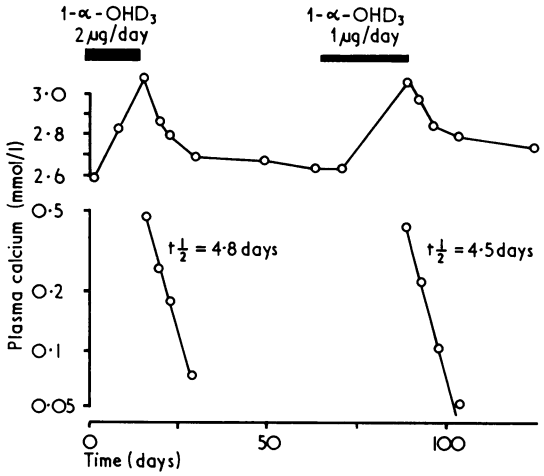

FIG 1—Case 11. (*a*) Responses of plasma calcium in an anaephric patient on haemodialysis to treatment with 1-α-OHD_3 (2 μg/day for 6 months). Hypercalcaemia diminished when treatment stopped but rapidly recurred during retreatment with smaller dose. Lower scale shows monoexponential rate of fall of plasma calcium when expressed on logarithmic scale. Half times of fall were similar on both occasions.

Conversion: SI to traditional units—Plasma calcium: 1 mmol/l≈4 mg/100 ml.

Details of patients studied

Case No	Daily dose (μg)	Duration of treatment (weeks)	Calcium value at end of treatment: Urine (mmol/24 h)	Calcium value at end of treatment: Plasma (mmol/l)	Half time for decrease of calcium (days): Urine	Half time for decrease of calcium (days): Plasma	Diagnosis
				1-α, 25-$(OH)_2D_3$			
1	0·5	1	1·18		2·0		CRF
2	2	12		3·91		0·8	CRF (D)
3	2	2	4·08		1·7		VDRR*
4	2	1	5·28		2·5		VDRR*
5	2	1	2·75		1·0		VDRR*
6	0·7	1	10·00		1·3		HP
7	1	1	7·85		2·0		Healthy
8	2	1	13·00		1·0		Healthy
9	2	1	13·49		0·8		Healthy
				1-α-OHD_3			
10	1	20		3·08		3·6	CRF (D)
10	2	50		4·13		3·0	CRF (D)
11	2	24		3·08		4·8	CRF (D+N)
11	1	4		3·10		4·5	CRF (D+N)
3	2	1	4·40		4·5		VDRR
6	1·4	1		2·95		4·2	HP
12	1·4	2		2·13		2·9	HP
13	1·4	2	0·95		2·4		HP
7	3	1	6·60		1·8		Healthy
8	3	1	7·63		1·9		Healthy
				Calciferol			
1	540	170		3·28		16·5	CRF
14	2700	28		3·40		17·4	CRF
2	5400	4		3·85		9·6	CRF (D)
2	2700	6		3·03		10·0	CRF (D)
15	4050	12		3·30		8·5	CRF (D)
16	4050	76		3·38		30	CRF+HP (D)
17	2700	61		3·10		84	CRF+HP (D)
17	700	17		3·15		81	CRF+HP (D)
18	1350	28		2·53		25	OP
19	2700	46		4·45		13	OP
				Dihydrotachysterol			
12	1000	4	5·00	2·53	43	45	HP

*These patients received 1, 25-$(OH)_2D_3$ prepared biologically rather than by chemical synthesis and have been reported elsewhere.[11]
CRF = Chronic renal failure. D = Maintenance haemodialysis. N = Bilateral nephrectomy. VDRR = Hypophosphataemic (type 1) vitamin D resistant rickets. HP = Hypoparathyroidism. OP = Osteoporosis.

Conversion: SI to traditional units—Urinary calcium: 1 mmol/24 h≈40 mg/24 h. Plasma calcium: 1 mmol/l≈4 mg/100 ml.

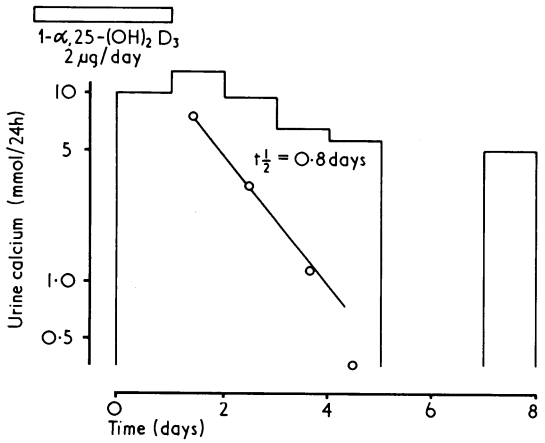

FIG 2—Case 9. Total urinary calcium and its monoexponential fall in normal subject after stopping 1-α, 25-$(OH)_2D_3$.
Conversion: SI to traditional units—Urinary calcium: 1 mmol/24 h ≈ 40 mg/24 h.

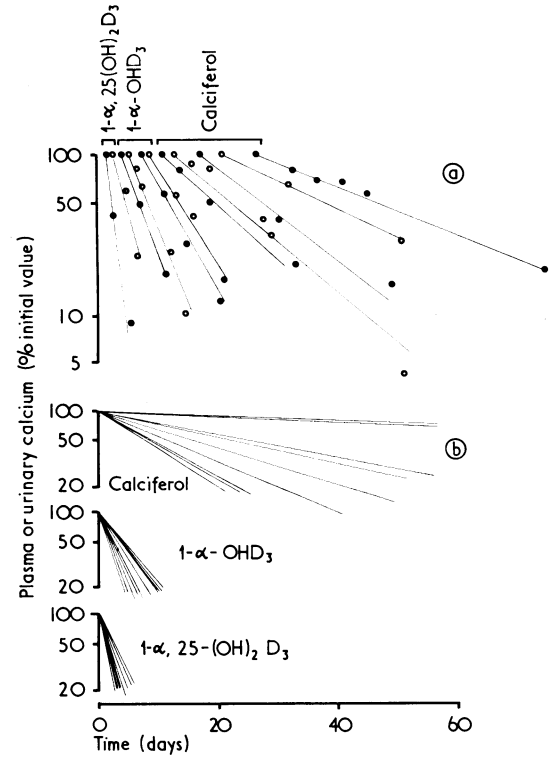

FIG 3—Fall of urine or plasma calcium levels (shown on logarithmic scale and expressed as percentage of initial value given in table) after stopping treatment with vitamin D or its 1-α-hydroxy-derivatives in (*a*) 11 studies on six patients with chronic renal failure and (*b*) all patients. On the upper diagram where data points are given, values from patients are shown alternately by open and closed symbols.

the previous length of treatment or the degree of toxicity induced (compare cases 2, 10, and 17). The rates of reversal after stopping 1-α-OHD_3 or 1-α, 25-$(OH)_2D_3$ were faster in normal subjects (100 ± 16% of mean normal response) than in patients with vitamin D resistant disorders (168 ± 17%; $P < 0.05$).

In one patient (case 19) synthetic salmon calcitonin (10 μg daily) given 29 days after stopping calciferol significantly increased the rate of fall of plasma calcium (fig 4).

Discussion

Apart from the difference in effective dose, there is no evidence that the vitamin D metabolites and analogues produce therapeutic effects in any way different from the parent compound. The 1-α-hydroxylated metabolites are used because in vitamin D-resistant disorders in which 1-α-hydroxylation may be impaired (chronic renal failure, hypoparathyroidism, and vitamin D dependent rickets), it may be easier to achieve a therapeutic effect than with calciferol. Also the effective dose of the 1-α-hydroxylated derivatives, perhaps unlike calciferol, may not differ widely from patient to patient, and individual requirements may also change less abruptly.[12] Finally, hypercalcaemia induced by these metabolites may be more readily reversed when treatment is stopped.

Though some of these potential advantages remain to be proved, our results suggest that the toxic effects of vitamin D-like compounds may indeed be more readily reversed when the metabolites are used; and this more rapid reversal may be the major if not the sole advantage of these metabolites over vitamin D itself. Our results also illustrate the frequency with which hypercalcaemia occurred during long-term treatment with the 1-α-hydroxylated derivatives in chronic renal failure. Though seemingly unpredictable, this hypercalcaemia often occurred after several months of treatment for bone disease at which time bone turnover had been reduced (unpublished observations).

The rate of fall of plasma calcium after poisoning with vitamin D or its derivatives must be due to the reduction of vitamin D-like activity on the chief target organs, including the gut, kidney, and bone, which may each have a different relative importance in different diseases. The response may also depend on factors such as the length of treatment and the storage[13,14] and metabolism of the agent given. For example, the loss of the ability to eliminate calcium through the kidneys in chronic renal failure may account for the slower return of plasma calcium than in normal subjects. In hypoparathyroidism the rate of return may depend more on the duration of the intestinal response.[9] Under other conditions increased bone resorption may also contribute to sustained hypercalcaemia since it can be reversed rapidly with calcitonin (fig 4).

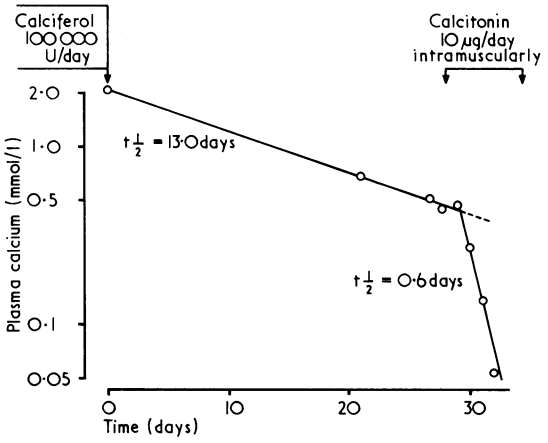

FIG 4—Case 19. Change in plasma calcium (observed—asymptotic value) after stopping treatment with calciferol. Rate of fall, shown on logarithmic scale, was increased twentyfold by treatment with synthetic salmon calcitonin.

When hypercalcaemia induced by 1-α-OHD_3 has diminished, retreatment with a lower dose may be associated with an immediate recurrence (fig 1). This phenomenon has also been described during treatment with calciferol,[15] but no comparable data are yet available for 1-α-25$(OH)_2D_3$. Intestinal absorption of calcium in chronic renal failure, which increases during the early phases of treatment with 1-α-hydroxylated derivatives, may, however, increase still further during longer term administration of 1-α-OHD_3 but not with 1-α, 25-$(OH)_2D_3$.[7] This

suggests, as do our data, that responses to 1-α-OHD_3 and 1-α, 25-$(OH)_2D_3$ are different enough to have important implications in treatment. Although hypercalcaemia remains a serious risk with all vitamin D derivatives the rapid reversal that is possible after 1-α, 25-$(OH)_2D_3$ treatment makes this agent preferable to calciferol and possibly to 1-α-OHD_3. This is particularly so in patients in whom hypercalcaemia is most likely to be troublesome —for example, those with precarious renal function, or those in whom hypercalcaemia has been previously induced.

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We are grateful to Leo Laboratories for supplies of synthetic 1-α-OHD_3; to Roche Products Ltd for synthetic 1-α, 25-$(OH)_2D_3$; and to Professor J A Strong and Drs J G G Ledingham, D O Oliver, and R Smith, who allowed us to study patients under their care.

References

1 DeLuca, H F, *New England Journal of Medicine*, 1973, **288,** 359.
2 Brickman, A S, *et al*, *New England Journal of Medicine*, 1972, **287,** 981.
3 Henderson, R G, *et al*, *Lancet*, 1974, **1,** 379.
4 Catto, G R D, *et al*, *British Medical Journal*, 1975, **1,** 12.
5 Balsan, S, *et al*, *Paediatric Research*, 1975, **9,** 586.
6 Pierides, A M, *et al*, *Lancet*, 1976, **1,** 1092.
7 Brickman, A S, *et al*, *Journal of Clinical Investigation*, in press.
8 Kooh, S W, *et al*, *New England Journal of Medicine*, 1975, **293,** 840.
9 Russell, R G G, *et al*, *Lancet*, 1974, **2,** 14.
10 Fraser, D, *et al*, *New England Journal of Medicine*, 1973, **289,** 359.
11 Russell, R G G, *et al*, *Clinical Science and Molecular Medicine*, 1975, **48,** 177.
12 Avioli, L V, *American Journal of Medicine*, 1974, **57,** 34.
13 Stanbury, S W, *American Journal of Medicine*, 1968, **44,** 712.
14 Stanbury, S W, *Archives of Internal Medicine*, 1969, **124,** 674.
15 Leeson, P M, and Fourman, P, *Lancet*, 1966, **1,** 1182.

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SHORT REPORTS

Colour vision in vitamin A deficiency

Colour blindness is known to occur as a sex-linked genetic trait. A relatively high incidence of colour vision defects has been reported in patients with cirrhosis of liver.[1–3] Cruz-Coke postulated a common genetic basis for defective colour vision and cirrhosis,[1] while other workers have suggested that defective colour vision may be secondary to liver disease.[2] Bronte-Steward and Foulds observed that in patients with biliary cirrhosis who had impaired dark adaptation and defective colour vision vitamin A treatment produced a significant improvement.[3] It was suggested that these defects may be due to associated vitamin A deficiency. Vitamin A deficiency affects rod function with loss of dark adaptation, but little is known about the effect of hypovitaminosis A on cone function. We therefore investigated this point.

Patients, methods and results

Twenty-eight children, aged 4 to 12 years, with clinical signs of vitamin A deficiency were investigated. They showed conjunctival xerosis or Bitot spots, or both. Eighteen also had night blindness. The American Optical Hardy-Rand-Rittler (HRR) pseudoisochromatic plates were used to detect colour vision defects. Venous blood samples were obtained and serum vitamin A was estimated by a trifluouracetic acid method.[4] The children were treated with vitamin A 24 000 IU/day for 15 days.

Colour vision was normal in all the children. Serum vitamin A levels ranged from 0·14 to 0·70 μmol/l (4-20 μg/100 ml). Sixteen of the 28 children had vitamin A values below 0·35 μmol/l (10 μg/100 ml). Two weeks after treatment with vitamin A night blindness and conjunctival xerosis disappeared in all the children, but the Bitot spots persisted in some.

Comment

Vitamin A deficiency is a major nutritional problem among children in many developing countries. The classical manifestations of vitamin A deficiency are night blindness, conjunctival xerosis, and Bitot spots. Severe deficiency of vitamin A, resulting in keratomalacia and total blindness, is seen mostly in preschool children.

It is generally agreed that serum vitamin A levels under 0·70 μmol/l (20 μg/100 ml) indicate vitamin A deficiency. In our study only those children who had serum vitamin A concentrations below 0·70 μmol/l were tested and colour vision was found to be normal in all. Many had night blindness. These results indicate that vitamin A deficiency affects the rod function but not the cone function. Since vitamin A is required for regeneration of the visual pigments of both rods and cones in the retina, it has been postulated that hypovitaminosis A may lead to impaired dark adaptation as well as defective colour vision. Cone pigments, however, synthesise much more rapidly than rhodopsin,[5] so rod function is the first to be affected in vitamin A deficiency. Possibly cone function may also be affected in severe deficiency, but then it may be difficult to evaluate colour discrimination because of more serious corneal involvement.

Our findings disagree with those of Bronte-Stewart and Foulds.[3] They studied two patients with biliary cirrhosis who showed a significant improvement in colour vision six weeks after treatment with vitamin A. It is possible that hepatic function might also have improved by the time their patients were retested. Other workers have observed that in patients with cirrhosis of the liver the defects in colour vision disappeared after the patients recovered from their decompensated cirrhosis.[2] Our results show clearly that vitamin A deficiency per se does not affect colour vision. It may be argued that our method of testing colour vision is not sensitive enough to detect minimal changes. But such changes, even if they occur, may not have much practical importance.

1 Cruz-Coke, R, *Lancet*, 1965, **1,** 1131.
2 Fialkow, P J, Thuline, H C, and Fenster, L F, *New England Journal of Medicine*, 1966, **275,** 584.
3 Bronte-Stewart, J, and Foulds, W S, *Modern Problems in Ophthalmology*, 1975, **10,** 133.
4 Roels, O A, and Trout, M, *Standard methods of clinical chemistry*, 1972, **7,** 215.
5 Wald, G, Brown, P K, and Smith, P H, *Journal of General Physiology*, 1954, **38,** 623.

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Salty sweat and ichthyosis in Addison's disease

The clinical manifestations of primary chronic adrenocortical insufficiency are well known.[1–3] Recently we saw a patient with Addison's disease who had two unusual features—namely, "salty sweat" and ichthyosis. To our knowledge these features have not been reported before.

Case report

A 54-year-old Indian stevedore was admitted to hospital in August 1975 for investigation of suspected Addison's disease. He had noticed increasing darkening of his skin during the past year associated with asthenia and weight loss. He also said that his sweat tasted excessively salty, and he had noticed this at work when sweat dripped down his face. When it dried he sometimes found fine, white particles on his body that tasted like salt. He had also observed that the skin over his legs was dry. He had no salt craving or gastrointestinal symptoms, and there was no history of tuberculosis. His skin was hyperpigmented, particularly over the exposed areas, flexures, and palmar creases. There were irregular areas of hypermelanosis on the tongue gums, and buccal mucosae. Even the nails were black. The skin over his shins was ichthyotic. The blood pressure was 85/55 mm Hg. Nothing further was found on examination.