and Bianco, 1948), and by a raised fraction of Hb A_2 or Hb F or both (Silvestroni *et al.*, 1957). None of these alone is diagnostic for ß-thalassaemia trait, so for effective screening a combination of two or more methods would be necessary (Weatherall, 1965).

A practicable approach would be to test an accessible unmarried cohort of those people with one or both parents born in Cyprus—for instance, school-leavers—initially by a method which errs in picking up other conditions besides ß-thalassaemia trait—for example, indices or fragility. Positive cases could then be examined for raised Hb A_2.

ß-Thalassaemia trait is often an incidental finding in patients examined for other reasons. Because of the high genetic risk that it carries such a finding should always be followed up by haematological investigations of the rest of the family. If the patient is an adult married to another Cypriot the chances are 1 in 7 that the spouse will also be a heterozygote; if the patient is a child the chances are 1 in 7 that both parents will carry the thalassaemia trait. This should be investigated and such couples should be informed of the risk to any further children. Where only one parent carries thalassaemia trait half the offspring will be carriers: these should be detected and the parents clearly informed that their heterozygous offspring have a 1 in 7 chance of marrying another heterozygote if they chose a partner at random from the Cypriot community, but that such risks can be averted by using information derived from blood tests. ß-Thalassaemia trait is most commonly detected in pregnant women, and this presents particular problems. The husband's blood should always be tested. If he also carries ß-thalassaemia trait the infant should be followed up at six months for thalassaemia major or ß-thalassaemia trait. Only then should couples of heterozygotes detected at this time be informed of the 1 in 4 risk of subsequent children having thalassaemia major.

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PRELIMINARY COMMUNICATIONS

Latent Osteomalacia in Epileptic Patients on Anticonvulsants

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Summary

The bone mineral content was measured in 10 epileptic patients on long-term treatment with phenytoin before and during treatment with vitamin D. None of the patients showed biochemical signs of osteomalacia. Initially subnormal values for bone mineral content were found, which increased significantly during treatment. The results suggest the occurrence of latent osteomalacia in a fairly high proportion of epileptic patients on anticonvulsants.

Introduction

Osteomalacia with hypocalcaemia and raised serum alkaline phosphatase levels is found in a high proportion of epileptic patients on long-term treatment with anticonvulsant drugs (Kruse, 1968; Dent *et al.*, 1970; Richens and Rowe, 1970; Hunter *et al.*, 1971). The underlying mechanism seems to be a drug-induced increased breakdown of vitamin D in the liver. With a normal dietary intake of vitamin D this might lead to a relative deficiency of vitamin D (DeLuca, 1969; Kuntzman, 1969; Hahn *et al.*, 1971; Hunter *et al.*, 1971).

These findings raise the question of the incidence of latent osteomalacia in these patients and the best way of diagnosing it. Using a sensitive method, therefore, we have studied the bone mineral content in treated epileptics *without* biochemical signs of osteomalacia. The bone mineral content was measured before and during treatment with vitamin D.

Patients and Methods

Five women and five men aged 21 to 57 years (mean 38 years) consented to the study. They were all fully able to work and attended the epilepsy clinic at Glostrup Hospital at regular intervals. Long-term treatment with phenytoin had been instituted $1\frac{1}{2}$ to 14 years (mean 6·2 years) previously. During this investigation the mean dose was 5·7 mg (range 5·0 to 6·1 mg) per kg body weight, and on this regimen the serum levels (Larsen, 1971) averaged 9·6 mg (range 5 to 17 mg) per litre. None of the patients had hypocalcaemia or raised serum alkaline phosphatase levels.

The bone mineral content was determined by direct photon absorptiometry on both forearms. Cameron *et al.* (1968) showed a direct relation between the absorption of photons from ^{125}I and the bone mineral content. In our modified version of the method (Christiansen and Rødbro, 1972; Jensen *et al.*, 1972) the bone mineral content is expressed in arbitrary units as a mean value of six scans from each forearm. The standard

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deviation of duplicate measurements in the same patient on different days was 3·2%. Initially two measurements of bone mineral content were done. The second of these was termed "initial value"—100% at time t_0. This was compared in each case with the values in a group of normal subjects (Christiansen and Rodbro, 1972) matched for age and sex (see Table).

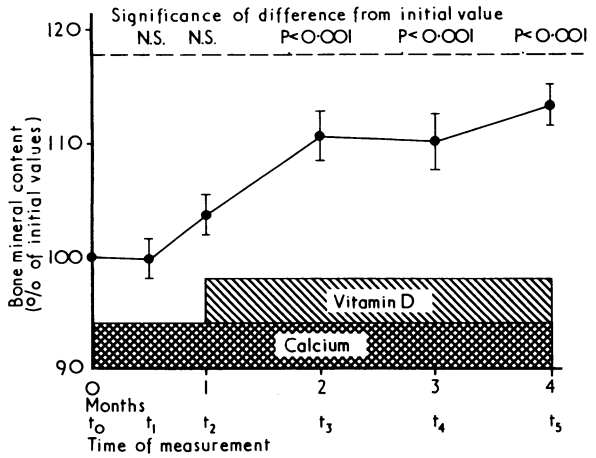
Thereafter the patients were treated with calcium lactate given by mouth (390 mg calcium daily) for one month (see Chart). Bone mineral content was determined 14 days (t_1) and one month (t_2) after calcium treatment was started. The calcium treatment was continued for another three months and supplemented with oral vitamin D (calciferol 2,000 IU daily). Bone mineral content was evaluated one, two, and three months after the treatment with vitamin D had begun (at times t_3, t_4, and t_5; see Chart).

The therapeutic trial was conducted over the months November 1971 to March 1972. Student's t test for pair differences was used for evaluating the effect of treatment.

Bone Mineral Content (B.M.C.) in Arbitrary Units in 10 Patients Before (t_0) and During Treatment with Calcium (t_1 and t_2) and Calcium Plus Vitamin D (t_3, t_4, t_5). Normal Values for Corresponding Sex and Age Group also given

Mean Normal Values for Corresponding Sex and Age Group (±1S.D.)	Patients			Bone Mineral Content Before and During Treatment					
	Case No.	Age (Years)	Sex	t_0	t_1	t_2	t_3	t_4	t_5
24·4 (±1·7)	1	21	F.	18·9*	17·4	17·5	20·3	18·0	20·1
27·2 (±2·8)	2	39	F.	25·6†	24·3	26·9	27·4	25·3	26·9
39·5 (±5·5)	3	23	M.	30·3‡	31·3	29·8	31·6	34·9	34·6
37·1 (±3·2)	4	40	M.	29·0*	30·5	30·7	30·6	33·6	33·5
37·1 (±3·2)	5	40	M.	24·5*	22·8	25·7	27·5	26·6	28·4
36·8 (±3·9)	6	51	M.	33·4†	34·3	33·6	35·8	36·7	37·9
26·7 (±4·2)	7	48	F.	20·9‡	20·2	21·1	23·9	24·3	23·4
21·4 (±4·5)	8	57	F.	18·8†	18·4	20·3	19·8	20·8	20·4
39·5 (±5·5)	9	23	M.	33·2‡	36·4	36·4	39·1	40·2	41·5
27·2 (±2·8)	10	33	F.	19·5*	19·9	21·8	24·7	21·5	23·0

†Relation to normal mean value: $\bar{x}$ > B.M.C./t_0 > ($\bar{x}$ − 1 S.D.).
‡Relation to normal mean value: ($\bar{x}$ − 1 S.D.) > B.M.C./t_0 > ($\bar{x}$ − 2 S.D.).
*Relation to normal mean value: ($\bar{x}$ − 2 S.D.) > B.M.C./t_0.



Average bone mineral content (% of initial value) as a function of time during treatment with calcium and calcium plus vitamin D (2,000 IU daily) in 10 epileptic patients treated with phenytopin. Each point on chart represents mean ±1 S.E. of mean.

Results

The individual bone mineral content values are given in the Table. None of the 10 initial values were higher than the corresponding normal mean value, and four of the 10 were *below* the normal range (mean ±2 S.D.). There was a slight, insignificant rise in the mean bone mineral value on calcium treatment. During treatment with vitamin D the mean bone mineral value rose significantly (see Chart).

Discussion

In larger studies of patients on long-term treatment with anticonvulsants the proportion of patients showing hypocalcaemia and raised serum alkaline phosphatase levels ranged from 15 to 30% (Kruse, 1968; Richens and Rowe, 1970; Hunter *et al.*, 1971). Continuous anticonvulsant therapy apparently increases the daily vitamin D requirement owing to an increased breakdown of the vitamin (Dent *et al.*, 1970; Richens and Rowe, 1970; Hahn *et al.*, 1971). Other workers showed that the mean bone mineral content in epileptic patients on long-term anticonvulsant therapy with a wide variety of drugs was significantly lower than that of a control group (Linde *et al.*, 1971).

Although our patients did not have biochemical signs of osteomalacia, they showed lower than normal values of bone mineral content. This fact and the reaction to vitamin D suggest the existence of "latent osteomalacia" in these patients. Osteomalacia probably shows a continuum; in the less severe cases discernible only by a low bone mineral content, and in the more severe cases by the presence of hypocalcaemia and raised serum alkaline phosphatase levels also. Whether the bone mineral content of normal people changes after small doses of vitamin D as used here is not known, though it is improbable, and this is under study in our departments.

The present findings indicate that latent osteomalacia may exist in a fairly high proportion of epileptic patients on anticonvulsants. They warrant further investigations into the possible implications for the treatment of epileptic patients with anticonvulsant drugs.

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