

HYPOCALCAEMIA AND SECONDARY HYPERPARATHYROIDISM IN INSTITUTIONALISED MENTALLY-RETARDED PATIENTS RECEIVING ANTICONVULSANT DRUGS: A SURVEY OF 292 PATIENTS

by

**ELIZABETH MACLAY, D. R. HADDEN, E. M. McILRATH
AND G. S. NESBITT**

Muckamore Abbey Hospital, Co. Antrim
and the Royal Victoria Hospital, Belfast

ATTENTION has been drawn to the possible adverse effects of anticonvulsant drugs on bone metabolism by a number of reports in recent years (Dent *et al*, 1970; Richens and Rowe, 1970; Hunter *et al*, 1971; Lifshitz and Maclaren, 1973; Stamp, 1974; British Medical Journal, 1976). The aim of the present study was to investigate this potentially serious side-effect of anticonvulsant therapy in the setting of Muckamore Abbey, a mental subnormality hospital in Northern Ireland.

POPULATION ON ANTICONVULSANT THERAPY

The hospital population consists of 850 patients of all grades of subnormality and of all ages, many of whom have been institutionalised for prolonged periods. They are housed in 20 villas according to age, sex, severity of retardation and presence of physical handicaps. An initial survey of the whole hospital revealed 316 patients on long-term (six months or more) anticonvulsant therapy. The present study comprised 292 (92 per cent) of these patients from whom it was possible to obtain a blood specimen. This was a therapeutic investigation of patients receiving usual hospital therapy who might be at risk from a recognised side-effects of the drug (Hahn, Hendin *et al*, 1972). Nevertheless, there were some patients among the total of 316 who refused to have the venepuncture and these were not assessed further.

There were 149 males and 143 females ranging in age from 3 to 81 years. The group included mentally subnormal patients suffering from a variety of associated and coincidental physical conditions, but excluding known disorders affecting bone metabolism. Nine patients were not suffering from any physical handicap. As would be expected with a group of patients receiving anticonvulsants, the majority were epileptic; 18 (6 per cent) were being treated with drugs such as sulthiame (Ospolot) and carbamazepine (Tegretol) to control behavioural problems. Over half had had at least one fit during the preceding year. Two hundred and twenty-six (77 per cent) had been on continuous anticonvulsant therapy for over five years and took a wide range of other drugs. All were Caucasian and domiciled in Northern Ireland. They were being offered an adequate diet but were not routinely given vitamin supplements. The amount of exposure to direct sunlight was dependent on the patient's degree of mobility. The majority were ambulant and able to get outside in fine weather, but a few of the most severely handicapped were confined to their villas.

Initial survey

Between October 1976 and January 1977, venous blood samples were obtained from the 292 patients, venous compression being used if necessary. The concentrations of calcium, phosphate and alkaline phosphatase in the serum were determined as follows: calcium and phosphate were measured on the Gilford 3500 analyser, using the methyl-thymol-blue method for calcium, and molybdate with reducing reagents for phosphate; alkaline phosphatase was measured in the Vickers D300 apparatus, with phenolphthalein monophosphate. The "usual hospital range" in a general hospital population using these techniques is: calcium 2.20 to 2.65 mmol/l; phosphate 0.8 to 1.5 mmol/l; and alkaline phosphatase 21 to 91 U/l (Belfast City Hospital Clinical Chemistry Department). The serum alkaline phosphatase level is more age-dependent than either the calcium or phosphate. The upper limit of normal values in health can extend to 200 U/l in childhood, whereas it should not exceed 91 U/l in adults. As the age distribution of the present study is wide, the data is presented as a frequency distribution for the actual population rather than applying correction factors for age or other possible variables. The laboratory upper limit for a usual value in health for serum alkaline phosphatase is thus expressed as a range of 91-200 U/l (Fig. 1).

A further blood sample was obtained (second survey) from 105 of the 133 patients in whom results of the first sample were abnormal. The two results for each individual who had a second test were averaged. There were 10 of these patients whose average calcium was less than 2.0 mmol/l. These 10 had further plasma samples analysed for 25-hydroxycholecalciferol and parathormone levels. Plasma 25-hydroxycholecalciferol and parathormone determinations were carried out by the Supraregional Endocrine Assay Service, using standard radioimmunoassay techniques.

Radiographic survey

Fifty-nine of the 113 patients with calcium values of less than 2.2 mmol/l, phosphate less than 0.8 mmol/l or alkaline phosphatase greater than 200 U/l, had radiographs of wrists and forearms. This was standardised as far as possible and most patients were exposed to 45 kv and 80 ma for 0.16 seconds. A few patients had less or more according to their build. Assessment of the radiographs was carried out by one of us (EMMcI) without knowledge of the clinical or biochemical findings. A subjective classification into normal, osteoporotic and osteomalacic was made and the transmitted light value measured.

Pharmacological survey

A "drug score" was calculated for each patient, using the technique of Richens and Rowe (1970). This derives a numerical score for the total daily dose of certain anticonvulsant drugs. A dose of 50 mg phenytoin or 30 mg phenobarbitone scored 1 unit and 250 mg primidone scored 1.5 units. A total daily score for each patient was calculated.

Control studies

Thirty-two patients were examined. These consisted of two or three patients from each ward in the same hospital who had been receiving no drug therapy for at least 3 months. Blood samples were obtained in the same way and serum concentrations of calcium, phosphate and alkaline phosphatase were measured.

RESULTS

Initial survey

The distribution of serum calcium, phosphate and alkaline phosphatase in the 292 patients is shown in Figs. 1, 2 and 3. The mean serum calcium was 2.26 (standard deviation 0.09) mmol/l, mean serum phosphate 1.09 (S.D. 0.31) mmol/l and the mean serum alkaline phosphatase 91.8 (S.D. 61.0 U/l). By comparison with the usual hospital range it is clear that there is a shift to the left of the serum calcium values for the patients taking anticonvulsant drugs; 60 (21 per cent) were below 2.20 mmol/l and none were above the upper limit. For serum phosphate 17 (6 per cent) were below 0.8 mmol/l and for alkaline phosphatase 14 (5 per cent) were above 200 U/l.

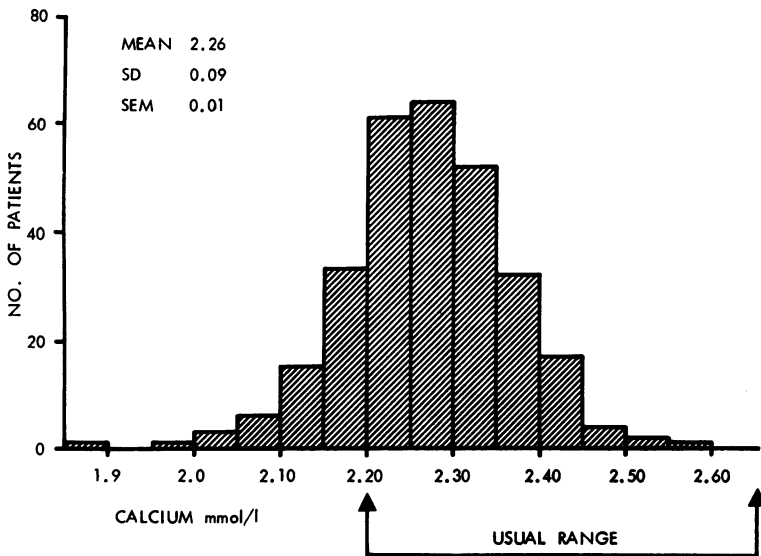


FIG. 1: Frequency distributions of serum calcium (mmol/l) in the 292 patients receiving long-term anticonvulsant therapy (initial survey).

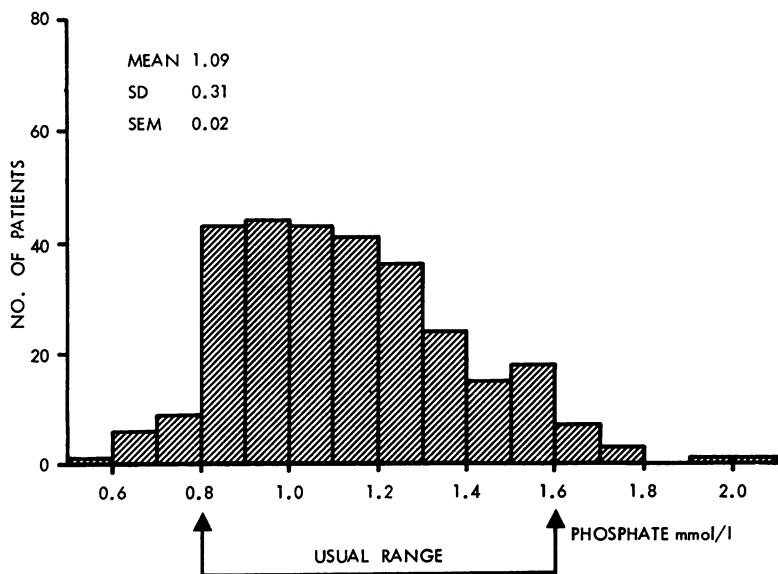


FIG. 2: Frequency distributions of serum phosphate (mmol/l) in the 292 patients receiving long-term anticonvulsant therapy (initial survey).

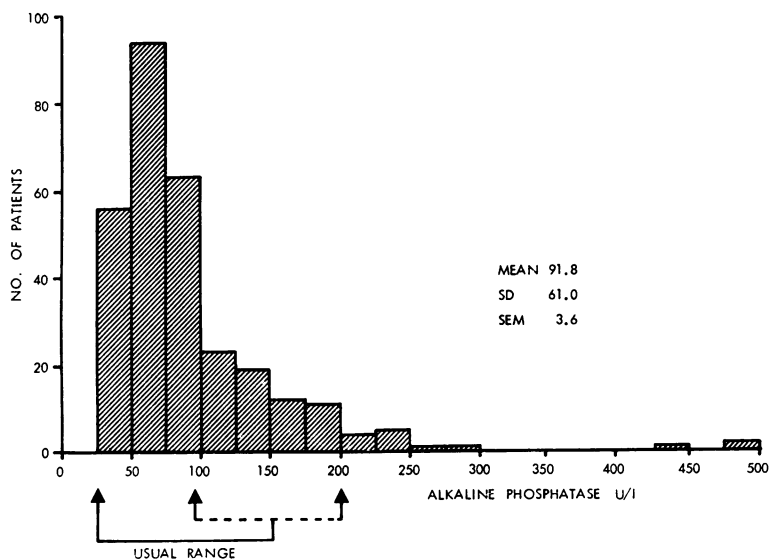


FIG. 3: Frequency distributions of alkaline phosphatase (U/l) in the 292 patients receiving long-term anticonvulsant therapy (initial survey).

The 32 control patients all had serum calcium within the quoted “usual hospital range” of 2.20 to 2.65 mmol/l; four control patients had a serum phosphate below and two above the usual hospital range of 0.8 to 1.6 mmol/l; none had an alkaline phosphatase above 200 U/l.

The relationship between serum calcium and phosphate in the 292 patients is shown in Fig. 4 ($r=0.10$). Six patients (2 per cent) had low values of both calcium and phosphate, but none of these had an alkaline phosphatase above 90 U/l.

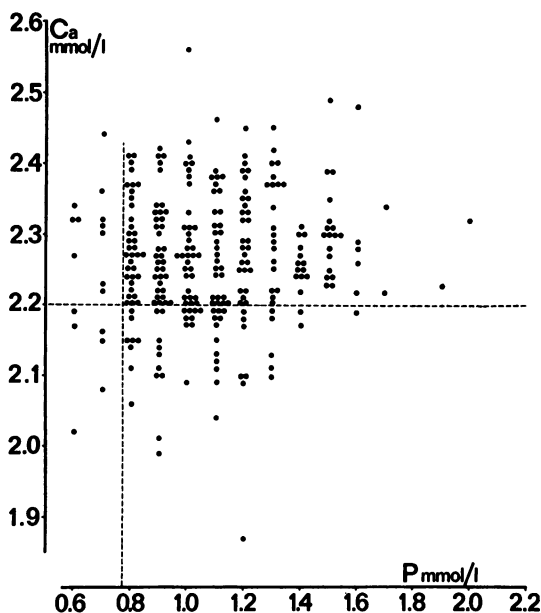


FIG. 4: The relation between serum calcium and phosphate in the 292 patients receiving long-term anticonvulsant therapy ($r=0.1$). Six patients had values for both calcium and phosphate below the usual hospital ranges (dotted lines).

Radiographic survey

Thirty-six of the radiographs were subjectively assessed as normal, fifteen as osteoporotic and eight as osteomalacic. Table 1 shows the biochemical and transmitted light values in these three groups. There was a tendency for those judged osteoporotic to be older and those judged osteomalacic to be younger than the usual group. The mean transmitted light value was lowest for the osteoporotic group and intermediate for the osteomalacic group, confirming the subjective diagnosis. There was no difference in the mean blood calcium values. The blood phosphate was lowest in the osteoporotic group and the alkaline phosphatase highest in the osteomalacic group (although these were considerably younger).

TABLE 1: RADIOLOGICAL SURVEY—59 PATIENTS
(Values are means \pm standard errors of the mean)

Subjective Radiological Diagnosis	No.	Mean Age	Transmitted Light Value (arbitrary units)	Calcium mmol/l	Phosphate mmol/l	Alkaline Phosphatase U/l
Normal	36	29	6.70 ± 0.14	2.19 ± 0.02	1.04 ± 0.05	99 ± 11
Osteoporosis	15	51	5.80 ± 0.18	2.14 ± 0.03	0.87 ± 0.05	93 ± 10
Osteomalacia	8	16	6.20 ± 0.40	2.14 ± 0.05	1.19 ± 0.10	315 ± 45

Pharmacological survey

The drug score (for the day on which the blood sample was obtained) for the 292 patients in the initial survey is shown in relation to the serum calcium in Fig. 5. The correlation coefficient r was -0.25 , and there was a general trend for those patients with the lowest calcium values to have a higher drug score.

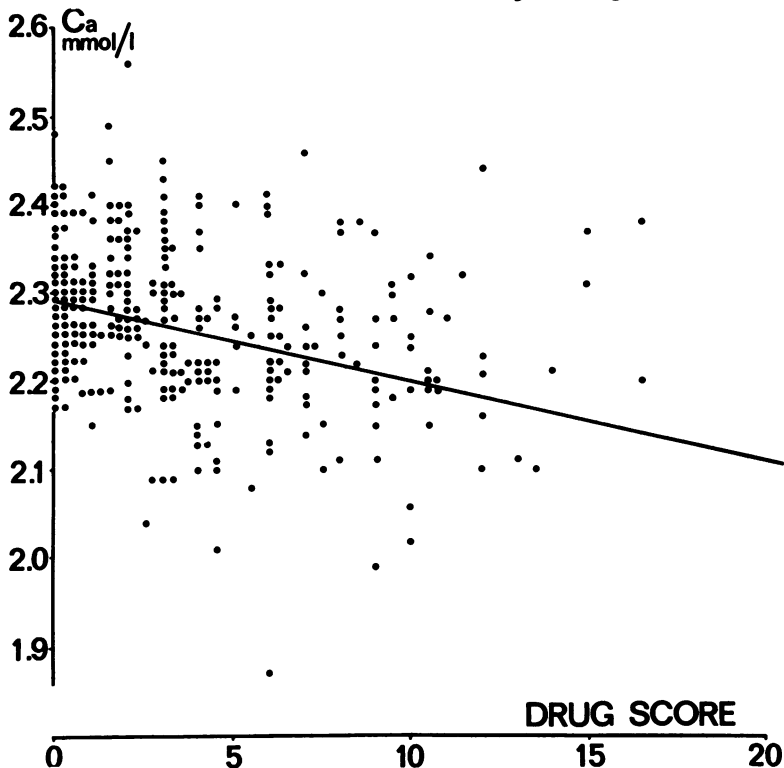


FIG. 5: The anticonvulsant drug score (see text) related to the serum calcium value on the same day in the 292 patients receiving long-term anticonvulsant therapy ($r = -0.25$).

Table 2 shows the frequency of hypocalcaemia in patients receiving the three most commonly administered anticonvulsant drugs (phenobarbitone, phenytoin or primidone). The greatest incidence of hypocalcaemia was found in patients taking primidone with or without other drugs (Table 2). However, most of the patients were on more than one of these drugs, so these data do not necessarily allow individual comparison of the effect of one or other drug alone. When two or three of these drugs were taken in combination, 82 patients (32 per cent) had a low serum calcium; when only one drug was taken, 142 patients (21 per cent) had a low serum calcium. For the 68 patients who received none of these three drugs, only four (6 per cent) had a low serum calcium.

TABLE 2: RELATION BETWEEN SERUM CALCIUM AND INDIVIDUAL ANTICONVULSANT DRUGS
(Many patients were receiving more than one drug concurrently)

Drug	Patients	Patients with serum calcium <2.20mmol/l	Mean serum calcium mmol/l	Mean daily dose mg
Phenobarbitone	141	31 (22%)	2.29	95
Phenytoin	120	36 (30%)	2.25	205
Primidone	60	22 (37%)	2.23	640

Parathormone and 25-Hydroxycholecalciferol data

Data for a third blood sample on ten patients found after the second survey with mean serum calcium below 2.0mmol/l are shown in Table 3. The serum calcium was still below 2.1mmol/l in all of the patients. Serum parathormone values were elevated above the upper limit or normal (0.73microg/l) in 3 and serum 25-hydroxycholecalciferol values were well below the normal range (3.5 to 30microg/l) in all of these patients.

TABLE 3: SERUM VALUES FOR A THIRD BLOOD SPECIMEN IN SEVERELY HYPOCALCAEMIC PATIENTS

Patient	Age	Sex	Calcium mmol/l	Phosphate mmol/l	Alkaline Phosphatase U/l	25-Hydroxy Cholecalciferol microg/l	Parathormone microg/l	Drug Score
AS	14	F	2.09	1.20	187	1.1	0.35	3.0
JMcC	14	F	2.01	0.90	480	1.9	1.20	4.5
BMcG	15	F	2.06	0.80	430	0.8	1.20	10.0
BM	16	M	2.09	1.10	476	0.8	0.66	3.0
MM	19	F	2.04	1.10	289	1.4	0.96	2.3
JF	30	M	2.09	1.00	39	2.6	0.20	3.0
EMcC	36	F	1.97	1.20	104	0.8	0.44	6.0
WMcC	46	M	1.99	0.90	87	0.8	0.34	9.0
TH	46	F	2.08	0.70	90	0.8	0.29	5.5
CG	81	F	2.02	0.60	90	0.8	0.44	6.6
Mean	32		2.03	0.95	176	1.2	0.62	6.3
SEM	±8		±0.07	±0.07	±56	±0.2	±0.12	±0.8

DISCUSSION

Mechanism by which anticonvulsant drugs alter calcium metabolism

During chronic therapy with certain drugs a gradual decline in the plasma level of the drug may be observed. This results from the ability of some compounds to stimulate their own metabolism by inducing an increased production of liver microsomal enzymes. There are various enzyme systems in the liver and some have an effect, not only on the drugs which induce them, but also on normal body constituents such as the steroid hormones (Kuntzman, 1969). Cholecalciferol (Vitamin D₃) is chemically similar in structure to certain steroids and there is strong evidence that the increased incidence of osteomalacia observed in patients on anticonvulsant therapy may be the result of an accelerated conversion of cholecalciferol and its active metabolite 25-hydroxycholecalciferol to inactive metabolites by drug-induced liver microsomal enzymes (Hahn, Birge *et al*, 1972).

Significance of biochemical findings

The findings in this study are consistent with those of other studies as regards the prevalence of low serum calcium and raised alkaline phosphatase. Richens and Rowe (1970) studied 160 patients aged 16-70 years in an epileptic centre and found a subnormal calcium in 22.5 per cent and raised alkaline phosphatase activity in 29 per cent. Hunter *et al* (1971) studied 105 children in a residential school and found low calcium in 30 per cent and raised alkaline phosphatase activity in 24 per cent. The other authors did not examine serum phosphate (and this was below 0.8mmol/l in only 6 per cent of patients in the present study).

Albright and Reifstein (1948) graded osteomalacia into four stages. Thus, about 20 per cent of the Muckamore Abbey population on anticonvulsant drugs could be said to have at least biochemical rickets (Stage I, with persistently low calcium and/or phosphate and normal alkaline phosphatase and Stage II, with elevated alkaline phosphatase). Of these, eight patients (1.6 per cent) had unequivocal radiological changes (Stage III). There were no patients with the overt full clinical syndrome (Stage IV, with myopathy, painful bones and skeletal deformities).

Hypocalcaemia, if not compensated by secondary hyperparathyroidism, may lead to tetany, which can progress to convulsions and eventually to intellectual deterioration and dementia. These features in a mentally subnormal epileptic population might not arouse clinical interest and could be overlooked. This would be the more so because mentally subnormal (or mentally ill) patients may not complain of early symptoms. Vague bone pains, one of the most characteristic features of osteomalacia, might easily be labelled "neurotic" and obscure the correct diagnosis. Stamp (1974) has reported cases in which a vicious circle was set up, epilepsy treated with anticonvulsants producing hypocalcaemia, leading to an increased frequency of fits, leading to an increase in anticonvulsant therapy, in turn aggravating the hypocalcaemia. Secondary hyperparathyroidism in response to chronic hypocalcaemia would be expected to protect these patients from tetany at the expense of further skeletal decalcification.

The fact that hypocalcaemia in patients on anticonvulsant therapy is associated with low serum 25-hydroxycholecalciferol is now well established (Hahn, Hendin *et al*, 1972; Stamp *et al*, 1972). This is supported by the consistently low levels found in the ten hypoglycaemic patients in this study. The response of the parathyroid glands to drug-induced osteomalacia has also been the subject of investigation (Greenlaw *et al*, 1972) and the raised parathormone level in three of the ten hypocalcaemic patients shows that secondary hyperparathyroidism has occurred; why this is not so in all the cases is not clear.

Radiological assessment

The radiographic survey did not suggest that the techniques for identifying demineralisation were sensitive enough to be used for routine screening of patients at possible risk, although it was helpful in diagnosis when the biochemical results were suggestive. Whether long-term radiological follow-up of those patients with decalcified bones would be justified is also doubtful, and it is probable that simple biochemical measurements will be sufficient for this purpose. All methods of measurement of bone density by X-rays other than by microradiography or computerised axial tomography (E.M.I. scans) are suspect. Even sophisticated methods involving cortico/medullary ratios, or water-bath radiography using aluminium or calcium hydroxyapatite step wedges have been shown to be erroneous. It is also relevant that osteoporosis and osteomalacia can affect the axial skeleton markedly with little subjective or objective change in the peripheral bones and therefore the hand and wrist is not an ideal area to study.

The prevalence of biochemical and radiographic osteomalacia in this mentally-retarded institutionalised population of all ages points to the need for administration of Vitamin D supplements (Hunter *et al*, 1971; Hahn, Hendin *et al*, 1972; Maclaren and Lifshitz, 1973). There is still uncertainty as to the correct therapeutic dose of Vitamin D (or one of its more active metabolites) in this situation, for there is evidence of considerable resistance to the usual preparation of cholecalciferol (Vitamin D₃) and of rapid biochemical improvement with small doses of 25-hydroxycholecalciferol. As this latter preparation or the close derivative 1-alpha hydroxycholecalciferol is now available for clinical use, it would seem important to study the effect of routine supplementation with a small dose of one of these substances in a population at risk.

SUMMARY

A biochemical and radiographic survey of 292 patients who were receiving long-term anticonvulsant therapy at the Muckamore Abbey Hospital has been carried out. Twenty-one per cent of these patients had biochemical hypocalcaemia. Only six patients had both serum calcium less than 2.20mmol/l and phosphate less than 0.8mmol/l.

Radiographs of the forearms and wrists were less sensitive in demonstrating minor abnormalities. Fifteen were assessed as osteoporotic and eight as osteomalacic. There was a greater prevalence of hypocalcaemia with primidone than with phenytoin or phenobarbitone and combinations of these drugs had an addi-

tive effect. Among the ten most severely hypocalcaemic patients, all had very low values of 25-hydroxycholecalciferol and three had clear evidence of secondary hyperparathyroidism.

This study supports others that there is a definite risk of chronic decalcifying bone disease among institutionalised patients on long-term anticonvulsant therapy. None of these patients showed any overt clinical sign usually associated with chronic bone disease.

ACKNOWLEDGMENTS

E.M. would like to thank Dr. B. Scally, Dr. J. Calvert and Dr. P. Darragh, Consultants at Muckamore Abbey Hospital, for allowing her to investigate patients under their care; Dr. D. T. Glass, who supervised the radiological survey; Dr. G. Welshman and the staff of the Belfast City Hospital Clinical Chemistry Department; and the nurses and radiographers for the parts they played in this study. We are grateful to Mrs. Bridget Briggs and to Mrs. Jean McCrory for typing the manuscript.

Reprint requests to Dr. E. Maclay, Muckamore Abbey Hospital, Muckamore, Co. Antrim.

REFERENCES

- ALBRIGHT, F. and REIFENSTEIN, E. C. (1948). *The Parathyroid Glands and Metabolic Bone Disease*. Baltimore: Williams and Wilkins.
- DENT, C. E., RICHENS, A., ROWE, D. J. F. and STAMP, T. C. B. (1970). Osteomalacia with long-term anticonvulsant therapy in epilepsy. *British Medical Journal*, *4*, 69.
- GREENLAW, R., PRYOR, J., WINNACKER, J., HAHN, T., HADDAD, J. and ANAST, C. (1972). Osteomalacia from anticonvulsant drugs: therapeutic implications. *Clinical Research*, *20*, 56.
- HAHN, T. J., BIRGE, S. J., SCHARP, C. R. and AVIOLI, L. V. (1972). Phenobarbital-induced alterations in vitamin D metabolism. *Journal of Clinical Investigation*, *51*, 741.
- HAHN, T. J., HENDIN, B. A., SCHARP, R. C. and HADDAD, J. G. (1972). Effect of chronic anticonvulsant therapy on serum 25-hydroxycalciferol levels in adults. *New England Medical Journal*, *287*, 900.
- HUNTER, J., MAXWELL, J. D., STEWART, D. A., PARSONS, V. and WILLIAMS, R. (1971). Altered calcium metabolism in epileptic children on anticonvulsants. *British Medical Journal*, *4*, 202.
- KUNTZMAN, R. (1969). Drugs and enzyme induction. *Annual Review of Pharmacology*, *9*, 21. Leading Article: Anticonvulsant osteomalacia (1976). *British Medical Journal*, *4*, 1340.
- LIFSHITZ, F. and MACLAREN, N. K. (1973). Vitamin D-dependent rickets in institutionalised, mentally retarded children receiving long-term anticonvulsant therapy. I. A survey of 288 patients. *Journal of Pediatrics*, *83*, 612.
- MACLAREN, N. K. and LIFSHITZ, F. (1973). Vitamin D-dependency rickets in institutionalised, mentally retarded children on long-term anticonvulsant therapy. II. The response to 25-hydroxycholecalciferol and to vitamin D. *Pediatric Research*, *7*, 914.
- RICHENS, A. and ROWE, D. J. F. (1970). Disturbance of calcium metabolism by anticonvulsant drugs. *British Medical Journal*, *4*, 73.
- STAMP, T. C. B. (1974). Effects of long-term anticonvulsant therapy on calcium and vitamin D metabolism. *Proceedings of the Royal Society of Medicine*, *67*, 2.