Child, C. M. (1915). *Senescence and Rejuvenescence.* Chicago: University Press.
Dawidoff, C. (1924). *C.R. Acad. Sci., Paris*, **179**, 1222.
Frohawk, F. W. (1935). *Entomologist*, **68**, 184.
Fukuda, M. & Sibatani, A. (1953). *Biochem. J., Tokyo*, **40**, 95.
Gardner, T. S. (1948). *J. Tennessee Acad. Sci.* **23**, 291.
Gardner, T. S. (1948). *J. Gerontol.* **3**, 1.
Gardner, T. S. (1948). *J. Gerontol.* **3**, 9.
Haydak, M. H. (1953). *Ann. ent. Soc. Amer.* **46**, 547.
Holeckova, E., Fábry, P. & Poupa, O. (1959). *Physiol. bohemoslov.* **8**, 15.
Hruza, Z. & Fábry, P. (1957). *Gerontologia*, **1**, 279.
Ingle, L., Wood, T. R. & Banta, A. M. (1937). *J. exp. Zool.* **76**, 325.
Jones, D. B. (1951). *J. Nutr.* **44**, 465.
King, J. T., Lee Y. C. P. & Visscher, M. B. (1955). *J. Nutr.* **57**, 111.
King, J. T. & Visscher, M. B. (1950). *Fed. Proc.* **9**, 70.
Köhler, W. (1940). *Biol. Zbl.* **60**, 34.
Kopeć, S. (1924). *Biol. Bull.* **46**, 1.
Lane, P. W. & Dickie, M. M. (1958). *J. Nutr.* **64**, 549.
Lee, Y. C. P., Visscher, M. B. & King, J. T. (1956). *J. Gerontol.* **11**, 364.
McCance, R. A. & Widdowson, E. M. (1955). *Ciba Fdn Colloquia on Ageing*, **1**, 186.
McCay, C. M. & Crowell, M. F. (1934). *Sci. Mon., N.Y.*, **39**, 405.
McCay, C. M., Maynard, L. A., Sperling, G. & Barnes, L. L. (1939). *J. Nutr.* **18**, 1.
McCay, C. M., Maynard, L. A., Sperling, G. & Osgood, H. S. (1941). *J. Nutr.* **21**, 45.
McCay, C. M., Pope, F. & Lunsford, W. (1956). *Bull. N.Y. Acad. Med.* **32**, 91.
McCay, C. M., Sperling, G. & Barnes, L. L. (1943). *Arch. Biochem.* **2**, 469.
Maurizio, A. (1959). *Ciba Fdn. Colloquia on Ageing*, **5**, 231.
Norris, M. J. (1934). *Proc. zool. Soc. Lond.* p. 334.
Osborne, T. B. & Mendel, L. B. (1914). *J. biol. Chem.* **18**, 95.
Pelton, R. B. & Williams, R. J. (1958). *Proc. Soc. exp. Biol., N.Y.*, **99**, 632.
Pflugfelder, O. (1948). *Biol. Zbl.* **67**, 223.
Riesen, W. H., Herbst, E. J., Walliker, C. & Elvehjem, C. A. (1947). *Amer. J. Physiol.* **148**, 614.
Robertson, T. B., Marston, H. K. & Walters J. W. (1934). *Aust. J. exp. Biol. med. Sci.* **12**, 33.
Rockstein, M. (1959). *Ciba Fdn Colloquia on Ageing*, **5**, 247.
Rudzinska, M. A. (1951). *Science*, **113**, 10.
Samuels, L. T. (1946). *Recent Progr. Hormone Res.* **1**, 147.
Saxton, J. A. (1945). *Biol. Symp.* **11**, 177.
Saxton, J. A. & Kimball, G. C. (1941). *Arch. Path. (Lab. Med.)*, **32**, 951.
Sherman, H. C. & Trupp, H. Y. (1949). *Proc. nat. Acad. Sci., Wash.*, **35**, 90.
Silberberg, M. & Silberberg, R. (1951). *Physiol. Rev.* **35**, 347.
Silberberg, M. & Silberberg R. (1954). *Amer. J. Physiol.* **177**, 23.
Silberberg, M. & Silberberg, R. (1957*a*). *Lab. Invest.* **6**, 372.
Silberberg, M. & Silberberg, R. (1957*c*). *J. Gerontol.* **12**, 9.
Silberberg, R. & Silberberg, M. (1955). *Canad. J. Biochem. Physiol.* **33**, 167.
Silberberg, R. & Silberberg, M. (1957*b*). *Yale J. Biol. Med.* **29**, 525.
Silberberg, R., Silberberg, M. & Riley S. (1955). *Amer. J. Physiol.* **181**, 128.
Sinclair, H. M. (1955). *Ciba Fdn Colloquia on Ageing*, **1**, 194.
Sperling, G., Lovelace, F., Barnes, L. L., Smith, C. A. H., Saxton, J. A. & McCay, C. M. (1955). *J. Nutr.* **55**, 399.
Tannenbaum, H. (1947). *Ann. N.Y. Acad. Sci.* **49**, 6,
Templeton, H. A. & Ershoff, B. H. (1949). *Amer. J. Physiol.* **159**, 33.
Thomasson, H. J. (1955). *J. Nutr.* **57**, 17.
Visscher, M. B., King, J. T. & Lee, Y. C. P. (1952). *Amer. J. Physiol.* **170**, 72.
Will, L. C. & McCay, C. M. (1943). *Arch. Biochem.* **2**, 481.

Osteoporosis and calcium deficiency

By B. E. C. Nordin, *University Department of Medicine, Gardiner Institute, Western Infirmary, Glasgow, W.1*

It is generally assumed that there is little or no calcium deficiency in the western world. This assumption rests on two considerations. The first is that the average

calcium intake in all modern societies is substantially above the supposed calcium requirement. The second is that if there were any dietary deficiency of calcium it would produce nutritional osteomalacia, which is in fact virtually non-existent in this country. Both these assumptions are open to question.

Calcium requirement

The calcium requirement of an adult is considered to be the amount which maintains calcium balance; this is certainly the minimum. Mitchell & Curzon (1939) examined 139 balance studies in normal subjects and showed that the mean requirement was about 10 mg/kg body-weight/day. I have arrived at the same mean figure from an analysis of ninety-two balance studies on normal subjects collected from the recent literature (Nordin, 1960*a*). However, this mean figure conceals a wide individual variation since the standard deviation of intake on output is no less than 4 mg/kg. It means that, if the whole population were taking 18 mg/kg/day, 95% would be in balance. If they were all taking 22 mg/kg/day, 99% would be in balance.

The figures for dietary intake of the population in the United Kingdom can be obtained from the National Food Survey, although unfortunately the last edition of it that provides some statistical analysis was published in 1955 (Ministry of Agriculture, Fisheries and Food: National Food Survey Committee, 1955). This survey shows that the mean calcium intake of the population of this country in 1953 was about 1000 mg calcium/day; the coefficient of variation was 27%. If we assume that the mean weight of a member of the population studied was 50 kg then the mean intake was 20 mg/kg/day and the standard deviation was 5·4 mg/kg/day. In other words, 95% of the population were taking more than 9·2 mg/kg/day and 99% were taking more than 3·8 mg/kg/day.

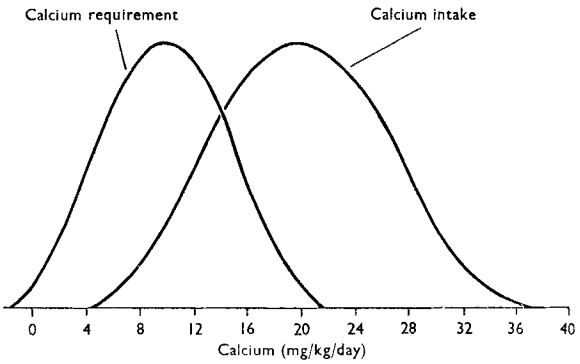

Fig. 1. Distribution of calcium requirement in ninety-two normal subjects and of calcium intake calculated from the National Food Survey for the year 1953 (see this page).

The relationship between requirement and intake is illustrated in Fig. 1, which shows the distribution of requirement and intake calculated from the above figures. It will be seen that the two curves overlap considerably. Although the majority of the population is consuming more calcium than 99% of it requires, a substantial

proportion is obtaining less than this amount. Clearly, if there exist individuals whose calcium requirement is near the upper end of the normal range but whose intake happens to be near the lower end, they will be in danger of being in negative calcium balance. On a purely statistical basis, the proportion of the population that might theoretically be in negative calcium balance in the light of these findings is about 7%.

It may be argued that these results only apply to short-term balances and that normal people can adapt to restricted calcium intake by lowering their urinary calcium and possibly by improving their calcium absorption. This is certainly the view of Hegsted, Moscoso & Collazos (1952) and is supported by the work of Walker, Fox & Irving (1948). However, the fact that some people can adapt to calcium restriction does not mean that everyone can do so. The only really long-term work on low-calcium diets has been done by Malm (1958) and that shows clearly that some individuals remain in negative calcium balance for years on end.

The bone disease of calcium deficiency

The second reason why calcium deficiency is not considered to occur is the rarity of nutritional osteomalacia in our society. The assumption that calcium deficiency would produce osteomalacia is, however, itself a highly questionable one. It is based upon the known reduction in the ash content of osteomalacic bone and the malabsorption of calcium which is known to accompany vitamin D deficiency. These two well-established facts have long been connected in the literature and it has been widely assumed that vitamin D deficiency produces rickets because it produces malabsorption of calcium, with the implication that calcium deficiency must produce the same effect as deficiency of vitamin D. This is not true, however, of experiments on animals which I have reviewed elsewhere (Nordin, 1960*b*), the most recent example being the work of Greaves, Scott & Scott (1959) which was recently reported to the Physiological Society. Animal experiments, which go back to the beginning of the century, show that simple calcium deficiency unaccompanied by vitamin D deficiency produces loss of bony tissue (osteoporosis) without any reduction in ash content. The explanation appears to be that vitamin D deficiency lowers the product of calcium and phosphate concentrations in the blood whereas simple calcium deficiency does not.

If it is correct that low-calcium diets produce osteoporosis in animals, is there any reason why the same should not be true in man? At the present time it is widely believed that osteoporosis—by which we mean a reduction in the amount of bone present in the skeleton or part of the skeleton—is a disorder of protein rather than of calcium metabolism. This assumption is based on the work of Albright (Albright & Reifenstein, 1948) who probably developed his hypothesis in the belief that calcium deficiency must produce osteomalacia and could therefore not be responsible for osteoporosis.

Osteoporosis and calcium deficiency in man

Since osteoporosis simply signifies a reduction in bone mass, the condition could be due to a reduction in rate of bone formation or an increase in the rate of destruction. An increase in the rate of destruction would be produced by negative calcium

balance, and negative calcium balance can of course be produced by inadequate intake, malabsorption or excessive urinary excretion of calcium. Is there any evidence that any or all of these factors are operating in clinical osteoporosis?

We have tried to study this problem in several ways. In the first place we are, with the help of Miss McCombie and her staff, collecting diet histories in cases of osteoporosis and comparing them with histories obtained by the same dietitians from control subjects. We have so far obtained diet histories from eighty-one consecutive cases of osteoporosis and from ninety-six control subjects. The age and sex distribution of the two groups is shown in Fig. 2. There is a slightly higher proportion of men among the controls than among the patients but we are satisfied that it cannot explain the results given below.

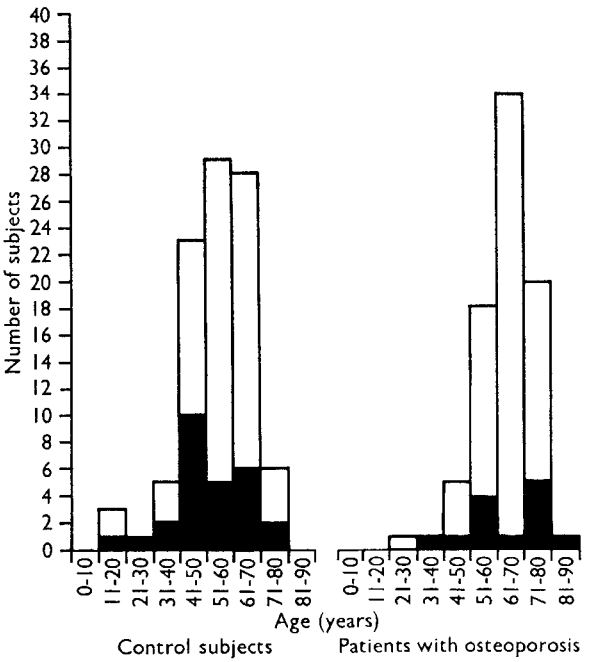

Fig. 2. Frequency distribution of age and sex in control subjects and in patients with osteoporosis (see this page). ■, male; □, female.

In this series of eighty-one consecutive cases of primary osteoporosis, ten patients out of fifty-three tested had steatorrhoea. It seems reasonable to suppose that malabsorption of calcium might be present in these cases and it has been confirmed by balance studies in five of them.

For the remaining seventy-one patients, the mean dietary intake of calcium calculated from the diet histories was 13·4 mg/kg/day as compared with 17·9 mg/kg in the control subjects (Fig. 3). The mean intakes of protein and vitamin D were also lower in the patients with osteoporosis than in the control subjects (Figs. 4 and 5). In each instance the difference was highly significant (Table 1). If the results are

https://doi.org/10.1079/PNS19600035 Published online by Cambridge University Press

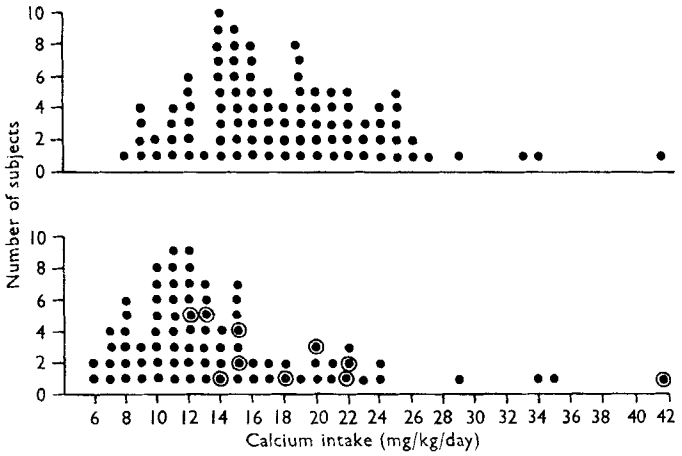

Fig. 3. Dietary intake of calcium in control subjects (upper) and in patients with osteoporosis (lower). ◉, steatorrhoea. (See p. 132.)

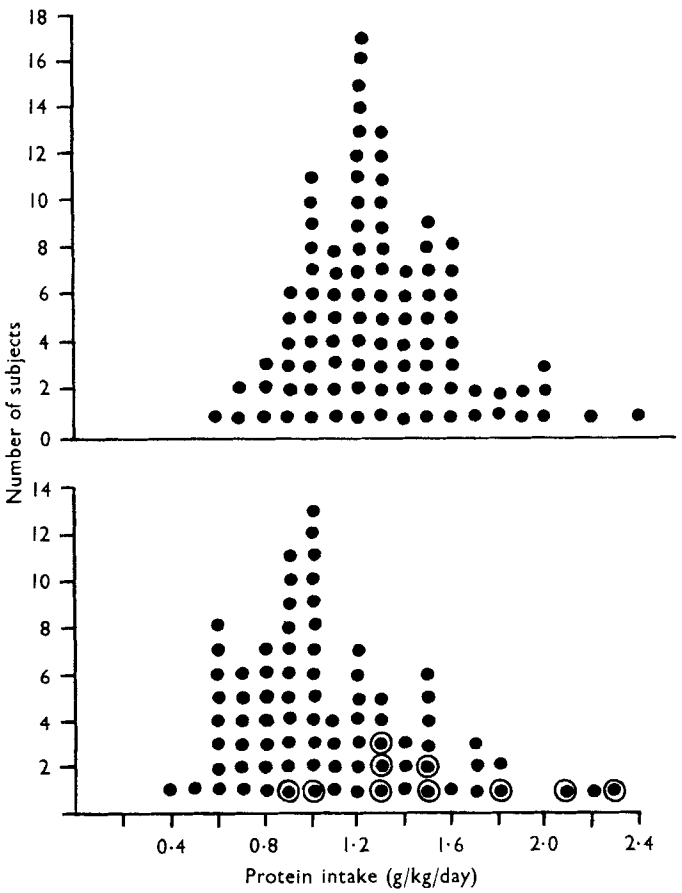

Fig. 4. Dietary intake of protein in control subjects (upper) and in patients with osteoporosis (lower). ◉, steatorrhoea. (See p. 132.)

https://doi.org/10.1079/PNS19600035 Published online by Cambridge University Press

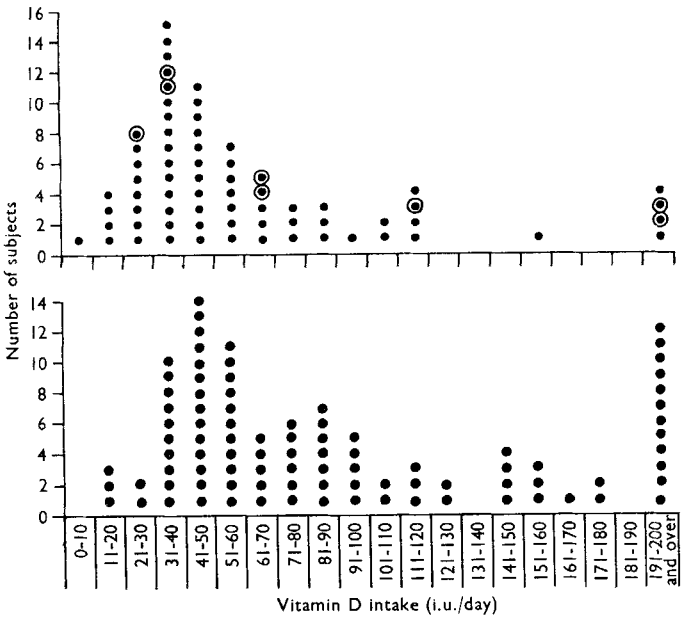

Fig. 5. Dietary intake of vitamin D in control subjects (lower) and in patients with osteoporosis (upper). ◉, steatorrhoea. (See p. 132.)

expressed in crude figures unrelated to body-weight the difference is even more striking because the mean weight of the patients was 51 kg and the mean weight of the control subjects was 65 kg.

Table 1. *Mean values with twice their standard errors for dietary intake of calcium, protein and vitamin D by ninety-six control subjects and eighty-one patients with osteoporosis*

Nutrient	Controls	Osteoporotics	Significance of difference
Calcium (g/kg/day)	17·9 ± 1·3	13·4 ± 1·5	$P < 0{\cdot}01$
Protein (g/kg/day)	1·28 ± 0·09	1·02 ± 0·08	$P < 0{\cdot}01$
Vitamin D (i.u.)	107 ± 18	64 ± 12	$P < 0{\cdot}01$

The cases of osteoporosis can be classified into spinal, involving the spine only (group 1); peripheral, involving cortical bone only (group 2); and mixed (group 3). When this division is made, the dietary calcium intake appears to have been lowest in group 3 (Table 2).

It has already been indicated that calcium balance must be a function of the relationship between intake, absorption and excretion. As far as absorption is concerned, we have found that about half the patients with osteoporosis whom we have studied on calcium balance are well able to absorb calcium, but others are unable to do so, which suggests that malabsorption may be present in some cases. We cannot say more about these results at the moment.

https://doi.org/10.1079/PNS19600035 Published online by Cambridge University Press

Table 2. *Mean values with twice their standard errors for calcium intake of patients with osteoporosis, grouped according to bones affected*

Group no.	No. of subjects	Ca intake (mg/kg/day)	Significance of difference
1 (spine only)	33	14·1 ± 2·5	$P < 0.05$
2 (periphery)	17	14·2 ± 2·6	$P < 0.05$
3 (both)	21	12·1 ± 0·5	$P < 0.01$
Controls	96	17·9 ± 1·3	$P < 0.01$

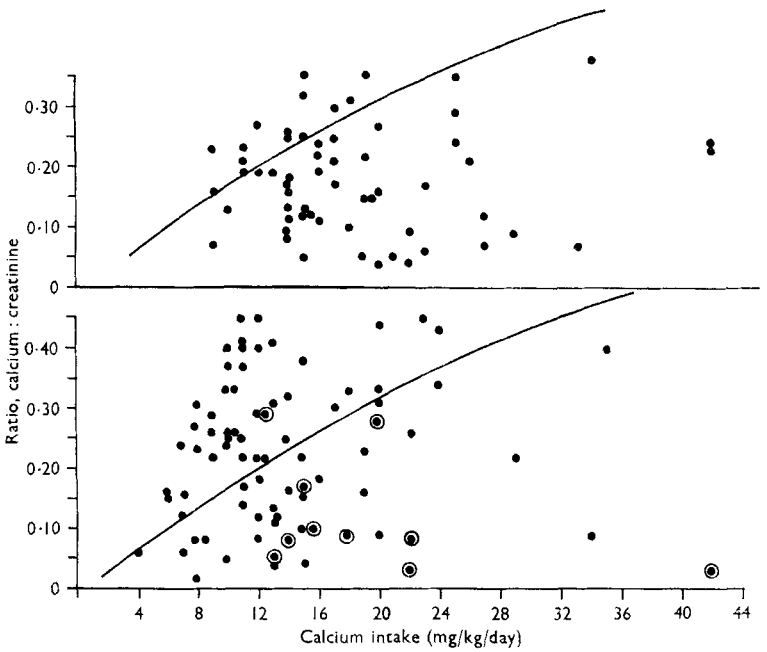

Fig. 6. Relationship between dietary intake of calcium and urinary calcium:creatinine ratio in control subjects (upper) and in patients with osteoporosis (lower). The curves represent the approximate values at which calcium balance would be achieved if 20% absorption of dietary calcium is assumed. ◉, steatorrhoea. (See this page.)

We have measured the urinary calcium: creatinine ratio (Nordin, 1959*b*) in all the eighty-one patients in the series and in the majority of the control subjects. Fig. 6 shows that not only is calcium intake lower in the osteoporotics than in the controls, but calcium excretion tends to be higher; the relationship between dietary intake and urinary excretion is therefore very different in the two groups. This relationship can be simply expressed in one figure by dividing the dietary calcium by the calcium: creatinine ratio. The result of doing so is shown in Fig. 7 and Table 3. The data show that the relationship between dietary and urinary calcium is significantly different in patients with spinal osteoporosis from that in normal controls, but that it may not be true of osteoporosis of the peripheral bones.

https://doi.org/10.1079/PNS19600035 Published online by Cambridge University Press

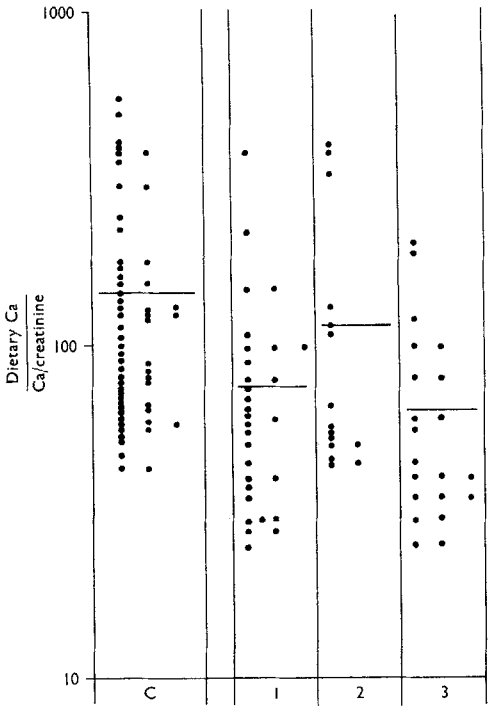

Fig. 7. Relationship between dietary intake and urinary excretion of calcium in control subjects (C) and in patients with spinal (1), peripheral (2) or mixed (3) osteoporosis, expressed by division of the value for calcium intake (mg/kg/day) by the value for the calcium:creatinine ratio in the urine (each in mg/100 ml). (Logarithmic scale.)

Table 3. *Relationship between intake and urinary excretion of calcium in patients with osteoporosis and in controls*

(Mean values with twice their standard errors)

Group	Calcium intake ÷ urinary Ca:creatinine ratio (expressed as in Fig. 7)	Significance of difference from controls
1 (33)	77 ± 18	$P < 0.01$
2 (17)	115 ± 54	Not significant
3 (21)	64 ± 23	$P < 0.01$
Controls (57)	145 ± 6	—

Figures in parentheses are the numbers of subjects.

Conclusions

It appears that the dietary calcium intake of the population is not necessarily as adequate as it is generally assumed to be, and that by analogy with animal experiments negative calcium balance might be expected to produce osteoporosis in man. The data we have collected so far are compatible with this concept, which is further supported by radiocalcium studies on rate of bone formation (Heaney & Whedon, 1958; Nordin, 1959*a*) and by the results of therapy with calcium supplements and of calcium balances, which will be reported elsewhere.

REFERENCES

Albright, F. & Reifenstein, E. C. Jr. (1948). *The Parathyroid Glands and Metabolic Bone Disease.* Baltimore: Williams and Wilkins.

Greaves, J. P., Scott, M. G. & Scott, P. P. (1959). *J. Physiol.* **146**, 36.
Heaney, R. P. & Whedon, G. D. (1958). *J. clin. Endocrin.* **18**, 1246.
Hegsted, D. M., Moscoso, I. & Collazos, C. (1952). *J. Nutr.* **46**, 181.
Malm, O. J. (1958). *Calcium Requirement and Adaptation in Adult Men.* Oslo: University Press.
Ministry of Agriculture, Fisheries and Food: National Food Survey Committee. (1955). *Domestic Food Consumption and Expenditure*, 1953. London: H.M. Stationery Office.
Mitchell, H. H. & Curzon, E. G. (1939). *The Dietary Requirement of Calcium and its Significance.* Paris: Hermann & Cie.
Nordin, B. E. C. (1959*a*). *Proc. R. Soc. Med.* **52**, 351.
Nordin, B. E. C. (1959*b*). *Lancet*, ii, 368.
Nordin, B. E. C. (1960*a*). In *Bone as a Tissue.* [K. Rodahl, editor.] Philadelphia: McGraw-Hill.
Nordin, B. E. C. (1960*b*). *Clinical Orthopedics.* (In the Press.)
Walker, A. R. P., Fox, F. W. & Irving, J. T. (1948). *Biochem. J.* **42**, 452.

Disorders of the nervous system in malnutrition

By C. J. EARL, *The National Hospital, Queen Square, London, W.C.*1

Disorders of the nervous system resulting from malnutrition have been recognized since the last century. Their occurrence during the recent war, among prisoners and populations subsisting on inadequate diets, stimulated at that time a great deal of interest, and the important monographs of Denny-Brown (1947) and Spillane (1947) contain a large number of clinical observations. There are, however, still very many problems to be solved in this field, even in the definition of the clinical syndromes which result from particular dietary deficiencies.

I think that today the important aspects of the subject to consider are those conditions which do occur in this country and which in the elderly might easily remain undiagnosed if the possibility of nutritional disorder were not entertained.

I would like to take first the abnormal neurological state thought to be due to nicotinamide deficiency, because it is the one which in the elderly, and in this country, could give rise to the greatest difficulty in diagnosis. It is probably uncommon here but is apparently seen much more frequently in the large cities of the United States among those addicted to alcohol.

It was first described by Jolliffe, Bowman, Rosenblum & Fein (1940) in New York, who defined a condition which would respond to treatment with large doses of nicotinic acid given parenterally while the patient was maintained on a diet low in vitamins of the B complex. The condition was named nicotinic-acid deficiency encephalopathy.

The onset of the illness is insidious and the nervous manifestations protean in character. The earliest symptoms are often psychological. Fatigue, irritability, depression or nervousness are all noted and it is easy to imagine how difficult the diagnosis can be at this stage. Later an impairment of intellectual function supervenes followed by stupor and coma. Many of the patients described in the literature were stuporose by the time they were admitted to hospital.

Associated with this clouding of consciousness there are other neurological signs. Rigidity of the limbs (of the sort seen in Parkinsonism) is found, and grasp and sucking reflexes are often present. The plantar responses may be extensor and the