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EDITORIAL

Calcium metabolism and mental disorder[1]

This is an uncertain, neglected and misunderstood corner of organic psychiatry. Calcium disturbances are clinically the concern of physicians interested in bone diseases, in malabsorption or nutritional deficiencies, and opinions vary on whether such illnesses are accompanied by emotional and behavioural disorder: at least psychiatrists are not usually called in. Parathyroid disease is generally granted to have frequent psychiatric accompaniments (e.g. see Granville-Grossman, 1971) but is very rare in the psychiatric clinic, and possibly under-diagnosed there. Laboratory aids tend to be underused or inadequately applied. Total plasma calcium as a screening test cannot be understood without at least a plasma protein measurement as well; but serum phosphate, parathormone and plasma 1,25-dihydroxycholecalciferol levels, urinary calcium and magnesium, and Ca^{45}, may all have roles in fuller investigation (Nordin, 1976).

There is in all this a question of intellectual orientation. Is the purpose in the psychiatric clinic simply to recognize the established medical disorders, of bone, intestine or whatever, and perhaps to decide whether they are caused by, causative of, or simply coincident with psychiatric illness? Or is it also to investigate the possibility that there are calcium disorders of the brain underlying some psychiatric syndromes?

The plasma calcium is the resultant momentary balance of a three-way control: the limitation of access of calcium to the body from the food through the intestine; the regulation of loss of calcium from the body in the urine, and the rate of deposition or release of calcium in bone. Its major controls are certain peptides released from the parathyroid (and sometimes from neoplasms elsewhere), and the steroid 1,25-dihydroxycholecalciferol produced from vitamin D by metabolism first in the liver and then in the kidney. Renal disease may prevent this second step, induction of liver enzymes by phenytoin, barbiturates and some psychotropic drugs may diminish the first, and so diminish the steroid control. Other hormones also modify calcium balance, however. Oestrogens damp down the release of calcium from bone, a control largely lost at the menopause. Corticosteroids decrease intestinal absorption and increase renal loss; as does thyroid hormone, which also stimulates release from bone. Growth hormone may stimulate both gut absorption and renal excretion. Changes in these controls can result in hyper- or hypo-calcaemia, which may incidentally alter the functioning of a brain intolerant of deficiency or superfluity in its calcium supply. But this is the somatic macrophysiology of calcium.

The cerebral physiology, and the subcellular dynamics, of calcium are less well understood, but at least it is clear that calcium is essential to the release of neurotransmitters such as noradrenaline, or of hormones such as vasopressin, and that cells have metabolic machinery for ejecting calcium or moving it into mitochondria (Cuthbert, 1970; Manery, 1969). Calcium introduced into the cerebrospinal fluid of experimental animals is said to cause drowsiness, but to antagonize the analgesic action of morphine (Kakunaga *et al.* 1966). It is plausible, therefore, that there might be purely local (intracerebral) derangements of calcium metabolism resulting in symptoms but without abnormality of plasma calcium. Their detection would require a strategy different from conventional medical diagnosis.

Hypercalcaemia is a condition which may be symptomless, or present only with vague symptoms of lack of energy, fatigue and irritability, headache, depression. Boonstra & Jackson (1965) screened 25800 successive referrals to medical out-patients in Indiana by blood test and discovered 31 cases of hyperparathyroidism, 23 of whom would have been quite unsuspected on medical grounds, and another 17 cases of hypercalcaemia due to malignant disease. Looking at it a different way, Watson (1968) noted in a survey of 200 cases of hyperparathyroidism seen over several years at one London

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clinic that 8 had presented as psychiatric cases, and 17 had been discovered by accident. Hypercalcaemia is not always present in hyperparathyroidism, or not at the moment of a screening blood test, but one wonders what would turn up if a single plasma calcium and protein measurement were made routinely on a large psychiatric out-patient population. There are, of course, other tests, such as provocation by cortisone (e.g. see Williams, 1974; Labhardt, 1974), which might be adapted for smaller groups of patients with greater likelihood of concealed parathyroid disease, such as early dementias, chronic depressions, neurotic complaints of late onset.

A plasma calcium above 7 mM/l (normal range 4·5–5·1 mM/l) is quite often accompanied by an abnormal EEG (non-specific slow waves, see Kurtz, 1976) and by pronounced psychiatric symptoms, an agitated depression, paranoid delusions with degrees of disorientation, or a full confusional state or even catatonic stupor (Hockaday *et al.* 1966; Cooper & Schapira, 1973). A plasma calcium below 3·5 mM/l may run with a similarly abnormal EEG, with the addition of spikes, and the patient may have epileptic fits, depression, and impaired memory, though the psychiatric picture is less common and certain than that of hypercalcaemia (Fourman *et al.* 1963). However, correction of the plasma calcium (by removal of parathyroid adenoma, or treatment with calcium and vitamin D) does not abolish the abnormal EEG or mental state for days or weeks after the blood level is normal. Nor does acute infusion of calcium solutions into normal men (Nordin & Fraser, 1956), or of ethylene diamine tetra-acetate to complex the calcium and reduce the effective plasma level (Fourman *et al.* 1963) provoke EEG change or evident mental abnormality. Furthermore, it has long been known (Herbert, 1933), and frequently confirmed, that the calcium content of lumbar cerebrospinal fluid remains remarkably constant in spite of big changes in plasma calcium in parathyroid disease. There is a paradox here: clinically, exposure to high calcium disturbs the brain, but physiologically a blood–brain barrier guards the brain against calcium change (Wallach *et al.* 1964).

All the evidence agrees that calcium is transported inwards by metabolic process, working independently of the external calcium concentration (Oppelt *et al.* 1963; Samachson *et al.* 1959; Schain, 1964), and that its intracellular distribution involves crossing further membrane barriers. It is not so surprising, therefore, that if once the calcium is excessively inside it takes a long time to come out again. But how does it get in, or is there some other explanation?

One possibility is that mental symptoms only appear in those in whom the blood–brain barrier has broken down, perhaps after very chronic exposure to changed plasma calcium. There is a need for a comparison of lumbar puncture analyses in hypercalcaemic patients with and without EEG and psychiatric evidence of change. These analyses should be for protein (Edwards & Daum, 1959) and all electrolytes in case the explanation of brain disturbance lies rather in some related electrolyte imbalance. Hypercalcaemia is sometimes accompanied by polyuria and thirst, and water shifts, hypokalaemia and hypernatraemia may be expected, while a magnesium loss has been blamed also (Gatewood *et al.* 1975). It would be a great help if a clinical survey confirmed that chronic hypercalcaemia, however caused, always produced some mental signs, not necessarily gross psychosis; or if controlled variation of the plasma calcium for brief periods in patients who had had an abnormal EEG in the past could bring back the abnormality at will. It should not be forgotten that plasma calcium might sometimes be an epiphenomenon, and not the true agent of cerebral toxicity. At a time when peptides such as vasopressin, angiotensin and endorphin are found to have cerebral actions, the possibility of neuroactive peptides from parathyroid or from neoplasms must be remembered.

Vitamin D and the parathyroid work together, and a secondary hyperparathyroidism may develop in response to a lack of vitamin D or of its active metabolites. The diet, particularly in Britain and especially among the elderly, is often low in vitamin D, and its supplementation by the action of sunshine on skin steroids somewhat problematic. Deficiency is at its worst towards the end of winter, with a sudden spring improvement. Thus a variety of environmental and behavioural factors play on calcium metabolism – the dark, winter inactivity, the post-menopausal state, anorexia. Pregnancy, and even more, lactation in the puerperium, are times of dramatic change in internal calcium flow, but D. Riley (personal communication, 1977) could find no change in total plasma calcium or magnesium to connect with puerperal psychosis. Total plasma calcium normally consists of about

46% protein-bound calcium, 8% complexed calcium, and 46% ionized calcium, which is the pharmacologically active fraction and can be measured directly by bioassay or by special electrode. Infusion of lactate, provocative of anxiety symptoms, complexes more calcium and reduces the ionized fraction (see *British Medical Journal*, 1968). Overbreathing also reduces this fraction, in favour of more protein-binding. Chronic overbreathing is a feature of some psychiatric syndromes (Damas Mora *et al.* 1976). Whether any of these factors has clinical psychiatric relevance remains open.

In a series of papers Flach (see Faragulla & Flach, 1970) reported classical calcium balance studies on depressed patients treated with ECT or imipramine. Recovery was associated with calcium retention, probably due to new bone storage. The mechanism of this was obscure, but it is likely to have been an endocrine effect of either treatment or the recovery process and not relevant to the aetiology of depression. The adult human brain contains a total of about 180 mg calcium (Documenta Geigy, 1962), of the same order as, or rather less than one day's average urinary excretion of calcium, and much less than the diet or the bones where calcium is measured in grams. Balance studies, where urine and faecal calcium losses are compared with food intake, are bound to be too crude to detect changes in brain calcium, supposing there to be any.

Brain calcium may, however, be open to direct enquiry in two ways. Radioactive calcium penetration into cerebrospinal fluid or into brain tissue after various time intervals could be studied in neurosurgical or post-mortem material. The effects of drugs suspected to modify intracellular calcium distribution could be examined, first physiologically, then clinically; indomethacin (Northover, 1972) and lithium (Bjørum *et al.* 1975) – high levels of which cause symptoms like those of hypercalcaemia – may be examples of such substances. Clinical studies will benefit from the application of repeatable psychological tests in controlled situations, as pioneered by Christie-Brown (1968).

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REFERENCES

Bjørum, N., Hornum, I., Mellerup, E. T., Plenge, P. K. & Rafaelsen, O. J. (1975). Lithium, calcium and phosphate. *Lancet* i, 1243.

Boonstra, C. E. & Jackson, C. E. (1965). Hyperparathyroidism detected by routine serum calcium analysis. *Annals of Internal Medicine* **63**, 468–474.

British Medical Journal (1968). Editorial: Calcium in psychiatry, ii, 5.

Christie-Brown, J. R. W. (1968). Mood changes following parathyroidectomy. *Proceedings of the Royal Society of Medicine* **61**, 1121–1123.

Cooper, A. F. & Schapira, K. (1973). Case report: depression, catatonic stupor and EEG changes in hyperparathyroidism. *Psychological Medicine* **3**, 509–515.

Cuthbert, A. W. (1970). *Calcium and Cellular Function*. Macmillan: London.

Damas Mora, J., Grant, L., Kenyon, P., Patel, M. K. & Jenner, F. A. (1976). Respiratory ventilation and carbon dioxide levels in syndromes of depression. *British Journal of Psychiatry* **129**, 457–464.

Documenta Geigy (1962). *Scientific Tables* 6th edn, p. 516, Manchester.

Edwards, G. A. & Daum, S. M. (1959). Increased spinal fluid protein in hyperparathyroidism and other hypercalcaemic states. *A.M.A. Archives of Internal Medicine* **104**, 29–36.

Faragulla, F. F. & Flach, F. F. (1970). Studies of mineral metabolism in mental depression. 1. The effects of imipramine and ECT on calcium balance and kinetics. *Journal of Nervous and Mental Disease* **151**, 121–129.

Fourman, P., Davis, R. H., Jones, K. H., Morgan, D. B. & Smith, J. W. G. (1963). Parathyroid insufficiency after thyroidectomy. Review of 46 patients with a study of the effects of hypocalcaemia on the electroencephalogram. *British Journal of Surgery* **50**, 608–619.

Gatewood, J. W., Organ, C. H. & Mead, B. T. (1975). Mental changes associated with hyperparathyroidism. *American Journal of Psychiatry* **132**, 129–132.

Granville-Grossman, K. (1971). *Recent Advances in Clinical Psychiatry*, pp. 222–231. Churchill Livingstone: London.

Herbert, F. K. (1933). The total and diffusible calcium of serum and the calcium of CSF in human cases of hypo- and hyper-calcaemia. *Biochemical Journal* **27**, 1978–1991.

Hockaday, T. D. R., Keynes, W. M. & McKenzie, J. K. (1966). Catatonic stupor in elderly women with hyperparathyroidism. *British Medical Journal* i, 85–87.

Kakunaga, T., Kaneto, H. & Hano, K. (1966). Pharmacological studies on analgesics. VII: significance of the calcium ion in morphine analgesia. *Journal of Pharmacology and Experimental Therapeutics* **153**, 134–141.

Kurtz, D. (1976). The EEG in parathyroid dysfunction. In *Handbook of Electroencephalography and Clinical Neurophysiology* (ed. A. Rémond), pp. 77–87. Elsevier: Amsterdam.

Labhardt, A. (1974). *Clinical Endocrinology: Theory and Practice*, pp. 845–946. Springer Verlag: Berlin.

Manery, J. F. (1969). Calcium and membranes. In *Mineral Metabolism*, vol. III, *Calcium Physiology* (ed. C. L. Comar and F. Bronner), pp. 405–452. Academic Press: New York.

Nordin, B. E. C. (1976). *Calcium, Phosphate and Magnesium Metabolism*. Churchill Livingstone: London.

Nordin, B. E. C. & Fraser, R. (1956). A calcium infusion test. *Lancet* i, 823–826.

Northover, B. J. (1972). The effects of indomethacin on calcium, sodium, potassium and magnesium fluxes in various tissues of the guinea-pig. *British Journal of Pharmacology* 45, 651–659.

Oppelt, W. W., Owens, E. S. & Roll, D. P. (1963). Calcium exchange between blood and CSF. *Life Sciences* no. 8, 599–605.

Sammachson, J., Kabakow, B., Spencer, H. & Laszlo, D. (1959). Comparative passage of Ca^{45} and Sr^{85} from plasma into CSF in man. *Proceedings of the Society for Experimental Biology and Medicine* **102**, 287–290.

Schain, R. J. (1964). Cerebrospinal fluid and serum cation levels. *Archives of Neurology* **11**, 330–333.

Wallach, S., Bellavia, J. V., Schorr, J. & Reizenstein, D. L. (1964). Tissue distribution of electrolytes, Ca^{47} and Mg^{28} in acute hypercalcaemia. *American Journal of Physiology* **207**, 553.

Watson, L. (1968). Clinical aspects of hyperparathyroidism. *Proceedings of the Royal Society of Medicine* **61**, 1123.

Williams, R. H. (1974). *Textbook of Endocrinology*, 5th edn, pp. 660–773. Saunders: Philadelphia.