epileptics with elevated serum alkaline phosphatase showed a rise in level of the bone isoenzyme. Apparently Mr. Rowe's opinions—or his methods—have undergone some change over the past three years.

It is correct that our photon absorptiometry method cannot tell whether a low B.M.C. is due to osteoporosis or osteomalacia; it is also correct that patients with osteoporosis do not respond to treatment with 2,000 IU of vitamin D₂ daily for three months. Our 116 epileptics on this treatment showed a highly significant increase in B.M.C., while the control group of 110 patients showed unchanged B.M.C. values. Mr. Rowe and Dr. Stamp will have a hard task in convincing the public—or us—that epileptics on anticonvulsants do not show signs of vitamin D deficiency. In trying to do this they seem to overlook some essential facts which may not fit their preconceived opinions but which nevertheless remain facts.

We have studied with interest the results of classical calcium balance studies in three patients reported by Mr. Rowe and Dr. Stamp (together with other authors) in two articles.^{2,3} A common feature of these three patients was that calcium balance was studied in three consecutive periods: a control period, a period on vitamin D₂, and a period on vitamin D₃ (or 25-OH-D₃). If the effect of each vitamin had been studied for three months in these three patients it would have been relevant to compare the findings with our results in 116 patients.

Whether or not a dose of 2,000 IU of vitamin D daily can "heal anticonvulsant rickets or even . . . prevent its occurrence" is a question raised by Mr. Rowe and Dr. Stamp and certainly not by us. Our patients were between 21 and 70 years of age, a period of life where "anticonvulsant rickets" is seen rather infrequently, at least in Denmark.

We wonder why Mr. Rowe and Dr. Stamp remained silent when, in 1972, an authoritative British journal stated editorially that "though [anticonvulsant osteomalacia] may be only at a biochemical level, sound medical practice is to offer prophylactic vitamin therapy before frank bone disease develops."⁴ This statement challenged us, but we should like to stress once more, as we did in our article, that it was not possible from our results to tell whether epileptics should be treated prophylactically with vitamin D.

Our article supports a number of previous publications and demonstrates a definite effect of vitamin D. We are therefore somewhat bewildered that Mr. Rowe and Dr. Stamp do not see the point of a possible benefit of prophylactic vitamin D treatment in such patients, as also proposed by other authors.^{4,5}—We are, etc.,

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Metastatic Processes

SIR,—Your reviewer of *Chemotherapy of Cancer Dissemination and Metastasis* (4 May, p. 286) asks, "Why does primary melanoma of the eye metastasize to the liver, breast cancer to the ovary, and Hodgkin's disease to the spleen?" I suggest that malignant cells metastasize to particular sites because they are able to obtain in those situations elements (such as amino-acids or hormones) on which they are dependent for their continued growth and survival. The process appears to be analogous to chemotropism, "an orienting response to a chemical stimulus, as in a plant root."

On this hypothesis primary melanoma of the eye metastasizes to the liver, "the greatest chemical factor of the body," to obtain the amino-acid tyrosine, the parent substance of melanin. It may be noted that in the case of melanotic carcinomas of the skin metastases also occur particularly in the liver. Some breast cancers appear to be ovarian hormone-dependent and thus metastasize to the ovaries. They have been known to regress after bilateral oophorectomy. In lymph nodes affected by Hodgkin's disease there is hyperplasia of the reticuloendothelial cells. These metastasize to the spleen, which has the largest aggregation in the body of cells of the reticuloendothelial system, possibly to obtain a hormone (reticuliculin M) produced by this system.—I am, etc.,

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Serological Tests for Amoebiasis

SIR,—I was surprised to see the letter (6 April, p. 39) from Dr. F. Scott minimizing the value of serology in amoebiasis. It would be a pity if, as a result of his letter, the use of this valuable tool was restricted. The number of tests we in Durban have carried out now runs into several tens of thousands, and the enthusiasm of our clinicians is indicative of the confidence they have in the test.

Using the micro-gel-diffusion or the latex tests (which avoid the difficulty of interpretation of titre) we know that many cyst-passers, especially from temperate zones, show no antibodies. We interpret this as meaning that the commensal *Entamoeba histolytica* responsible for the cysts has not made the parenteral contact necessary for the stimulation of antibody. On the other hand when patients are passing haematophagous trophozoites the proportion showing antibodies at some time is well over 95%. In proved amoebic liver abscess the figure is over 99%. These are impressive figures for any serological test. In infants the results are more erratic—possibly the appropriate mechanisms have not been established. The test cannot be blamed for the negative result.

The persistence of antibodies might be regarded as a nuisance, particularly in endemic areas, limiting the tests to exclusion of invasive amoebiasis. However, sero-epidemiology based on this fact is proving most useful. When one appreciates the many pitfalls in the morphological identification of *E. histolytica* and the lack of laboratories able to appreciate these the value of serology in amoebiasis is self-evident.

The workers at Loon Lake are to be congratulated on their operation, which has high-lighted the association between invasive amoebiasis and density of human population in the absence of adequate hygiene.—I am, etc.,

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Drugs for Gastric Ulceration

SIR,—Unlike Dr. A. B. S. Mitchell (1 June, p. 501) I thought your leading article (27 April, p. 186) gave an excellent survey and I entirely agreed with its conclusion that carbenoxolone seems still to be the drug of choice. It seems to work by improving the defence mechanisms of the stomach by stimulating mucus production and by lengthening the life cycle of the epithelial cells, both facilitating the repair process.

I was associated with the first studies on this drug in this country and have followed closely the world literature ever since. Its beneficial effects have been repeatedly confirmed in many countries. It is clear that this treatment enables gastric ulcers to be treated in the ambulatory patient—a very considerable economic advantage. Like other modern effective drugs such as corticosteroids, carbenoxolone has to be used with some care and discretion and a few simple precautions observed. Used in this way it is an effective and safe treatment.—I am, etc.,

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Studies of Resistance to Long-acting Adrenergic Beta-stimulators in Asthmatic Patients

SIR,—Since the report of Conolly and others¹ the development of resistance to long-acting adrenergic beta-stimulators has been much discussed. We have begun a study to see whether resistance develops in the beta-receptors in the bronchi, heart, and skeletal muscle during oral terbutaline treatment of patients with chronic obstructive bronchitis who have not previously taken beta-stimulating drugs. We first observed the effect on forced expiratory volume, heart rate and blood pressure, and muscular tremor of increasing intravenous doses of isoprenaline. After this treatment was started with terbutaline 5 mg thrice daily orally. So far we have repeated the observations of the effect of intravenous isoprenaline in increasing dosage after one, two, and three months' terbutaline treatment. The figure shows the mean values in eight patients. The dosage of isoprenaline was so selected that the highest dose caused nearly maximum bronchodilation. All tests were performed in the morning after the patient had been without terbutaline for 10 hours.

The higher basal value in the morning during terbutaline treatment suggests that the patients did not develop resistance to their own adrenaline or noradrenaline. In addition the same maximum bronchodilation was obtained with isoprenaline, suggesting that no resistance occurred during terbutaline treatment. All patients experienced powerful muscular tremor towards the

¹ Richens, A., and Rowe, D. J. F., *British Medical Journal*, 1970, 4, 73.

² Dent, C. E., et al., *British Medical Journal*, 1970, 4, 69.

³ Stamp, T. C. B., et al., *British Medical Journal*, 1972, 4, 9.

⁴ *Lancet*, 1972, 2, 805.

⁵ Hahn, T. J., et al., *New England Journal of Medicine*, 1972, 287, 900.