(4) Tetracyclines. It is recommended that, given parenterally, "the total dose should never exceed 1 g in 24 hours (less in patients with impaired renal function) because of the danger of liver damage." Nothing whatever is said in this section about the anti-anabolic action of these agents and other possible effects on the kidney, which have led the authors of at least three standard texts,^{2,4} to interdict the use of tetracyclines altogether (with the exception of doxycycline) in patients with impaired renal function.

(5) Fusidic acid (Fucidin) is stated to be "active against a wide spectrum of organisms." How can fusidic acid possibly be described as a wide-spectrum drug? All "coliform" organisms are resistant to it, and even in the Gram-positive range its activity against the pneumococcus and other kinds of streptococci is poor.

(6) The section ends with some advice on the choice of drugs for various infections, among them acute meningitis and peritonitis. The paragraph describing the chemotherapy of meningitis caused by "coliform" organisms is written in a particularly confusing way. At one point, dealing with the treatment of pyocyanus (sic) meningitis in an infant, the author could be read as saying that though gentamicin is the drug of first choice chloramphenicol and kanamycin are permissible alternatives. For the chemotherapy of peritonitis when no bacteriological information is available ampicillin is said to be "the drug most likely to be effective." The blind chemotherapy of peritonitis is a highly debatable topic, but there is one point at least on which I think there would be wide agreement and that is that ampicillin, if given alone, is not the drug most likely to be effective in this condition.

Considerations of space forbid me to make more than a selection of the criticisms which might be levelled at this section of the *B.N.F.*, which I suggest is in urgent need of revision. The prospect of its use until 1976 by any who are inexperienced in this field is one that I find alarming.—I am, etc.,

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¹ *British National Formulary* 1974-76, pp. 94-110. London: British Medical Association and Pharmaceutical Society of Great Britain, 1973.

² Kucers, A., *The Use of Antibiotics*, pp. 146, 288. London: Heinemann, 1972.

³ Garrod, L. P., Lambert, H. P., and O'Grady, F., *Antibiotic and Chemotherapy*, 4th edn., p. 157. Edinburgh and London, Churchill Livingstone, 1973.

⁴ de Wardener, H. E., *The Kidney*, 4th edn., p. 312. Edinburgh and London, Churchill Livingstone, 1973.

Isolation System for General Hospitals

SIR,—Dr. A. G. Ironside (1 June, p. 501) poses the rhetorical question whether "dermatitis with severe sepsis [is] more infectious than any other wound or burn infection." In fact for many years infected, non-surgical skin lesions have been recognized to be a peculiarly dangerous source of hospital cross-infection. Numerous demonstrations of this can be found in the literature. For example, 14 patients died as a result of the admission of a patient with skin sepsis to a medical ward¹; and similar catastrophes have occurred in surgical wards.²

The bacterial contamination of the hospital environment by patients with infected dermatological lesions can be truly prodigious.³ It is important, however, to note that similar bacterial dispersal can follow simple colonization of lesions with *Staphylococcus aureus*, *Streptococcus pyogenes*, or Gram-negative bacilli such as *Proteus vulgaris* and *Pseudomonas aeruginosa*.⁴ Though eczema with clinically apparent infection is rightly regarded as a particularly dangerous hazard in hospital, experiments on bacterial dispersal from individual patients have shown that clinically non-infected conditions, notably psoriasis, are the sources of some of the highest air counts.⁴ This is a reflection of the greatly increased turnover of the epidermis and the production of profuse air-borne squames in such diseases.

The traditional practice of nursing dermatological patients in surgical wards is now clearly indefensible. Many cases of post-operative sepsis over the years have been due to this form of negligence. But the risks of treating skin patients in general medical wards are also considerable. Whenever possible, patients with extensive skin disease should be nursed in single-bedded rooms with exhaust ventilation. The practicability of converting existing ward accommodation to house dermatological cases at only modest expense has been shown at Westminster Hospital. For a medium-sized general hospital suitable facilities for seven or eight patients should be adequate. In the absence of suitable accommodation the minimum requirement is that the lesions of dermatological patients should be declared bacteriologically safe before admission to an open ward. Further bacteriological examination is essential during each patient's stay since skin lesions readily become colonized with pathogens in hospitals.⁴—I am, etc.,

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¹ Vogel, R. A., et al., *New England Journal of Medicine*, 1959, 261, 1301.

² Barber, M., and Dutton, A. A. C., *Lancet*, 1958, 2, 64.

³ Selwyn, S., *Journal of Hygiene*, 1965, 63, 59.

⁴ Selwyn, S., and Chalmers, D., *British Journal of Dermatology*, 1965, 77, 349.

A Case of Pyrexia of Undetermined Origin

SIR,—I would like to suggest another possible, if unlikely, condition to explain the P.U.O. in the patient considered in a recent Clinicopathological Conference (20 April, p. 157). This is the protozoal disease babesiosis, which many features in the patient's illness might suggest.

(1) She spent her holidays in a caravan in Devon, where "red water fever" in cattle occurs and ticks transmitting the infection are ubiquitous. In the only other human case of babesiosis in the British Isles the patient contracted the disease on a caravan holiday under similar circumstances in Ireland.

(2) Haematuria is a cardinal feature in babesiosis.

(3) Splenomegaly and anaemia are characteristic features in babesiosis.

(4) The P.U.O. which failed to respond to medication would favour a babesial infection not treated appropriately.

(5) Finally, the failure to see *Babesia* parasites in the blood film would not exclude

the infection; after the acute stage parasitized red cells may be extremely few and very difficult to find.

Babesia sp. is probably the most widely distributed blood parasite in mammals throughout the world and the sources of infection are therefore equally ubiquitous. In the British Isles alone *Babesia* sp. is found in bovines, rodents, insectivora, and chiroptera. Nevertheless, my observations do not profess to have cleared up this problem but only suggest one further line of research which might have been followed in an otherwise extremely thorough investigation of a very puzzling case which under the circumstances must remain a case of P.U.O.—I am, etc.,

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The Coroners' So-called 24-hour Rule

SIR,—There has been and still is a general belief among medical staff of junior and senior grades that patients dying within 24 hours of admission to hospital are "cases to be referred to the coroner." Even in 1974 this view obtains, as is confirmed by answers given by postmortem room technicians in many parts of the country to a recent examination question on the kinds of cases referred to the coroner.

This belief is erroneous. The Human Tissue Act 1961 contains specific provisions relating to postmortem examinations and section 2(1) affords clear permission for such an examination to be carried out on any patient to establish or confirm the causes of death.—I am, etc.,

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Anticonvulsant Osteomalacia and Vitamin D

SIR,—Mr. D. J. F. Rowe and Dr. T. C. B. Stamp (2 March, p. 392) make some critical comments on our paper on anticonvulsant osteomalacia (22 December 1973, p. 695). Contrary to their previously expressed opinions they now seem to believe that epileptics on anticonvulsant therapy do not have osteomalacia but osteoporosis, though they do not give any direct evidence to support this statement. Their arguments are: hypocalcaemia is seen without other biochemical changes and without histological sign of osteomalacia; mean levels of alkaline phosphatase of bone origin are no higher in adult epileptics than in normal adults; the low levels of bone mineral content (B.M.C.) found with our method can be caused by osteoporosis, since the method cannot distinguish this condition from osteomalacia; and the effect of treatment with vitamin D₂ (not vitamin D₃, as incorrectly stated by Mr. Rowe and Dr. Stamp) observed by us is at variance with the results of calcium balance studies.

The fact that hypocalcaemia is common in epileptics in the absence of histological bone abnormalities may be due to bone biopsy being a rather insensitive method for estimating osteomalacia in its milder forms. As to our findings of elevated serum alkaline phosphatase levels, we should like to draw attention to the fact that three years previously Mr. Rowe, together with Dr. A. Richens,¹ reported that 18 (38%) out of 47

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 reticulo-endothelial 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 (reticulic 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.