intense loneliness, having never been without a dog before. I am now hopeful she may now change her mind, at least to the extent of a Siamese cat, and that this may eventually permit corticosteroids to be tailed-off without relapse of her arteritis in one of its more unpleasant guises. This happened to a patient from the same practice only a few months back who stopped taking her prednisone, prescribed for her temporal arteritis, because the doctor emigrated. Her cardiac infarction, at first thought unremarkable, was followed by pericarditis and mental confusion, both of which, like her previous temporal arteritis, responded at once to prednisone.

It seems likely that further studies on deprivation by death or other means of close relatives or pets will show significant results, not only in mortality in the aged from cardiac infarction but also in morbidity and mortality from the other protean manifestations of giant cell arteritis.—I am, etc.,

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REFERENCE

- ¹ Paulley, J. W., and Hughes, J. P., *British Medical Journal*, 1960, **2**, 1562.

Testing the Pill

SIR,—Your leading article (8 March, p. 592) confuses the issue of assessing the separate roles of oestrogens and progestogens in the contraceptive pill by calling norethisterone a progestogen, and thus implying that it is solely progestogenic. This is not so. Studies of its metabolism¹ and its clinical effect² clearly demonstrate some oestrogenic activity. It is most important in assessing these drugs to appreciate the exact biological as well as chemical effect of each component before assigning any side-effects to one or the other.—I am, etc.,

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- ¹ Brown, J. B., and Blair, H. A. F., *Proceedings of Royal Society of Medicine*, 1960, **53**, 433.
² Appleby, B., *Lancet*, 1962, **1**, 407.

** It is true that norethisterone is not purely progestogenic. The purpose of the leading article was to point out that the actions of progestogens and oestrogens can overlap, and to assign side-effects to one or other group of compounds on the basis of rather crude and ill-understood liver function tests is unwise. Only experimentation in animals can clarify the issue in a reasonable period of time.—ED., *B.M.J.*

Indomethacin Therapy

SIR,—In reply to the letter of Dr. J. H. Swallow (22 March, p. 783), we have been careful to avoid stating that gastric ulceration is caused by indomethacin. We felt that there was likely to be a causal relationship on the basis of the rapid healing which followed withdrawal of the drug in seven patients who had no gastric symptoms, either before or since taking indomethacin (21 December, p. 734).

In three patients who developed gastric ulcers while taking oral indomethacin, symptoms continued, and healing failed to occur when suppositories were substituted. In these cases healing occurred rapidly with relief of

symptoms when suppositories were withdrawn, suggesting that they were at least perpetuating the process. We agree that no firm conclusions can be drawn from only three cases of such an unpredictable disease.—We are, etc.,

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Hyperbaric Oxygen in Carbon Monoxide Poisoning

SIR,—The controversy on this subject in your columns seems to be losing perspective. In our original paper¹ we stated that "the treatment of choice for patients with severe CO poisoning is to expose them to hyperbaric oxygen." In your leading article following this paper you amended our suggestion by saying that "where this is available, exposure to hyperbaric oxygen at 2–2½ atmospheres pressure is the treatment of choice." Quite reasonably, Matthew and Proudfoot^{3,4} object to this counsel on the grounds that the prognosis for CO poisoning is excellent with mannitol infusions and conventional oxygen therapy, without resorting to the more complex hyperbaric chambers.

Unfortunately the situation is not so simple, since, as Dr. J. G. B. Thurston has pointed out (15 February, p. 446), the importance of hyperbaric oxygen is not so much in reducing the already low mortality rate, but in reducing the very significant chronic neurological and other sequelae. Permanent brain damage is rare,⁵ but profound disability due to visual, dysphasic, dyspraxic, and complex agnosic defects may last for months or years¹ before a functionally useful degree of recovery has taken place. In deciding the optimal treatment in the acute stage of the illness, these facts should not be neglected. I have previously pointed out⁶ that the main problem is the restricted availability of pressure chambers; and the difficulty in deciding where to send the patient must also be affected by the distance involved and the related time delay in instituting treatment. The level of carboxy-haemoglobin did not seem to be a reliable index in predicting the severity of sequelae in our patients,¹ and therefore this estimation on admission to hospital is of little help in deciding the need for hyperbaric oxygen.

I would agree with Dr. Thurston that patients should be transported to the listed centres where hyperbaric oxygen chambers are available, but would add the riders that this is contraindicated if:

- (1) The distance to be covered in the ambulance unduly delays the inception of treatment. In this event conventional oxygen and carbon dioxide with mannitol infusion at the nearest hospital is indicated.
- (2) The duration of exposure is short, the patient is young, and there is no impairment of consciousness or neurological deficit when the victim of poisoning is first seen. In this sort of case the risks of brain damage are remote.

These suggestions are of necessity generalizations, and, as I have previously stated,⁶ the severe case, with profound impairment of conscious level, or with signs of acute multifocal cerebral cortical ischaemia,¹ should

be given the benefit of hyperbaric oxygen at 2–2½ atmospheres for approximately two hours.—I am, etc.,

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REFERENCES

- ¹ Garland, H., and Pearce, J., *Quarterly Journal of Medicine*, 1967, **36**, 445.
² *British Medical Journal*, 1968, **1**, 398.
³ Matthew, H. J. S., and Proudfoot, A. T., *British Medical Journal*, 1968, **1**, 638.
⁴ Matthew, H. J. S., and Proudfoot, A. T., *British Medical Journal*, 1969, **1**, 187.
⁵ Shillito, F. H., Drinker, C. K., and Shaughnessy, T. J., *Journal of the American Medical Association*, 1936, **106**, 669.
⁶ Pearce, J., *British Medical Journal*, 1968, **1**, 767.

Urinary Tract Infections

SIR,—The two papers reporting on the value of the trimethoprim-sulphamethoxazole combination in the treatment of urinary tract infections (1 March, p. 541 and p. 545)¹ help to establish this compound as a chemotherapeutic agent of major importance. This will no doubt increase the number of requests for bacterial sensitivities, and in this respect I would like to draw attention to a possible source of error in the performance of such tests which could be overlooked.

The action of trimethoprim can be blocked by the presence of antagonists in much the same way as para-aminobenzoic acid antagonizes the action of sulphonamides. The composition of a medium used for testing sensitivity to the trimethoprim-sulphamethoxazole combination is therefore critical in that it must be free from both sulphonamides and trimethoprim antagonists, otherwise organisms which are sensitive to these drugs may appear to be resistant. Oxoid diagnostic sensitivity test (D.S.T.) agar, which is probably widely used, contains small amounts of trimethoprim antagonists, although it is free from sulphonamide antagonists. In order to make this medium suitable for testing sensitivity to trimethoprim it is necessary to neutralize these trimethoprim antagonists, and this can be done by the addition of 0.25% lysed blood.¹—I am, etc.,

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REFERENCE

- ¹ Darrel, J. H., Garrod, L. P., and Waterworth, P. M., *Journal of Clinical Pathology*, 1968, **21**, 202.

Diverticulosis of the Colon and Diet

SIR,—Wide regional variations are known to exist in the incidence of diverticula of the colon. Thus, although common in many parts of Europe and North America, the condition is rare among the negroes of Africa and among the native populations of India and of the Far East. In the U.S.A., however, the incidence of this condition among the whites and negroes is approximately the same. This phenomenon has been correlated with the type of diet ingested; colonic diverticula appear to occur in areas where a low roughage diet is eaten in contrast to their rarity when a bulky vegetable diet is used.¹

Some support for this dietary aetiology was given by two reports on the development of

colonic diverticula in the experimental situation. Wierda² found diverticula of the colon of three rats fed on a high fat diet for from 90 to 111 weeks. Each rat had a diverticulum of the colon within 2 cm. of the caecum, and one had a second diverticulum along the length of the large bowel. No colonic diverticula were found in rats on the same diet sacrificed when 25 to 50 weeks old. Carlson and Hoelzel³ reported the development of diverticula—usually one, or occasionally two or three, in number—within 1 cm. of the caecum in about 20% of a group of 252 rats in life span studies on various diets. Rats on bulky diets showed the least evidence of diverticulosis, but diverticula developed in those rats kept on a low residue diet and, more particularly, in those who were first fed a bulky diet and who were later switched to a low residue diet.

We have recently had the opportunity of studying the intestines of 38 black and white Lister rats fed on a low roughage diet for between 52 and 70 weeks. The diet comprised 60% sucrose, 20% casilan, 15% arachis oil, and 5% mineral salts and vitamins. Weight at death varied from 350 to 450 g. In one rat a rather sacular caecum was found, but histological examination revealed no evidence of diverticula. The colon in all the other animals was free from diverticula but was invariably very contracted and contained little food residue.

Diverticular disease of the colon is becoming an increasingly important problem in current clinical practice, and yet its aetiology remains essentially unknown. The production of colonic diverticula in the experimental animal would obviously be of considerable value in the investigation of this condition. Our own negative findings in this small series should not discourage others from investigating the association between diet and colonic diverticula both in different strains of rats and in other experimental animals.

A longer period of study than ours is obviously necessary.

We wish to thank Professor John Yudkin for access to the experimental material.

—We are, etc.,

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REFERENCES

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- Wierda, J. L., *Archives of Pathology*, 1943, **36**, 621.
- Carlson, A. J., and Hoelzel, F., *Gastroenterology*, 1949, **12**, 108.

Of Voles and Men

SIR,—A leading article on vole bacillus vaccination (1 March, p. 527) was based upon a recent study by Dr. Anne Maguire. Unfortunately her report¹ contained a number of factual misstatements about the Medical Research Council's trial of this vaccine. These have been given quite undue publicity by your leading article, and we therefore wish to correct them.

All the subjects in the Medical Research Council's trial of B.C.G. and vole bacillus vaccines in the prevention of tuberculosis were children in their penultimate term at school, and aged about 14½ years on entry to the study. No institutional patients were included. The trial started in September 1950 in the London area, and vole bacillus vaccine was not used until the trial was

extended to the Birmingham and Manchester areas in January 1951. The trial was undertaken by the Medical Research Council's Tuberculosis Research Unit, under the general direction of their Tuberculosis Vaccines Clinical Trials Committee. Full progress reports on this trial appeared in 1956,² 1959,³ and 1963.⁴

Dr. Maguire's report¹ concerns a group of about 180 mongol and other mentally defective patients given vole bacillus vaccine at Calderstones and Brockhall Hospitals in May 1950, when they were over 15 years of age. They thus comprise a completely separate group of subjects given a different batch or batches of vole bacillus vaccine at an earlier date than the participants in the M.R.C. trial. Dr. Maguire's group was included in a series of studies of vole bacillus vaccine, mainly in similar subjects, which was started by the late Dr. A. Q. Wells and his colleagues in 1944, with a grant from, but otherwise independently of, the Medical Research Council. Most of Wells's studies were made in mentally defective subjects living in institutions because they were known to be a group which was particularly susceptible to tuberculosis and therefore in particular need of the protection which vaccination was believed (and later found) to confer; when his studies started there was no effective tuberculosis chemotherapy, and, of course, no chemoprophylaxis. Two reports on this series of studies appeared in 1954,^{5,7} and provide the first accounts of lupoid reactions at the site of vole bacillus vaccination.

Dr. Maguire's confusion of these two quite separate investigations has clearly led to the blatant inaccuracies in the second and third sentences of your leading article. But this does not excuse your failure to put her findings in their proper perspective by an adequate review of the literature on this topic. In particular, you make no mention of the important report by Wylie, Bennett, and Swithinbank⁶ on the lesions found in Dr. Wells's studies. Nor apparently did you consult any of the main reports on the M.R.C. trial²⁻⁴ (all of which appeared in your columns), only a commentary⁸ upon the first of these reports. Moreover, you have misquoted this commentary; the incidence of lupus which required treatment, at the vaccination site, was about three per thousand subjects given vole bacillus vaccine in the M.R.C. trial, not 3%.

Wylie and others⁶ found a much higher incidence of lupoid reactions among mongols than among other mental defectives, and stated that they had not seen any such reactions among mentally normal subjects. They attributed this predisposition to lupoid formation in mongols to the peculiar texture and histology of the skin, rather than to an increased susceptibility to tubercle bacilli. They suggested that "the most important single factor in the development of a lupoid reaction seems to be secondary infection" at the vaccination site, that opportunities for secondary infection in mental deficiency institutions were high, and that scratching of the papules at the eruptive stage might also predispose to their subsequent infection.

The first report on the M.R.C. trial² stated that 22 cases of lupoid lesions requiring treatment (increased to 23 in the second report³) had been discovered by examination of the vaccination sites in the vole bacillus vaccinated participants. All had been referred for treatment before July 1955²—that is, all had developed within four and a half years of entry to the trial. No further cases were discovered, despite continued examination of the vaccination sites, up

to January 1959³—that is, during the next three and a half years. The third report⁴ contains no further reference to this topic because there was nothing further to report, and no further lesions of this type have come to notice, although the M.R.C. Tuberculosis and Chest Diseases Research Unit maintained personal and postal contact with participants until September 1960, and postal contact until December 1967. Thus a continuous review of the M.R.C. trial subjects has been made. No further review, as suggested in your leading article, appears to be called for, especially as Maguire reports that the lesions began to appear, in her patients also, between two and three years after vaccination.¹ Moreover, all the 23 cases in the M.R.C. trial occurred among the 3,778 participants given the "standard" batches of vaccine (substrains 2 to 4) and none among the 2,039 given the "sub-standard" batches (substrain 1).^{3,9} (This last substrain, incidentally, showed a protective efficacy against tuberculosis of 74% during a 10-year period, which is of the same high order as the other substrains of vole bacillus vaccine, and as the B.C.G. vaccine.) Wylie and others⁶ had also found an association between the development of lupoid lesions and the strength of the vaccine. Moreover, in 1959 Wells and Wylie¹⁰ described a method of preparation of vole bacillus vaccine which appeared to avoid the risk of development of lupoid lesions; 385 of their subjects had been given vaccine prepared in this way more than four years previously, and none had developed a lupoid lesion.

The explanation of the very different findings in the subjects now examined by Maguire,¹ compared with those in the M.R.C. trial, may thus be attributed both to differences in the populations studied and to technical shortcomings in the earliest batches of vole bacillus vaccine prepared by Wells.

If you had taken these reports into consideration in your leading article, we believe that this would have strengthened the case, which you advanced in your final paragraph, for a reconsideration of vole bacillus vaccination. Mitchell¹¹ reviewed the evidence in the light of his own observations, and put forward the same case, in 1962. His conclusion then was that "the development of lupus at the vaccination site may now be considered to be of historical interest only and is no longer a contraindication to the use of vole bacillus vaccine as a vaccinating agent in the future." There is nothing in Dr. Maguire's report¹ which need modify this conclusion.—We are, etc.,

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