ence is that in parts of Africa multiple disease is the rule and not the exception. As long as large amounts of money are spent on malariology and minimal attention is paid to paediatrics and mother and child health such figures should be treated with suspicion, if not despair.—I am, etc.,

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1 Sagnet, H., Morineaud, J. P., Revil, H., Thomas, J., and Masart, Y., *Médecine Tropicale*, 1967, 27, 606.

Radioactive Bromide Partition Test

SIR,—Any test that will help in the speedy and accurate diagnosis of tuberculous meningitis is to be welcomed, and the paper by Dr. B. K. Mandal and his colleagues (18 November, p. 413) provides useful information on this topic. I was, however, surprised both at their figures and those quoted of Bazin *et al.*¹ for the demonstration of *Mycobacterium tuberculosis* on direct microscopy of the cerebrospinal fluid (C.S.F.) in cases of tuberculous meningitis. Using the conventional technique of examining a thick film (4-5 drops) of C.S.F. stained with Ziehl-Neelsen stain we have demonstrated acid-alcohol-fast bacilli (A.A.F.B.) in 30 of the 32 cases of tuberculous meningitis seen at this hospital between March 1960 and the present time. A.A.F.B. were seen in the first specimen examined in 25 cases. Of the remaining five cases A.A.F.B. were first seen in the second specimen in three cases, in the third in one case, and in the fourth in the other case. *M. tuberculosis* was isolated from the first specimen cultured in 27 cases and from the second in one. Four specimens which were film-positive did not yield *M. tuberculosis* on culture (guinea-pig inoculation was not used).

These figures show that by using standard technique, with careful and prolonged searching of the film by more than one observer if necessary to avoid fatigue, more than 75% of cases should be diagnosed on the day of admission. If the cases diagnosed on the second C.S.F. specimen are included the figure rises to 87.5%, and these would be diagnosed before the time at which the bromide partition test result would be available. Furthermore, our cases covered a wide age range, from 2 months to 68 years, so that there was no selection of cases by age; nor was there any selection by acuteness of onset and hence stage of disease. This is not to decry this test but to emphasize what can be achieved in routine practice. It is clear that in four of our cases the bromide partition or some similar test would have been of considerable help in arriving at a confident diagnosis, as well as in cases of viral meningitis where there was a lowered C.S.F. sugar or a prolonged illness.

One of the factors which may have contributed to our high rate of positive films is that not only the cell content but also the sugar and protein levels in the C.S.F. were known at the time the film was examined and these, together with an accurate clinical history, have helped to spur on the sometimes flagging microscopist to greater effort! As noted by Dr. Mandal, the C.S.F. sugar may be normal in some cases and this was so in 13% of our cases (>45 mg/100 ml).

In a further 16% the level was in the equivocal range of 40-44 mg/100 ml. Hence I would agree that a normal C.S.F. sugar cannot be taken to exclude tuberculous meningitis any more than it can exclude any other common form of bacterial meningitis.^{2,3}—I am, etc.,

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- 1 Bazin, C., Blayo, M. C., Gaudebout, C., and Emile, J., *Presse Médicale*, 1969, 77, 623.
- 2 Fallon, R. J., *British Medical Journal*, 1964, 1, 1252.
- 3 Fallon, R. J., in *Annual Report on the Work of the Infectious Disease Hospitals and their Associated Laboratory Services 1970*, Glasgow, Western Regional Hospital Board, 1971.

Temperature Change and Multiple Sclerosis

SIR,—In a leading article (2 December, p. 506) you discuss the mechanism of the temperature effects in multiple sclerosis. This review makes no reference to the known alterations in physiological properties of nerve fibres produced by demyelination and deals in detail only with a recent paper¹ based on the study of a single patient.

The hypothesis that the aggravation of symptoms produced by a rise in body temperature is related to a direct effect of temperature on conduction is rejected on the following grounds: (1) that in the patient reported there was a discrepancy in the time course of rectal temperature change and symptomatology; and (2) the fact that a rise in temperature produces a small increase in conduction velocity in normal nerve fibres. The latter ground depends on the implicit assumption that when symptoms arise as a result of damage to nerve fibres they do so because of changes in conduction velocity. While such changes may contribute to disturbances of function when they are large and of unequal severity in different fibres subserving the same function, another property of demyelinated nerve fibres is likely to be more important. This is conduction block. There is direct experimental proof that demyelinating lesions produce conduction block both in peripheral² and central³ nerve fibres. This effect is temperature-sensitive. Davis and Jacobson⁴ have shown experimentally that reversible conduction block can develop in demyelinated nerve within 1°C of normal body temperature. And Rasminsky⁵ has shown that an increase of 0.5°C can lead to conduction block in a critically demyelinated internode and that a decrease of the same amount leads to restoration of conduction. Conduction block at just one demyelinated internode is the equivalent in functional terms of removing the affected fibre. From what is known of internodal length in central nerve fibres⁶ there must be many hundreds of internodes on each chain of fibres running from the eye to the visual cortex. Bearing in mind the frequency and size of plaques in the visual system in multiple sclerosis, it is to be expected that small alterations in temperature will produce a significant change in the number of fibres conducting through to the cortex.

There is, then, in the known physiological properties of demyelinated fibres, a sufficient explanation of the temperature effects in multiple sclerosis. This is not to deny that the hypothesis of Hopper *et al.* might be relevant. It does, however, seem an unnecessarily vulnerable hypothesis, given the

absence of any direct evidence about the effect of "hormones released in the thermoregulatory response to a cold stimulus" on nerve conduction and synaptic transmission. Their observations remain interesting. The mechanism of the discrepancies they found is not obvious, but clearly any physiological explanation must take into account the special properties of demyelinated nerve fibres.—We are, etc.,

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- 1 Hopper, C. L., Matthews, C. G., and Cleeland, C. S., *Neurology*, 1972, 22, 142.
- 2 McDonald, W. I., *Brain*, 1963, 86, 501.
- 3 McDonald, W. I., and Sears, T. A., *Brain*, 1970, 93, 583.
- 4 Davis, F. A., and Jacobson, S., *Journal of Neurology, Neurosurgery and Psychiatry*, 1971, 34, 551.
- 5 Rasminsky, M., *Archives of Neurology*. In press.
- 6 McDonald, W. I., and Ohlrich, G. D., *Journal of Anatomy*, 1971, 110, 191.

Drugs in Infertility

SIR,—I found Dr. G. I. M. Swyer's comments (18 November, p. 425) on the "Today's Drugs" article on drugs in infertility (21 October, p. 167) most interesting. He presented the traditional view that the postcoital test should be one of the preliminary investigations, whereas your expert had suggested that a seminal fluid analysis only was necessary in the initial assessment. I would also regard the postcoital test as one to be performed later, when information concerning the seminal fluid quality, the presence of ovulation, and hence the quality of the cervical mucus are known and the correct timing of the test can be arranged. These data are required for adequate interpretation of an abnormal postcoital test, a frequent occurrence in regularly cycling women with persistent infertility, and commonly seen when the patient is treated with clomiphene, presumably because of its anti-oestrogenic effect.

Hyperstimulation resulting from clomiphene, I would agree, is uncommon, but unless precautions similar to those described are taken it is more likely to occur.

Regarding the time of ovulation induced by clomiphene, if it occurs 8-12 days after a five-day course this would be a good reason for increasing the dose, as these time relationships within a cycle are not normal. In fact, optimum dosage should maintain the normal timing of ovulation, and the use of short courses of clomiphene to reduce cycle variance has in my experience not been very successful in leading to pregnancy. The use of clomiphene supplemented by HCG has in the hands of most workers been unrewarding, and I was interested to read of Dr. Swyer's success.

I was also pleased to see his comments on the use of mesterolone. In one of my eunuchoid patients treated with 150 mg mesterolone daily for 6 months measurement of plasma binding of testosterone showed that it was reduced, and plasma testosterone levels measured by a specific method for testosterone were increased to near normal male levels. This was associated with increased libido although there were no clinical signs of increased androgenicity. I am not aware of any measurement of testosterone production rates in these patients under treatment with mesterolone,

and such data would obviously be worth having.—I am, etc.,

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Intramuscular Injection and Coagulation Defects

SIR,—I read with interest the remarks of Dr. P. M. Jones (24 June, p. 770) on the danger of intramuscular injections in haemophiliacs. The danger also exists—and to a greater extent—in patients receiving anticoagulant therapy, especially heparin. In haemophiliacs only one system of coagulation is disturbed—that is, the intrinsic—whereas anticoagulant therapy influences both the intrinsic and the extrinsic systems. Heparin has also, through its antithrombin action, some effect on platelet aggregation. I have seen several patients treated with heparin by intravenous drip and one receiving an indanedione preparation in whom, after intramuscular injections, large intragluteal haematoma developed, extending into the muscles of the thigh. The haematoma formation was associated with acute exsanguinating anaemia and hypotension, necessitating prompt blood transfusion. One elderly patient—in another hospital—died because of rapidly progressive exsanguination and shock. Intramuscular injections should be avoided in every patient actually on anticoagulant treatment as well as in patients with other coagulation defects.

On the other hand, in my experience, the danger of intramuscular injections is far less in various thrombocytopenic states (idiopathic thrombocytopenic purpura, leukaemias, pancytopenias); it is known that platelets are not necessary for extrinsic coagulation. In such situations I have observed only transient extravasations (but without permanent crippling) and never large exsanguinating haematomas in the gluteal musculature. This was especially evident in several patients with severe thrombocytopenia due to marrow aplasia treated for many months with large intramuscular doses of testosterone propionate.—I am, etc.,

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1 Dyk, T., Piotrowski, M., and Kostecka, W., *Polski Tygodnik Lekarski*. In press.

Asthma Deaths

SIR,—In suggesting in your leading article (28 November, p. 443) an answer to the question of the cause of the recent rise in mortality from asthma you seem to rely entirely on the paper by the epidemiologist Stolley.¹ He found that asthma mortality had increased decisively only in those countries in which aerosol bottles containing five times the usual concentration of isoprenaline were available. Unfortunately, there are too many exceptions to this rule. Thus in Denmark and Sweden, with modest but definite increases in asthma mortality, no strong-isoprenaline aerosols were available. Japan also had none of these preparations but had a high mortality throughout. Norway had, as you mention, a definite rise in asthma mortality, but it had only one-quarter to one-tenth of the consumption of

strong-isoprenaline aerosols compared with the United Kingdom. The Netherlands, on the other hand, had some of these aerosols, but no rise in mortality at all. These incongruities make the assumption of Stolley most doubtful.

Much worse is that there is no evidence that isoprenaline is cardiotoxic. It has been used for 30 years, and if it had caused cardiac deaths this should have been noticed. Asthmatics who die suddenly in an attack (and often have used catecholamines a short time beforehand) usually show at necropsy as the most prominent change many viscous mucous plugs in the bronchi, which obstruct breathing. There is nothing to contradict the assumption that they die from lack of oxygen, and indeed the arterial oxygen tension is found to be dangerously low in such cases. This is much more likely to be the cause of death than the isoprenaline. Moreover, in those patients who inhale isoprenaline or other catecholamines incessantly tolerance to them quickly develops. Every practitioner who sees many asthmatics (but not the epidemiologist) knows patients who, at a sudden deterioration of their complaint, start inhaling every hour or half-hour and soon complain that "it does not help any longer." This is the first sign of tolerance, a danger signal not to be overlooked. It occurs with a concentrated aerosol as well as with a dilute one. I first described it 20 years ago² and have mentioned it repeatedly since.^{3,4} The tolerance has also been shown experimentally to develop in animals and in man.⁵

It follows that abuse of isoprenaline can have, at most, played an indirect part in the increase of asthma mortality by creating tolerance to itself. The patient with severe asthma who has no other treatment is then left with an isoprenaline nebulizer that no longer helps him, and he may become an easy victim of a renewed attack unless he has other efficient remedies—aminophylline, potassium iodide, or corticosteroids. It has been well documented that in most fatal cases the patient had little or no corticosteroid to protect him.

I believe this answer to your question should be considered.—I am, etc.,

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1 Stolley, P. D., *American Review of Respiratory Disease*, 1972, 105, 883.

2 Herxheimer, H., *The Management of Bronchial Asthma*, London, Butterworth, 1952.

3 Herxheimer, H., *Lancet*, 1968, 2, 216.

4 Herxheimer, H., *Lancet*, 1972, 1, 98.

5 Connolly, M., Davies, D. S., Dollery, C. T., and George, C. F., *British Journal of Pharmacology*, 1971, 43, 389.

Fracture of Lippes Loop

SIR,—Last¹ has recently reported 15 cases of fracture of the Lippes loop in utero; the average time the loop had been retained before fracture was 38 months, with a range of 22–67 months.

At this hospital we have seen a number of women whose loop has fractured apparently while being removed (though possibly it had broken spontaneously in utero in at least some cases). In virtually all these cases the loop had been inserted more than two years previously. Since every patient with a fractured loop has had to be admitted to hospital for removal of the remnant under anaesthetic, we have adopted the practice of removing loops after two years (that is, at the second annual check-up) and inserting

a fresh loop at the same clinic attendance. Many of the loops removed more than two years after insertion have had a rough, pitted surface and have lost their natural elasticity. Could this be due to a chronic "foreign body reaction" on the part of the endometrium?—I am, etc.,

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1 Last, P. A., *Journal of Obstetrics and Gynaecology of the British Commonwealth*, 1972, 79, 190.

Radiology of Swallowed Earthworm

SIR,—It is well known¹ that roundworms (*Ascaris lumbricoides*) may readily be demonstrated on contrast examination of the small gut. They may show both as an intraluminal filling defect and because the worm's alimentary canal is outlined with ingested barium suspension. So far as I can ascertain, no one has previously reported the radiological findings with earthworms (*Lumbricus terrestris*) in the human alimentary tract.

The accompanying plain abdominal radiograph of a 3-year-old child shows material which is pretty obviously "dirt," yet it is arranged in an orderly fashion in a coil. Accordingly there was no hesitation in identi-

fying the opaque parts as ingested soil in the alimentary tract of an earthworm lying in the stomach. This was confirmed when the history was obtained. The child had indeed swallowed an earthworm and the worried parents had brought him up for reassurance.—I am, etc.,

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1 Shanks, S. C., in *A Textbook of X-Ray Diagnosis*, ed. S. C. Shanks, and P. Kerley, Vol III, 3rd edn. London, H. K. Lewis, 1958.

Trichuris trichiura Infestation

SIR,—It should be emphasized that the *Trichuris trichiura* infestations reported by Dr. D. M. Lynch and others (14 October,