Thymectomy for Myasthenia Gravis

SIR,—In your leading article (2 September, p. 543) you discussed the evidence for the existence of a transmissible agent responsible for neonatal myasthenia gravis. Dr. A. D. Korczyn offered an alternative suggestion (30 December, p. 793) implicating anticholinesterase drugs. If the latter were true a higher incidence of neonatal myasthenia would occur in women taking high doses of medication or for more prolonged periods, or both. This, however, is not the case. Furthermore, several cases of neonatal myasthenia gravis have been reported where the mother was not receiving medication.¹ In addition, drug requirements decrease in approximately one-third of pregnant women. Other reports provide data that do not support Dr. Korczyn's suggestions.²

It has become increasingly evident that thymectomy is followed by improvement and stable remissions in a significant percentage of cases.³ Yet no attempt has been made to investigate differences in the incidence of neonatal myasthenia between the pre-thymectomy and postthymectomy groups. In any such analysis it is important to consider the clinical classification of the disease⁴ because: (1) children born to women with ocular myasthenia gravis do not develop neonatal myasthenia;¹ (2) thymectomy is not generally performed in ocular myasthenia, and therefore this category should be excluded; (3) the severity of the disease (that is, the clinical classification at the peak of symptoms) influence the prognosis both before and after thymectomy; and (4) symptoms during pregnancy are variable and do not necessarily reflect the severity of the disease.

Review of the reported series shows a wide discrepancy in the incidence (4-50%).¹ Among the lowest (4%) is the one reported by Fraser⁵ consisting predominately of patients who had undergone thymectomy. A previous report from this institution⁶ recorded 10 out of 69 (14%) cases of neonatal myasthenia. We have now examined the incidence of neonatal myasthenia among 800 myasthenic women (190 postthymectomy). The incidence of neonatal myasthenia gravis in women who had not undergone thymectomy was twice that in the thymectomy group. Our late colleague Dr. K. E. Osseman⁶ indicated that 26% of pregnancies in myasthenic mothers resulted in spontaneous abortion. Our present review indicates that spontaneous abortions are more common in the non-thymectomy group. Several of the more severe cases of myasthenia, particularly in the non-thymectomy group, had their pregnancies interrupted for medical reasons, and in any comparison of the incidence of neonatal myasthenia these factors must be considered.

Our preliminary data confirm that the variability of the symptoms during pregnancy does not appear to be related to the incidence of neonatal myasthenia gravis. Mothers who gave birth to children with neonatal myasthenia were primarily those in whom the disease reached the more severe forms either before or after the pregnancy. It is obvious that when this factor is taken into consideration the difference is even more pronounced. The effects of thymectomy on myasthenia may be delayed for months or even years.³ All cases of neonatal myasthenia in our thymectomy group occurred in women

who had not as yet reached complete remission.

These data seem to indicate that the presence of the thymus and possibly a thymic factor play a role in neonatal myasthenia gravis.—We are, etc.,

ANGELOS E. PAPATESTAS
GABRIEL GENKINS
ALLAN E. KARK

Mount Sinai Hospital and School of Medicine,
City University,
New York

- 1 Namba, T., Brown, S. B., and Grob, D., *Pediatrics*, 1970, 45, 488.
- 2 Stern, G. M., Hall, J. M., and Robinson, D. C., *British Medical Journal*, 1964, 2, 284.
- 3 Papatestas, A. E., Alpert, L. I., Osseman, K. E., Osseman, R. S., and Kark, A. E., *American Journal of Medicine*, 1971, 50, 465.
- 4 Osseman, K. E., *Myasthenia Gravis*. New York, Grune and Stratton, 1958.
- 5 Fraser, D., and Turner, J. W. A., *Proceedings of the Royal Society of Medicine*, 1963, 56, 379.
- 6 Osseman, K. E., in *Medical, Surgical and Gynecologic Complications of Pregnancy*, ed. J. J. Rovinsky and A. F. Guttmacher. Baltimore, Williams and Wilkins, 1965.

Subclinical Brucellosis

SIR,—Dr. Eirian Williams (31 March, p. 791) writes that in brucellosis the term "subclinical" "should be used with care." What is meant by this statement? Subclinical is a precise and self-explanatory term to describe a perfectly obvious state. Why then should it be used with care? If Dr. Williams does not recognize subclinical infection or doubts that it exists, then he is simply ignoring the observations of others; the subclinical state in brucellosis is well documented.¹⁻⁵

Further on in his article Dr. Williams admits that in symptomless veterinary surgeons who are continually exposed to brucella antigen all the usual serological tests are positive in high dilution. With the use of what term other than subclinical does he describe their infection?—I am, etc.,

R. J. HENDERSON

Public Health Laboratory,
Royal Infirmary,
Worcester

- 1 Cayton, H. R., Osborne, A. D., and Sylvester, D. G. H., *Lancet*, 1967, 2, 836.
- 2 Drole, P., *Archives of Internal Medicine*, 1932, 50, 373.
- 3 Foley, B. V., Clay, M. M., and O'Sullivan, D. T., *Irish Journal of Medical Science*, 1970, 3, 457.
- 4 Foley, B. V., and O'Flynn, J. G. A., *Irish Veterinary Journal*, 1971, 25, 42.
- 5 Henderson, R. J., *Lancet*, 1967, 2, 353.

Toxoplasma gondii Oocysts in the Faeces of Naturally Infected Cat

SIR,—In the course of a general survey of gastrointestinal parasites in domestic animals we found *Toxoplasma gondii* oocysts in one stray cat (out of 250 examined). Reports about naturally infected cats¹⁻⁴ are extremely rare, and this finding (the first case described in Italy) is reported because of its considerable epidemiological importance to man.

A 4-month-old male stray cat in apparently good health was captured in the outskirts of Bologna. A dye test (Aagaard's method⁵) showed a titre of < 1:10. His faeces were mushy and dark brown and microscopic examination showed many *Isospora felis* and *T. gondii* oocysts after concentration in sodium nitrate and sugar solution (specific gravity 1300). *T. gondii* oocysts kept in 2.5% potassium dichromate sporulated after 16 days. The sporulated oocysts were

washed in saline in a centrifuge and injected intraperitoneally into 5 dye-test-negative mice (< 1:10). Oocysts were also given orally to two cats (2-month-old), one of them (cat A) showing a dye test titre of < 1:10 and the other (cat B) of 1:50.

After four weeks all the inoculated mice had a dye test of > 1:250 and the microscopic examination of their brains showed typical toxoplasma cysts. The faeces from cat A were negative for *T. gondii* throughout the whole observation period (45 days) but a dye test on the 16th day reached 1:250. This fell to 1:50 on the 26th day and remained unchanged. On the third day occasional sporulated oocysts were found in the faeces of cat B, these apparently representing a transit of the ingested inoculum. The faeces became negative on the following day. On the 27th day new, abundant, and unsporulated *T. gondii* oocysts appeared. They persisted for three days. Later, however, the faeces remained negative. The original dye-test titre of 1:50 reached > 1:1,250 on the 16th day and remained so till the animal was killed (45th day). *T. gondii* cysts were isolated in mice injected with brain material from cat B.

These data confirm that cats may be responsible for the natural spread of *T. gondii* oocysts. The oocyst displays its infectivity after some days at sporont maturation (16 days in the present case) but sometimes seems to be already infective at emission (transit oocysts from contaminated food). The marked rise of the dye test titre associated with emission of oocysts in cat B (already positive before the experimental infection) seems to show that cats who have previously had *T. gondii* infection may become spreaders again by a renewed oral load of parasites. The results of the dye test in cats excreting *T. gondii* oocysts do not seem to represent a reliable indication for epidemiological investigations on cats, because their range may vary from comparatively high values (cat B) down to nothing (naturally infected stray cat).—We are, etc.,

S. PAMPIGLIONE
G. POGLAYEN
B. ARNONE

Cattedra di Parassitologia,
Facoltà di Medicina Veterinaria,
Università di Bologna,
Italy

F. DE LALIA

Istituto di Malattie Infettive,
Università di Milano,
Centro Studi sulla Toxoplasmosi,
Milano, Italy

- 1 Jacobs, L., in *Advances in Parasitology*, vol. 5, ed. B. Dawes. London, Academic Press, 1967.
- 2 Wallace, G. D., *Journal of Infectious Diseases*, 1971, 124, 227.
- 3 Janitschke, K., and Kühn, D., *Berliner und Münchener Tierärztliche Wochenschrift*, 1972, 85, 46.
- 4 Wermer, J. K., and Walton, B. C., *Journal of Parasitology*, 1972, 58, 1148.
- 5 Berengo, A., de Lalla, F., Bechelli, G., and Cavallini-Sampieri, L., *Minerva Medica*, 1969, 60, 377.

Smoking and Ischaemic Heart Disease

SIR,—It is stated in the interesting paper by Dr. Nicholas Wald and others (31 March, p. 761) that "there is a well recognized correlation between smoking and atherosclerosis." The data cited in support show, however, that there is an association between smoking and clinical ischaemic heart disease. It is at least possible that these are not two identical propositions.

It is true that death from myocardial ischaemia is unlikely in the absence of coronary atheroma but, as Morris¹ has said, many are susceptible to the latter but far

fewer suffer from the former. The degree of coronary atheroma discovered in persons killed accidentally has been studied in many parts of the world, and the condition has been found to be equally widely distributed in the United States and United Kingdom. Yet, in contrast, the mortality from ischaemic heart disease is markedly different in comparable populations, the U.S.A.F.:R.A.F. ratio approximating to 10:1.² The opinion expressed by Kannel³ that it is the presence of an effective collateral circulation which determines the clinical picture offers a reasonable explanation of the anomaly.

Carboxyhaemoglobin is easily determined and is therefore a convenient marker of the products of combustion. It is possible that, because of this, carbon monoxide is being artificially promoted as a cause of disease. Workers in Los Angeles⁴ have attempted to relate atmospheric CO levels to an increased fatality rate from myocardial infarction; in fact, any relationship must be attributed to atmospheric pollution as a whole. In the same way, postmortem studies designed to show atherogenic properties of cigarette smoke⁵ fail to take into account the life style of heavy smokers.

The case for an association between smoking and ischaemic heart disease seems proved beyond doubt. But rather than to attribute an atherogenic property to cigarettes in general and carbon monoxide in particular (Dr. Wald and his colleagues do not claim this to be necessarily so), it might be more valid, and in keeping with the "collateral" theory, to suggest that the carboxyhaemoglobin results reported by them were more significantly reflecting the levels of nicotine, which is known to have a marked pharmacological effect on the cardiovascular system.—I am, etc.,

J. K. MASON

R.A.F. Institute of Pathology and Tropical Medicine,
Haltom, Aylesbury, Bucks

¹ Morris, J. N., and Dale, R. A., *Proceedings of the Royal Society of Medicine*, 1955, 48, 667.

² Mason, J. K., *British Medical Journal*, 1963, 2, 1234.

³ Kannel, W. B., *New England Journal of Medicine*, 1970, 282, 1153.

⁴ Cohen, S. I., Deane, M., and Goldsmith, J. R., *Archives of Environmental Health*, 1969, 19, 510.

⁵ Auerbach, O., Hammond, E. C., and Garfinkel, L., *New England Journal of Medicine*, 1965, 273, 775.

Löffler's Syndrome

SIR,—I am grateful to Dr. Alex Sakula for his letter (7 April, p. 54) referring to the case reported by myself and Dr. C. C. Bailey (24 February, p. 460) of a 4-year-old boy with lymphosarcoma presenting as Löffler's syndrome. As Dr. Sakula reaffirms, Löffler's syndrome refers to a transient condition of eosinophilia with pulmonary radiological opacities; though originally described in association with *Ascaris lumbricoides* infestation, the same syndrome has been observed in a multitude of conditions since then and is thought to be an allergic manifestation.

We described this case as Löffler's syndrome because the lung changes were typical of this condition radiologically; they cleared within a few weeks, as the eosinophilia subsided, in response to steroid therapy. The radiological appearances have not recurred, even when the patient eventually developed his florid lymphosarcoma. We feel that this

is adequate evidence that the lung changes were part of an "eosinophilia syndrome" which is known as Löffler's syndrome, and not that they were, as Dr. Sakula suggests, due to lymphosarcomatous infiltration. To the best of our knowledge Löffler's syndrome, which has been described in association with many and varied conditions, has never before been observed with lymphosarcoma.—I am, etc.,

RICHARD H. CAMPBELL

Royal Hospital,
Sheffield

Advertising of Antibiotics

SIR,—I should like the opportunity to comment on the letter from Drs. J. D. Williams and A. M. Geddes (14 April, p. 116), particularly with reference to the paragraph about cephadrine. First they refer to the "advertising booklet produced by one of the companies" and at the end of the letter they "urge [the pharmaceutical companies'] medical departments to curb the enthusiasm of commercial colleagues in the content of their promotional literature." The publication referred to is a technical booklet available usually on request. This is prepared by the medical department for the purpose of providing technical information and, as such, can hardly be described as promotional.

Unfortunately at the time of the launching of cephadrine the only in vitro figure we had available in the United Kingdom for the minimum inhibitory concentration against penicillinase-producing staphylococci was the one quoted. This was against one strain available in the Squibb Institute, New Jersey. The claim that cephadrine is effective was based on clinical and bacteriological evidence in trials, using the disc sensitivity test. In common with your correspondents we noted the discrepancy between mean inhibitory and peak serum concentrations and initiated further in vitro tests which have been carried out in a number of hospital laboratories in this country. These have shown that the minimum inhibitory, and indeed bactericidal, concentration for the penicillinase-producing organisms to be almost invariably below the mean peak serum concentration following a 500-mg dose of cephadrine.

Drs. Williams and Geddes also criticize the fact that cephadrine's sensitivities are compared only with those of ampicillin, tetracycline, and chloramphenicol. I agree that it might have been more helpful to include other antibiotics, but it is logical surely to compare it with three widely used broad-spectrum antibiotics. While agreeing that chloramphenicol should be prescribed only for limited indications, in a world-wide company it was necessary to carry out this research bearing in mind the most common alternatives. Regrettable though it may be, chloramphenicol is still widely prescribed throughout the world and, to judge by last years' prescription figures, there has either been a higher incidence of typhoid than notified or else it is still being prescribed for less serious conditions in the United Kingdom. Is showing that a cephalosporin compares favourably with a more toxic alternative to be deprecated?—I am, etc.,

T. K. CLARKE

Medical Adviser,
E. R. Squibb and Sons Ltd.

Twickenham, Middlesex

"Hypersensitivity Hepatitis" Associated with Administration of Cyclizine

SIR,—Cyclizine (1-benzhydryl-4-methyl piperazine) hydrochloride, an antihistamine used mainly in the prevention and treatment of nausea and vomiting, has been available since 1954. During this time there has been no reported case of jaundice attributable to the drug. Nevertheless, we have recently seen a patient in whom a diagnosis of "hypersensitivity hepatitis" induced by cyclizine seems very likely.

The patient, an 8-year-old white girl, became ill with malaise, anorexia, nausea, vomiting, and jaundice in the middle of July 1972. The serum bilirubin concentration was 5.5 mg/100 ml, serum alanine aminotransferase (SGPT) 460 units, and alkaline phosphatase 45 K.A. units. Hepatitis B antigen was not found in the serum. A diagnosis of infective hepatitis was made and she was treated with bed rest alone. There were no known cases of infective hepatitis in the patient's family, among her friends, or at her school at that time. Starting eight days before the onset of the illness, she had taken 25 mg of cyclizine hydrochloride by mouth daily for five days to prevent motion sickness. She had not previously received this drug and had taken no others recently. There was a strong family history of penicillin sensitivity and the patient had on a number of occasions developed diarrhoea while receiving that antibiotic; whether or not the latter was due to penicillin sensitivity is not known. By the end of August she was well enough to return to school. On 24 September she was again given 25 mg of cyclizine by mouth to prevent motion sickness. The following day she felt ill and her urine was noted to be dark, and a day later jaundice was obvious. Her urine contained 1+ urobilin and 2+ bilirubin, the serum bilirubin level was 5.2 mg/100 ml, SGPT 400 units, and alkaline phosphatase 37 K.A. units. The serum was again negative for hepatitis B antigen. She was treated with bed rest alone. Eight weeks passed before she was considered well enough to get up and 16 weeks before the serum bilirubin level returned to normal. Liver biopsy was not performed. The patient's serum was examined for antibodies against cyclizine hydrochloride: both a cyclizine-induced Coombs test and a Coombs consumption test for "anti-liver" antibodies were positive. These tests were negative when repeated on the serum of other individuals receiving cyclizine and on jaundiced patients who had not taken the drug. An attempt to induce the patient's lymphocytes to transform with cyclizine failed.

While accepting that acute viral hepatitis cannot entirely be excluded as the cause of our patient's illness, we believe that the recurrence of hepatitis following an inadvertent challenge with cyclizine and the serological findings are more in keeping with a hypersensitivity reaction to the drug. The mechanism or mechanisms involved in "hypersensitivity (or allergic) hepatitis" have not been elucidated, but in some cases the drug is presumed to act as a hapten. This may explain our failure to induce the patient's lymphocytes to transform when exposed to cyclizine.—We are, etc.,

M. C. KEW

J. SEGEL

A. ZOUTENDYK

University of the Witwatersrand
South African Institute for Medical Research,
Johannesburg

Arterial Haemorrhage in a Drug Addict

SIR,—The recent paper by Mr. R. Pollard (31 March, p. 784) discussing some surgical complications of intravascular injections in