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 hypothesis (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 for more prolonged periods, or both. This, however, is not the case. Furthermore, several cases of neonatal myasthenias have been reported where the mother was not receiving medication. In addition, it is well recognized that 25% of patients with myasthenia gravis have a higher than normal incidence of thymectomy. Most of these patients have been female, and the proportion of cases is approximately one-third of pregnant women. Other reports provide data that do not support Dr. Korczyn's suggestions.

It has become increasingly evident that there is obvious benefit from improvement and stable remissions in a significant percentage of cases. Yet no attempt has been made to investigate differences in the incidence of neonatal myasthenia between the primary myasthenia and postthymectomy groups. Any such attempt is important to consider the clinical classification of the disease because: (1) children born to women with ocular myasthenia gravis do not develop neonatal myasthenia; (2) thymectomy is generally performed in ocular myasthenia, and therefore this category should be excluded; (3) the severity of the disease (that is, clinical classification of the case 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%). Among the lowest (4%) is the one reported by Fraser consisting predominately of patients who had followed by improvement. A previous report from this institution, recorded 10 out of 65 (14%) cases of neonatal myasthenia. We have now examined the incidence of neonatal myasthenia among 800 women with myasthenia gravis who have undergone thymectomy. The incidence of neonatal myasthenia gravis in women who had undergone thymectomy was twice that in the thymectomy group. Our late colleague Dr. K. E. Osmerman, who had performed thymectomy 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, drug requirements may 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. 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. Papastas, Gabriele Jenkins Allan E. Kirk

Mount Sinai Hospital and School of Medicine, New York.


Subclival Brucleosis

Sir,—Dr. Eirian Williams (31 March, p. 791) writes that in brucellosis the term "subclival" should be used with care. What is meant by this statement? Subclival 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 subclival infection or doubts that it exists, then he is simply ignoring the observations of others; the subclival state in brucellosis is well documented.

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 subclival does he describe their infection?—I am, etc.,

R. J. Henderson

Public Health Laboratory, Royal Infirmary, Worcester.


Toxoplasma gondii Oocysts in the Faces 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 natural infection 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 Bolonia. A dye test (Aaard's method) showed a titre of <1:10. His faeces were examined in dark brown and microscopic examination showed many Isospora felis and T. gondii oocysts after concentration by sucrose flotation (specific gravity 1:50). 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 intraperitonally 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 titre 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 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 >1:250 on the 16th day and remained so till the animal was killed (45th day). T. gondii cysts were isolated in mice infected 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 only after a delay of about 15 months (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 the cat infection (positive before the experimental infection) seems to show that cats who have previously had T. gondi infection may become spreaders again by a renewed oral load of oocysts. The results of not excruting 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. Foglayen

B. Argentina

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

F. de Lalia

Instituto di Malattie Infettive, Policlinico, Roma, Italy

Centro Studi sulla Toxoplasmosi, Napoli, Italy


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. We question the results 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 Morris 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. U.S.A.F.: R.A.F. ratio approximating to 10:1. The opinion expressed by Kannel is that it is the presence of an effective collateral circulation which determines the clinical picture; 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 Angeles have attempted to relate atmospheric CO levels to an increased fatality rate from myocardial infarction; in fact, any relationship must be attributed to atmospheric conditions as a whole. In the same way, postmortem studies designed to show atherogenetic properties of cigarette smoke failed to take into account the life style of heavy smokers. This renders for an association between smoking and ischaemic heart disease seems proved beyond doubt. But rather than to attribute an atherogenetic 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, Halton, Aylesbury, Bucks

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 cephradine. First they refer to the "advertising booklet produced by one of the companies" and at the end of the letter they say "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 bulletin 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 cephradine the only in vitro figure we had available in the United Kingdom for the minimum inhibitory concentration against penicillinase-producing staphylococci was one quoted. This was against one strain available in the Squibb Institute, New Jersey. The claim that cephradine 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. The latest results with a number of cephalosporins indicate that cephradine is a minimum inhibitor, and indeed bactericidal, concentration for the penicillinase-producing organisms to be almost invariably the mean peak serum concentration following a 500-mg dose. Drs. Williams and Geddes also criticize the fact that cephradine'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. Regrettably 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 it shown that a chlorosulphon compares favourably with a more toxic alternative to be deprecated?—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 cephradine. First they refer to the "advertising booklet produced by one of the companies" and at the end of the letter they say "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 bulletin 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 cephradine the only in vitro figure we had available in the United Kingdom for the minimum inhibitory concentration against penicillinase-producing staphylococci was one quoted. This was against one strain available in the Squibb Institute, New Jersey. The claim that cephradine 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. The latest results with a number of cephalosporins indicate that cephradine is a minimum inhibitor, and indeed bactericidal, concentration for the penicillinase-producing organisms to be almost invariably the mean peak serum concentration following a 500-mg dose. Drs. Williams and Geddes also criticize the fact that cephradine'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. Regrettably 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 it shown that a chlorosulphon compares favourably with a more toxic alternative to be deprecated?—I am, etc.,

RICHARD H. CAMPBELL

Royal Hospital, Sheffield

“Hypersensitivity Hepatitis” Associated with Administration of Cyclazine

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 the years from 1964 to 1972, there was 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 cyclazine seems very likely.

The patient, an 8-year-old white girl, became ill with malaise, anorexia, nausea, vomiting, and jaundice in the middle of February; the bilirubin concentration was 5·5 mg/100 ml, serum alanine aminotransferase (SGPT) 460 units, serum aspartate transaminase (SGOT) 500 units, and serum alkaline phosphatase 10 units. The 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 she was well enough to return to school. On 24 September she was again given 25 mg of cyclazine by mouth to prevent motion sickness. The following day she felt ill and her urine became dark, and a day later jaundice was obvious. Her urine contained 1+ urobilin and 2+ bilirubin, serum bilirubin level was 5·2 mg/100 ml, SGPT 500 units, SGOT 15 units, and alkaline phosphatase 120 units. The serum was again negative for hepatitis B antigen. She was treated with bed rest alone. Eight weeks post discharge 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 cyclazine hydrochloride: both a cyclazine-induced Coombs test and a Coombs test on the patient’s own serum were both positive. These tests were negative when repeated on the serum of other individuals receiving cyclazine and at least one of them had not taken the drug. An attempt to induce the patient’s lymphocytes to transform with cyclazine 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 cyclazine 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 cyclazine.—We are, etc.,

M. C. K. J. SIGEL 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