Rhesus Isoimmunization and Therapeutic Abortion

SIR,—Mr. W. L. Whitehouse (21 June, p. 759), like myself¹ and many others, again calls attention to the potential dangers of rhesus isoimmunization in therapeutic abortion. He asks that the extent of this problem be further and scientifically investigated.

There are, in fact, one or two further facets to be considered. Firstly, all of us are aware of the numbers of women whose first continuing pregnancy is complicated by rhesus isoimmunization induced by a previous criminal or spontaneous abortion, and it would seem clear that we should include within the scope of an investigation all primigravida women who are aborting, whether this be criminal, spontaneous, or therapeutic. Secondly, it has been claimed in some quarters that different techniques of therapeutic abortion carry different risks of rhesus isoimmunization, and this, in addition, should certainly be investigated.

Present stocks of anti-D immune globulin are far too low to allow of routine administration to all Rh-negative nulliparous women undergoing abortion, and it is doubtful if stocks would admit of administration to all such women in whom the Kleihauer test is positive. Up to now, therefore, there has been no clinical indication even to do the Rh test on women admitted with complete septic or spontaneous abortion and certainly not to perform the much more complicated and time-consuming Kleihauer test. I fancy that we are once more up against the problem of the peripheral hospitals with large numbers of cases having to preserve their laboratory facilities for real clinical necessity and the central hospitals with adequate laboratory facilities with small numbers of cases unable to obtain statistically significant data without undue delay.—I am, etc.,

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Survival after 204 Defibrillations

SIR,—We wish to report the case of a patient who required ventricular defibrillation 204 times in 48 hours and who subsequently returned to his previous employment. The administration of dexamethasone was followed by the cessation of the arrhythmia when other antiarrhythmic agents had failed. There was no disturbance of acid-base balance.

A 62-year-old clerical worker had a posterior myocardial infarction one year previously and was mildly hypertensive. He was being treated with digoxin and bendrofluazide with potassium chloride (Neo-NaClex-K). He was admitted to the coronary care unit on 15 July 1968, having collapsed for 10 minutes shortly after a brief period of strenuous exercise.

Two hours later a single short salvo of ventricular ectopic beats was observed, and he was given intravenous lignocaine at a rate of 2 mg./min. Twenty minutes later he

developed ventricular fibrillation with no premonitory ectopic beats. Defibrillation with a 150 watt-second shock successfully restored sinus rhythm within 90 seconds of the onset of the arrhythmia. Intravenous procainamide 400 mg. did not prevent a further attack of ventricular fibrillation eight minutes later, nor did intravenous phenytoin sodium 250 mg. appear to have any effect on the prevention of ventricular fibrillation. During the next 48 hours the patient required defibrillation 201 times for recurrent ventricular fibrillation, and between attacks full consciousness was regained. The following methods of treatment were tried:

- (1) Procainamide 100 mg. intramuscularly four-hourly and up to 200 mg. intravenous doses to a total of 2.5 g.; lignocaine 2 mg./min. intravenously and up to 200 mg. intravenous doses to a total of 7 g.; phenytoin sodium 100 mg. intramuscularly four-hourly and intravenous doses of up to 250 mg. to a total of 2 g.; mepyrmine 50 mg. intravenous and quinidine sulphate 300 mg. intravenously. None of these reduced the frequency of ventricular fibrillation.
- (2) Potassium-glucose-insulin infusion¹ was followed by an increase in the occurrence of ventricular fibrillation.
- (3) Transvenous pacing at rate of 90/min. (patient originally in sinus rhythm at 65/min.) was thought to provide marginal benefit.
- (4) Propranolol 5 mg. intravenously had no effect alone, but was followed by freedom from ventricular fibrillation of up to one hour on two occasions when combined with 0.6 mg. of atropine, but hypotension prevented its further use.
- (5) 40 ml. of magnesium sulphate 20% intravenously on three occasions was followed by remission of attacks of ventricular fibrillation of up to one hour. This was given because of the possibility of a diuretic-induced magnesium deficiency rendering the patient more susceptible to the toxic effects of digoxin.^{2,3} Serum magnesium was raised from 1.6 mEq/l. to 6.8 mEq/l.
- (6) Dexamethasone 4 mg. intravenously was followed by complete cessation of attacks of ventricular fibrillation. Intramuscular maintenance doses of dexamethasone were continued and lasted off over the next 10 days.

Sodium bicarbonate 100 mEq intravenously was given initially, but repeated estimations of arterial bicarbonate, pH, and PCO₂ showed virtually no deviation from normal throughout the 48-hour period. This absence of expected metabolic acidosis was attributed to immediate defibrillation. Nasal oxygen and intramuscular penicillin were administered throughout the period. Serum urea, sodium, potassium, and calcium levels remained within normal limits. Following a six-week otherwise uneventful stay in hospital, the patient was discharged receiving frusemide 40 mg. each morning. After three months he resumed work as a clerk, and after six months is maintaining reasonable health and mental agility. He shows no evidence of defect of personality or intellect.

It is felt that this case demonstrates a number of important points in the management of recurrent ventricular fibrillation. Firstly, that repeated ventricular fibrillation, especially in a person whose heart is not badly damaged, is not necessarily associated with a poor immediate or long-term prognosis; secondly, that intravenous dexamethasone appeared to have a dramatic prophylactic effect, where all other drugs partially or completely failed; thirdly, that magnesium sulphate may be of value in these circumstances; and, fourthly, that the body's

acid-base balance remains virtually unaltered if defibrillation is immediate and successful.

We would like to express our thanks to Dr. J. J. Bourke, Dr. G. M. Kirk, the sisters and nursing staff of the intensive and coronary care units.

—We are, etc.,

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Acute Infective Gastroenteritis

SIR,—Few things connected with the bowel are crystal clear. I have followed with interest the correspondence on the place of antibiotics in infective gastroenteritis, and now feel in need of reassurance. Dr. Mary J. Wilmers (31 May, p. 573) and Dr. T. P. Mann (28 June, p. 823) are, I take it, principally discussing alternative methods of minimizing the risk of cross-infection within a specialized gastroenteritis unit.

It would surely not be their intention that this controversy should be extended to the treatment of the individual patient with gastroenteritis contracted outside such a unit? Most paediatricians do not prescribe antibiotics if symptoms are mild, and certainly not until the results of stool culture are known. Conversely, few would feel justified, on the evidence presently available, in withholding antibiotics from a child judged to be "severely ill" when first seen. I know of no certain way of excluding *Escherichia coli* septicaemia, invasive salmonellosis, or Flexner dysentery on clinical grounds. It would be a pity if anyone were to interpret the correspondence as an advocacy for either the universal prescribing or the universal withholding of antibiotics in all new cases of infective gastroenteritis.

There is at the moment no adequate evidence to support either of these extreme views, and I do not believe either correspondent would wish to be interpreted in such a way.—I am, etc.,

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Creatinine Content of Urine and Bacterial Growth

SIR,—The estimation of creatinine clearance remains the most generally useful and practical measure of glomerular function in patients with renal disease,^{1,2} and has been used extensively in patients with urinary infection. There have, however, been some qualms about the possibility that bacteria might destroy creatinine or elaborate substances which interfere with its estimation. This was therefore investigated in the course of other studies on patients with urinary tract infection.

Ninety infected urine samples were examined. The infecting organisms were those commonly encountered in patients with urinary tract infections: *Escherichia coli* (34), *Proteus mirabilis* (10), *Pseudomonas aeruginosa* (8), and *Strepto-*

coccus faecalis (4). Mixed infections (including *Pseudomonas*, *Staphylococcus aureus*, *Klebsiella*, and *Proteus* spp.) were present in 21 urines from patients with gross urological abnormalities. In 13 instances urine samples were collected following the administration of antibiotics.

All samples were transferred to the laboratory immediately after collection, and bacterial counts carried out by the surface plating method. Part of the sample was immediately refrigerated, while the remainder was incubated at 37° C. overnight. At the end of this period further bacterial counts were carried out, and the creatinine content of both the refrigerated and incubated samples was measured on the Technicon auto-analyser.

In 12 urines which contained 10⁸ organisms/ml., and in nine urines from treated patients, the counts did not rise detectably on incubation. Otherwise, following overnight incubation the bacterial counts rose to 10⁸ or more per ml., representing a rise of more than 1,000-fold in 16 urines, 100-fold in nine, and 10-fold or more in the remainder. Urinary creatinine concentrations ranged from 14 to 236 mg./100 ml. In none of the 90 samples examined was there any change in urine creatinine content outside the analytical error of the method.

The results of these studies thus clearly show that over a wide range of creatinine concentrations bacterial multiplication within the urine over a period of up to 24 hours has no effect on urinary creatinine content. We have therefore concluded that estimations of urinary creatinine for clearance or other purposes are not invalidated by the presence of bacteria in the sample.—We are, etc.,

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Manson and Malaria

SIR,—The article on Aberdeen Medical School (28 June, p. 816) contains the statement that Sir Patrick Manson discovered the cause of malaria. This distortion of medical history ought not to be allowed to pass.

The malaria parasite was discovered by Alphonse Laveran in 1880 and its transmission by a mosquito by Ronald Ross in 1897. Manson must be given credit for the mosquito-malaria theory, which he formulated and put forward in 1894 and again in 1896, and which guided and stimulated Ross. It remained, however, only a theory until Ross and later workers actually transmitted the malaria parasite by the bite of a mosquito.

The scepticism with which the mosquito-malaria theory was received is illustrated by a story which Sir Patrick's son-in-law, the late Sir Philip Manson-Bahr, used to tell. One day a colleague caught sight of Manson on the other side of the street and remarked to his companion: "Do you know who that is? That's mosquito Manson," and tapped his head significantly.

Conclusive evidence of the part played by the mosquito was given by the experiments

devised by Manson in 1900, when it was shown that it was possible to escape infection in a highly malarious locality in Italy by living in a dwelling protected by wire gauze, and secondly that mosquitoes fed in Rome on patients suffering from malaria infected two persons in London by their bites.

I do not consider it necessary to give any references to the literature as the story is too well known.—I am, etc.,

H. G. CALWELL.

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Co. Antrim.

Paraneoplastic Hypercalcaemia and Renal Malignancy

SIR,—Paraneoplastic hypercalcaemia has been found in association with a wide variety of malignant processes.¹ Cytological specificity appears to exist in certain of the paraneoplastic syndromes.² The present communication considers the possibility of a renal cellular specificity with respect to the syndrome of paraneoplastic hypercalcaemia.

In the 19 cases of renal carcinoma reported in association with "pseudohyperparathyroidism," 11 indicate cell type. Of these, 77% are cells with a clear cytoplasm, and the remainder squamous or transitional cell carcinomas of the renal pelvis. These data suggest the importance of the clear cell in its association with the syndrome, considering that the clear cell renal-cell carcinoma is found in but 40% of renal malignancies.³ The tumour composed of renal cells with clear cytoplasm has already been signalled in association with paraneoplastic erythrocytosis (4 January, p. 51). However, among the 83 cases reporting that syndrome which presented cell type, no tumour of the renal pelvis was noted.

Thus there appears to be a tendency for the clear cell renal-cell carcinoma and the transitional or squamous cell carcinoma of the renal pelvis to be associated with "pseudohyperparathyroidism" more frequently than the cell with granular cytoplasm, Wilms's tumour, or other malignant renal lesion.—I am, etc.,

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Vitamin C and the Elderly

SIR,—We agree with Drs. J. C. Brocklehurst and L. L. Griffiths (28 June, p. 824) that daily doses of ascorbic acid larger than the 40- and 80-mg. doses we chose (17 May, p. 416) would accelerate the rise in leucocyte ascorbic acid concentration and are to be recommended for the correction of gross deficiency. Bowers and Kubik¹ reported in 1965 that a 120-mg. daily supplement of ascorbic acid raised initially low leucocyte concentrations of ascorbic acid to levels above

those of younger, healthy people in four weeks.

Our supplementation doses were chosen to be of the same order but in excess of the B.M.A.'s 30 mg.² and the then United States's 70 mg.³ (now 60 mg. for males and 55 mg. for females⁴) recommended daily dietary allowances. It was therefore surprising that these nutritional levels of supplementation were inadequate to produce a rapid response in our group of elderly subjects. A reduced renal threshold or an increased requirement for ascorbic acid could explain the slow leucocyte response. More investigation is necessary, including more study of the clinical significance of biochemically subnormal levels of ascorbic acid in the elderly, especially as the unsupplemented control group of Drs. Brocklehurst and Griffiths⁵ showed an 87% rise in the mean leucocyte ascorbic acid concentration to a level typical of young, healthy individuals during the first six months of the study.—We are, etc.,

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How Many Authors Can Collaborate?

SIR,—The recent paper "Liver Transplantation in Man—III . . ." (5 July, p. 12) appears under the authorship of no fewer than 17 authors—surely a near-record? It is my experience that such therapeutic committees merely provide opportunities for their members to add to the number of their publications.

One man may write a paper; two may, with difficulty, collaborate; three may conceivably achieve something without violence to conscience: but that 17 should agree passes the bounds of credibility or credulity.

As a convinced non-collaborator, my opinion is open to criticism; but 17 . . . —I am, etc.,

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Disodium Cromoglycate in Exercise-induced Asthma

SIR,—Various theories have been suggested to explain the bronchoconstriction that follows exercise: (1) a nervous reflex stimulated by hyperventilation and the movement of the bronchial walls; (2) the release of a humoral substance during exercise such