operation is in serious doubt. Such surgeons are prepared to make random allocation of matched groups to surgical or other treatment or to alternative surgical techniques. Moreover they often accept that the outcome is more reliably assessed by doctors who were not concerned with the initial treatment and who, if possible, remain "blind" as to what kind of surgery was done, if any.

To go further than this in scientific objectivity and to accede to Dr. Spodick's demand for sham operations in order to exclude placebo effects¹ would surely be unwise and unrealistic. This is not to deny such an effect of surgery nor to question the importance of Beecher's classic study² which demonstrated how powerful this may be. But in the light of recent developments in ethical attitudes it is doubtful whether such studies could now be repeated, let alone recommended as a requirement before any new surgical procedure was regarded as effective. Would Dr. Spodick expose his patients with coronary artery disease to sham operations, with the small but undeniable risks of anaesthesia, of wound infection, and of other postoperative hazards? Many patients with serious conditions would accept such risks if there was even a small chance of benefit. But would they do so if they knew the odds were only 50-50 that they would be given even that chance?

I hesitate to prolong a controversy which is almost as dated as debating whether women are fit to vote. But having recently exhorted my fellow-surgeons to be more critical about their work, I may perhaps risk reminding my medical colleagues of a statement made by one of their own kind last year.⁴ Pointing out that every clinician spends much time in activities which give little if any benefit, that most patients who have maladies susceptible to dramatic (medical) treatment have already been given it by their family doctor, and that many patients in medical wards are there largely for nursing and general care, the author concluded that "only surgeons spend much time actually giving benefit."—I am, etc.,

BRYAN JENNETT

Institute of Neurological Sciences,
Southern General Hospital,
Glasgow

¹ Spodick, D. M., *American Heart Journal*, 1973, 85, 579.

² Jennett, B., *Journal of the Royal College of Surgeons of Edinburgh*, 1974, 19, 1.

³ Beecher, H. K., *Journal of the American Medical Association*, 1961, 176, 1102.

⁴ Todd, J. W., *Lancet*, 1973, 1, 1106.

Late Onset of C.N.S. Leukaemia

SIR,—There is no doubt that the incidence of leukaemia of the central nervous system in acute lymphoblastic leukaemia can be greatly reduced by prophylactic radiotherapy and intrathecal chemotherapy, and such prophylaxis is now regularly included in the management of children with this disease. There must still be a number of children, however, diagnosed perhaps 2-3 years ago or more and still in their first remission, who have not received the benefit of early craniospinal prophylaxis. We write to draw attention to the risk of late onset of C.N.S. leukaemia and to suggest that there is still a place for prophylaxis in such cases, even after three years from diagnosis.

The incidence of C.N.S. involvement in children with acute lymphoblastic leukaemia seen at this hospital from 1958 to 1970 was approximately constant for the first 2½ years after diagnosis but then fell sharply.¹ A similar fall in incidence has also been observed by Evans *et al.*² For this reason, when the benefits of C.N.S. prophylaxis became apparent it was not felt justifiable to advise "late prophylaxis" for children who had already remained in complete remission for longer than 2½ years.

However, of 42 children with acute lymphoblastic leukaemia diagnosed during 1970-1—the last two years before the introduction of routine C.N.S. prophylaxis in this hospital—30 have so far developed C.N.S. leukaemia at times ranging up to 188 weeks after diagnosis. In contrast to our previous experience there has been no decline in incidence after 130 weeks; four children have had a C.N.S. relapse after this time, including two who had stopped systemic chemotherapy. This accords with experience in the St. Jude's Total IV programme, in which C.N.S. relapse occurred in five of eight patients who had not received prophylaxis and in whom chemotherapy was subsequently discontinued.³ This prolongation of the incidence curve of C.N.S. leukaemia may be an effect of improvements in the control of bone marrow disease by chemotherapy. Whether or not that is the case, it is clear that any child remaining in complete remission, even 3-4 years after diagnosis, who has not already had C.N.S. prophylaxis should be given it as soon as possible.—We are, etc.,

JUDITH M. CHESSELLS

R. M. HARDISTY

Department of Haematology,
Hospital for Sick Children,
Great Ormond Street,
London W.C.1

¹ West, R. J., *et al.*, *British Medical Journal*, 1972, 3, 311.

² Evans, A. E., Gilbert, E. S., and Zandstra, R., *Cancer*, 1970, 26, 404.

³ Simone, J., *Seminars in Hematology*, 1974, 11, 25.

Gentamicin-resistant *Escherichia coli*

SIR,—As gentamicin is widely relied upon in the treatment of serious Gram-negative infections we report two cases of *Escherichia coli* meningitis in which a strain of *E. coli* initially sensitive to gentamicin, developed resistance during therapy.

An 8-week-old girl developed *E. coli* septicaemia and meningitis. The organism isolated from blood and cerebrospinal fluid was resistant to ampicillin, chloramphenicol, co-trimoxazole, and kanamycin but sensitive to cephaloridine, gentamicin, and polymyxin B. The minimum inhibitory concentration of gentamicin for the organism was 1.2 µg/ml. She was treated with intravenous and intraventricular gentamicin at dosage giving pre-injection C.S.F. gentamicin levels of 10 µg/ml. After 10 days of gentamicin therapy two colonial variants were present in cultures from the C.S.F. The larger colonies were similar to those of the original culture but were very scanty and still sensitive to gentamicin. The smaller colonies were numerous and gentamicin-resistant but sensitive to cephaloridine and polymyxin B. Both large and small colonial forms were of serotype O20K. Treatment was changed to intraventricular cephaloridine and polymyxin B with intravenous cephalothin and 20 days after the onset of illness the C.S.F. became sterile.

A 2-week-old boy developed *E. coli* septicaemia and meningitis. The organism was resistant to ampicillin but sensitive to gentamicin, cephaloridine, and chloramphenicol. After four days' treatment with intramuscular cephaloridine 25 mg/kg

day and gentamicin 1.5 mg/kg/day he was transferred and treated with intravenous gentamicin 8 mg/kg/day and intraventricular gentamicin 2 mg/day, giving pre-injection C.S.F. gentamicin levels of 10 µg/ml. Four days later a small colonial variant resistant to gentamicin was present in C.S.F. cultures, while the original larger forms (still sensitive to gentamicin) were reduced in number. Despite treatment with intraventricular cephaloridine and intravenous chloramphenicol and cephalothin the patient died.

Thus two organisms, initially sensitive to gentamicin, developed resistance to the antibiotic during therapy. This phenomenon among *E. coli* has not hitherto been a clinical problem at this hospital and we have not heard of it elsewhere. Acquired gentamicin resistance is well documented for *Pseudomonas aeruginosa*, particularly in patients who have been given oral gentamicin.¹ Both infants were treated intensively with gentamicin alone for a time and the second infant was initially treated with low-dose gentamicin, which might have helped the emergence of a resistant strain. Clearly indiscriminate use of gentamicin is undesirable, and if it is to be used it should be given in amounts which give adequate levels in the infected tissue.—We are, etc.,

A. G. L. WHITELAW

HELEN HOLZEL

N. N. FARRAG

Hospital for Sick Children,
Great Ormond Street,
London W.C.1

¹ Greene, W. H., *et al.*, *Annals of Internal Medicine*, 1973, 79, 684.

Renal Damage Caused by Gentamicin

SIR,—It came to our attention during a study of the urinary excretion of cytoplasmic enzymes in patients who had received renal homografts that there was an increased excretion of the marker enzymes N-acetyl-β-D-glucosaminidase and β-galactosidase not only during rejection episodes¹ but also during treatment with gentamicin. Electron microscopy of proximal tubular epithelium of renal homografts revealed lipid droplets and dense laminated bodies in the cytoplasm. Similar laminae bodies have been found in the urine deposit of patients with other diseases treated with gentamicin.

Rats given daily intramuscular injections of gentamicin at dosages varying from 5 mg/kg/day (corresponding to human therapeutic dosage) to 100 mg/kg/day showed elevation of urinary enzymes similar to that found in man. Proximal tubular epithelial cell damage varied from cytoplasmic inclusion of lipid and laminated bodies at low dosage to tubular necrosis at high dosage. These changes occurred 5-21 days after commencing therapy.

It is not widely appreciated that gentamicin in therapeutic dosage may produce these biochemical and morphological changes in renal tubular epithelium, and this should be considered before higher dosage is given.—We are, etc.,

J. M. WELLWOOD

D. LOVELL

A. E. THOMPSON

J. R. TIGHE

St Thomas's Hospital,
London S.E.1

¹ Wellwood, J. M., *et al.*, *British Medical Journal*, 1973, 2, 261.