In a recent study of 1,263 children with acute leukaemia at the Children's Cancer Research Foundation in Boston we observed two patients with undifferentiated leukaemia and multiple neurofibromatosis.¹ This frequency is not significantly higher than the estimated incidence of neurofibromatosis in the general population (one case per 2,500-3,300 births).² The association of neurofibromatosis with leukaemia has occurred in two other children in the same clinic (not in our series) and has been described in three case reports from France.³⁻⁵ In one instance the combination of diseases affected siblings.⁴ The eight reported cases of neurofibromatosis and childhood leukaemia are of great interest, but the evidence is not sufficient as yet to indicate that the high cancer risk in neurofibromatosis extends to leukaemia.—I am, etc.,

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- 1 Fraumeni, J. F., jun., Manning, M. D., and Mitus, W. J., *Journal of the National Cancer Institute*, 1971, **46**, 461.
- 2 Crowe, F. W., Schull, W. J., and Neel, J. V., *A Clinical, Genetic, and Pathological Study of Multiple Neurofibromatosis*. Springfield, Ill., C. C. Thomas, 1956.
- 3 Mouriquand, Cl., Jeune, M., Charrat, A., and Muller, J.-M., *Pédiatrie*, 1960, **15**, 683.
- 4 Germain, D., *Médecine Infantile* (Paris), 1963, **70**, 325.
- 5 Germain, D., Robert, J. M., and Trouillas, P., in *4th International Congress of Human Genetics: International Congress Series No. 233*. Excerpta Medica, 1971, in press.

Leukaemia on Myeloma

SIR,—We are prompted by the letter of Dr. Judith A. W. Webb and others (23 October, p. 231) to report the case history of another patient who developed acute myeloblastic leukaemia after having been treated for four years with melphalan for myeloma.

A 40-year-old man presented with pleuritic chest pain in 1967 having had backache for two years. X-rays showed that there were widespread osteolytic lesions in the ribs, vertebrae, and skull. The blood count and serum protein pattern were normal and there was no Bence-Jones protein in the urine. A bone marrow aspirate contained more plasma cells than usual, but was not diagnostic of myeloma. Biopsy of one of the rib lesions demonstrated a plasma cell tumour. Therapy with melphalan was started in April 1967, and he had a short course of radiotherapy to his spine. (In May 1967 he developed asymptomatic hypercalcaemia which was treated with prednisolone. The prednisolone was stopped in March 1968.) He continued to take melphalan until August 1971. During the intervening period he was relatively well and his only other medication was analgesics to control lumbar back pain. X-rays showed no extensions of his osteolytic lesions and he did not develop an abnormal plasma protein.

In August 1971 he developed a 'flu-like illness and a routine blood count demonstrated that the majority of the white cells were blasts. The total white cell count was 7,500/mm³.

He was admitted to hospital one week later, when the only abnormal physical sign was purpura over both scapulae. The platelet count was then 66,000/mm³ and the white cell count had risen to 33,000/mm³. A bone marrow aspirate contained numerous hypercellular fragments and over 90% of the nucleated cells were typical and atypical blast cells which were periodic-acid Schiff negative.

There were no plasma cells. A diagnosis of acute myeloblastic leukaemia was made. The melphalan was stopped and treatment with daily intravenous cytosine arabinoside and oral thioguanine was substituted. There was an initial fall in the blast count but after two weeks of therapy he died of bronchopneumonia.

This case history is similar to a number of others recently reported,¹⁻⁵ where patients with myeloma have responded well to treatment usually including melphalan and finally have developed acute myeloblastic or myelomonoblastic leukaemia. Whether this is merely the natural history of the disease or related to the treatment remains to be decided.

We should like to thank Dr. P. H. Sanderson and Dr. M. Hulbert for allowing us to report this case.

—We are, etc.,

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- 1 Edwards, G. A., and Zawadzki, Z. A., *American Journal of Medicine*, 1967, **43**, 194.
- 2 Kyle, R. A., Pierre, R. V., and Bayrd, E. D., *New England Journal of Medicine*, 1970, **283**, 1121.
- 3 Osserman, E. F., *British Medical Journal*, 1971, **2**, 327.
- 4 Videbaek, A., *British Medical Journal*, 1971, **2**, 326.

Undesired Effects of Cloiquinol Therapy

SIR,—I would like to draw your attention to the misquotation of a reference by Dr. O'Sullivan and myself¹ on two occasions in the article by Dr. S. I. Terry (25 September, p. 745). Our article was a review of patients who had suffered from thalidomide neuropathy and there was no mention of cloiquinol. Dr. Terry quotes this article as describing the clinical picture of cloiquinol intoxication. This is very misleading. I would be grateful if you would draw the author's and your readers' attention to the error.—I am, etc.,

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- 1 Fullerton, P. M., and O'Sullivan, D. J., *Journal of Neurology, Neurosurgery, and Psychiatry*, 1968, **31**, 543.

* * We showed Dr. Le Quesne's letter to Dr. S. I. Terry, who writes: "I am grateful to Dr. Le Quesne for the opportunity to clarify two statements in my original article. My aim had originally been to draw attention to the similarity between the marked dysaesthesiae but lack of muscle weakness reported by Dr. O'Sullivan and herself in thalidomide toxicity (with its associated abnormal neuropathology) with the symptoms and signs described in the case of cloiquinol toxicity that I reported. Also, Sobue and others¹ described the marked leucocytosis and elevation of the erythrocyte sedimentation rate in the acute phase as a feature of their series of cloiquinol toxicity. Unfortunately, in condensing information for the original article the credit for these separate observations was transposed. I apologize for the inconvenience this may have caused."—ED., *B.M.J.*

- 1 Sobue, I., et al., *Neurology* (Minneapolis), 1971, **21**, 168.

Aluminium and Chronic Renal Failure

SIR,—Dr. V. Parsons and others (30 October, p. 273) have shown that bone biopsy specimens of patients with chronic renal failure occasionally have a high aluminium content. This is discussed in the context of the hypothetical toxicity of aluminium hydroxide and aluminium-containing resins in chronic failure.¹ It is perhaps relevant that the patients with the highest aluminium/calcium ratio had not received such medication nor did they manifest osteomalacia.

Unfortunately this work throws no light on the crucial clinical problem—the toxicity of aluminium in renal failure. Aluminium-containing compounds are administered in order to lower the serum phosphate level by the formation of insoluble aluminium-phosphate complexes. Since inorganic and organic phosphate compounds are of fundamental importance in every viable body tissue, phosphate depletion is likely to produce adverse sequelae. This has been shown in both humans² and experimental animals³ subjected to excessive or prolonged aluminium ingestion. Such results cannot logically be extrapolated to the situation where aluminium is trapped as an innocent bystander or where aluminium hydroxide is administered to reduce hyperphosphataemia.

We are currently examining this problem by administering food containing aluminium hydroxide to weanling rats. Normal rats show very little bone aluminium even at the end of a month of such treatment. Nevertheless, growth is impaired and rickety changes produced in the bones. Animals on a similar diet, to which disodium hydrogen phosphate is added, grow normally despite the fact that their bone aluminium content is three times normal. Animals with chronic renal failure also show elevated bone aluminium levels. It appears probable that aluminium deposition is in part related to the phosphate content of body fluids and that the toxic effects of aluminium upon growth depend upon phosphate depletion rather than any specific effect of the aluminium. The interesting observation that patients from different centres have different bone concentrations of aluminium may well be related to either differing intakes of phosphate or different serum phosphate levels.—We are, etc.,

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- 1 Berlyne, G. M., *Lancet*, 1970, **2**, 1253.
- 2 Lotz, M., Zisman, E., and Bartter, F. C., *New England Journal of Medicine*, 1968, **278**, 409.
- 3 Ondreicka, R., Kortus, J., and Ginter, E., in *Intestinal Absorption of Metal Ions, Trace Elements and Radionuclides*, ed. Skoryna, S. C., and Waldron-Edward, D., Pergamon Press, 1971, p. 293.

Trimethoprim/Sulphamethoxazole Mixture in Pregnancy

SIR,—The trimethoprim/sulphamethoxazole mixture sold under the names of Septrin and Bactrim seems to be fulfilling its early promise as an antibacterial agent, and is being widely used. Since the combination is well excreted by the kidney, and will eliminate many strains of proteus as well as *Escherichia coli*, it naturally cures a higher proportion of patients with urinary infections than would a sulphonamide used alone. On the face of it, trimethoprim/

sulphamethoxazole mixture is a drug of first choice for this condition, but there are others which are equally useful.

Trimethoprim is teratogenic in rats, and although it does not have the same effect in the rabbit there can be no guarantee that it will never damage the human fetus. Since it seems likely that the effect is through interference with fetal folate metabolism—and rare cases of impaired folate metabolism have already been recognized in adults taking trimethoprim—there is some slight reason to suppose that the human fetus may be more rat-like than rabbit-like. The above information is all part of the “full information supplied on request” by the manufacturers of both Septrin and Bactrim, but the average doctor contents himself with a much smaller amount of reading material which can only contain the hackneyed phrase “contraindicated in pregnancy” common to nearly every new drug.

I have talked to many doctors in general practice and in teaching hospitals. Almost all have used trimethoprim/sulphamethoxazole mixture. None of them have specifically known this risk. Even a recent textbook on antibiotics omitted the information. One can only presume that “wolf, wolf” has been cried once too often.

Professor W. Brumfitt in the August issue of the *Prescribers' Journal*¹ states the risk, but suggests that the drug combination is suitable therapy for the bacteriuria of pregnancy. He also states that “so far there is no evidence of any adverse effect on the human foetus.”

Experience with thalidomide has made us aware of the hazards of the use of drugs in pregnancy, but has also led to the assumption that fetal abnormalities induced by a particular drug will be easily recognizable because they follow a consistent pattern and will probably be of unusual type. This is not necessarily going to be the case next time. Since the usual incidence of human fetal abnormalities is about 2% of live births, it would be necessary to give trimethoprim/sulphamethoxazole mixture to a large number of pregnant women in a prospective trial in order to establish that it produces no increase in the above figure. This trial would obviously be unethical.

For the moment trimethoprim/sulphamethoxazole mixture should only be used in pregnancy if there is no suitable alternative. With the modern therapeutic armamentarium this should be a rare event, but if the Royal College of Obstetricians and Gynaecologists were to provide a centre for the prospective reporting of all instances in which trimethoprim/sulphamethoxazole mixture had been used in pregnancy, an acceptable statistical answer might be available within a few years.—I am, etc.,

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¹ Brumfitt, W., *Prescribers' Journal*, 1971, 11, No. 4, 94.

Chorea and the Oral Contraceptives

SIR,—I read with interest the latest report of oral-contraceptive-related chorea by Dr. D. Riddoch and others (23 October, p. 217) and their comment on the absence of previous episodes of chorea or rheumatic fever in five of their six cases. Similar absence of past history was also my experience in

Canada with a further case,¹ where the development of hemichorea in a young woman afforded the opportunity of recording her hand and wrist movements by sequential and multiple exposure photography. This 20-year-old, nulliparous married woman developed hemichorea after taking an oral oestrogen-progestogen preparation for three months. Immediate improvement followed withdrawal of the hormonal agent and the institution of oral penicillin treatment; within 10 weeks the movements had entirely disappeared.

Dr. Riddoch and his colleagues achieved complete remission of symptoms by withdrawal of the oral contraceptive alone, but I would submit that we are not yet in a position authoritatively to exclude penicillin from the treatment of oral-contraceptive-related chorea. Its administration in classical Sydenham's chorea is intended to prevent relapses of the chorea and valvular involvement consequent upon the carditis, which may often be clinically silent.² In children it is well recognized that chorea may be the sole manifestation of acute rheumatic fever,³ and in a study of 1,033 children⁴ chorea alone was the clinical feature of the first attack in 12%. Evidence for supposing that lone non-hereditary chorea in the adult can be a rheumatic manifestation is analysed by Paradise,⁵ who shows that, although such diseases as systemic lupus erythematosus may be responsible, there is still a sound basis for believing that clinically isolated chorea is often due to acute rheumatic fever. The validity of a clinical diagnosis of rheumatic chorea in the absence of cutaneous, joint, cardiac, serological, or haematological abnormality seems well accredited.^{2,5}

Furthermore, in the absence of convincing neuro-anatomical proof it seems improper to highlight vascular mechanisms in discussing the pathogenesis of chorea associated with oral contraceptives, as, for example, one author⁶ has assembled references to more than 40 illnesses in which chorea has been observed including encephalitides, febrile exanthemata, arteritides and other vascular lesions, degenerative disorders, industrial and drug intoxications, drug reactions, vitamin deficiencies, and metabolic and endocrine disturbances.

In seeking the proximate cause for oral-contraceptive-related chorea, we must surely eschew an unjustifiably simplistic view of cerebral function in vascular/structural terms. As for the place of penicillin in treatment the question hinges upon whether or not there is causal relation with streptococcal infection, as in acute rheumatic fever. Answers will come only through careful follow-up of these cases as countrywide (or even international?) interest brings more to light.—I am, etc.,

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¹ Malcolm, A. D., and Howell-Jones, M., *Medical and Biological Illustration*, 1971, in press.

² Thiebaut, F., *Handbook of Clinical Neurology*, Vol. 6, ed. P. J. Vinken and G. W. Bruyn, p. 409. Amsterdam, North Holland Publishing Co., 1968.

³ Wannamaker, L. W., in *Textbook of Pediatrics*, ed. W. E. Nelson, V. C. Vaughan, and R. J. McKay, p. 533. Philadelphia, Saunders, 1969.

⁴ Perry, C. B., *Annals of the Rheumatic Diseases*, 1969, 28, 471.

⁵ Paradise, J. L., *New England Journal of Medicine*, 1960, 263, 625.

⁶ Greenhouse, A. H., *Archives of Internal Medicine*, 1966, 117, 389.

Reversible Sterilization in the Female

SIR,—Mr. E. A. Williams's letter (30 October, p. 297) on this topic is of paramount importance at a time when all gynaecologists are being asked to perform more and more sterilizations in their patients. For some years I have been using the method of diathermy coagulation owing to the ease, speed, and what I feel must be its great effectiveness, and the facility with which this can be done via the laparoscope is adding enormously to the popularity of this method, with both gynaecologist and patient. Other correspondents have also emphasized the increasing number of young patients requesting sterilization, and the time must inevitably come when a fair sprinkling of these young mothers may have cause to regret their insistence in asking for this operation. As Mr. Williams points out, if their tubes have undergone diathermy coagulation there will be so little viable tube left that reconstitution will be out of the question.

I agree with Mr. Williams that so long as there is little loss of tube, however, there should be a reasonably good prospect of anastomosing the ends together. Many years ago a patient in whom I had removed one appendage for a large ovarian cyst, and had at the same time dissected a fimbrial cyst from the other broad ligament, was later found on salpingography to have developed a stricture in the one remaining tube. This stricture was excised and end-to-end anastomosis carried out and pregnancies soon followed. Although I am normally reluctant to consider total surgery in infertility, I suspect that the overall poor results of these operations are due to the damage sustained by the tubal mucous lining by previous inflammation. If there has been no infection in the tube, however, so that its ciliated epithelium is working normally, the prospect of success should be greatly enhanced.

It is, therefore, my practice, where the possibility of reconstitution might arise, to carry out the sterilization by dividing and ligating the tubes near to the junction of isthmus with ampulla and opposite an avascular window in the broad ligament. With mosquito forceps the layers of the broad ligament are then separated and the ends of the ligated tubes buried in this space with a fine atraumatic suture. Though I have not yet been requested to reconstitute tubes after this operation, I feel that if this should happen there should be reasonable hope of success.—I am, etc.,

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Aetiology of Bell's Palsy

SIR,—Your recent leading article on “Aetiology of Bell's Palsy” (2 October, p. 2) fails to mention two specific conditions connected with increased frequency of peripheral facial weakness. One is hypertension, and you dedicated a leading article to this connexion five years ago (24 December 1966, p. 1547). It is more than a century now since W. Moxon showed pathological evidence of haemorrhage into the fallopian canal in a man with Bright's disease (and presumably hypertensive) with facial weakness. The connexion between hypertension and Bell's palsy has been demonstrated repeatedly, particularly in children. In a series of 130 patients seen here hypertension existed in 21 (16%),