of acute leukaemia in seven of their series of 100 cases of aplastic anaemia in children. Four of their cases were of the constitutional type, which may be especially prone to leukaemic transformation;¹ five had received anabolic steroids.

The point is that an aplastic or hypoplastic bone marrow is unstable. Recovery, with or without therapy, may be complete; on the other hand, some become chronic, and a small minority will develop a clone of abnormal haemopoietic cells which declares itself by a new clinical picture, which may be acute leukaemia, paroxysmal nocturnal haemoglobinuria, or (as in one personally observed case) sideroblastic anaemia. Drugs which stimulate surviving marrow tissue in this unstable environment may accelerate the appearance of abnormal clones.

It may be that the very efficacy of oxy-methalone in producing remission in aplastic anaemia renders it especially liable to cause proliferation of "wild" clones of haemopoietic cells. The fact that therapy with anabolic steroids is not associated with an increased incidence of acute leukaemia in other clinical situations is not relevant, because in these there is no marrow instability.—We are, etc.,

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¹ Smith, Carl H., *Blood Diseases of Infancy and Childhood*, 1966, 2nd edn. London, Kimpton, p. 253.

Cremation Regulations

SIR,—One has every sympathy with Dr. H. C. Maingay's desire to interpose some expert appraisal of the medical evidence on which a coroner has judged that nothing further of the sort is required. As one of the coroners to whom he kindly refers (25 September, p. 770) and who appreciate his tactful co-operation, I have seen many post-mortem reports that he would not have found acceptable as the basis of any sort of disposal of the body before further medical exploration and even alteration.

However, the theory is and is likely to remain that a coroner without any medical knowledge at all is the final competent authority to judge the validity and relevance of all medical evidence without further medical assistance. That is the predicament of most coroners, and the majority of bodies are disposed of purely on the basis of their appraisal of medical reports. Undoubtedly there is a strong case for a full and final medical assessment in all circumstances, but with respect to Dr. Maingay, I would point out that he can hardly expect to be welcomed as a sort of professional "long-stop" when the official view is that the amateur wicket-keeper is in fact stopping everything that comes down his pitch.—I am, etc.,

J. SHACKLETON BAILEY

Eye,
Suffolk

SIR,—I read Dr. H. C. Maingay's letter (25 September, p. 770) with interest because as medical referee to the Cheltenham Crematorium I raised the same point when the new regulations were published in 1965. I did not

consider that the coroner's Form E omitting the cause of death gave me authority to sign Form F, certifying that I had satisfied myself "that the cause of death has been definitely ascertained."

I took legal advice on this matter and after it was considered by the Crematorium Committee the coroner was informed by the Crematorium Authority that the issue of Form E must be interpreted by the medical referee as certifying that he (the coroner) had satisfied himself that the cause of death had been adequately ascertained—that is, the responsibility was the coroner's although the medical referee signed Form F.

At the same time an approach was made to the Federation of British Crematorium Authorities. The secretary replied that it was the opinion of his committee that it was difficult, if not impossible, for the medical referee to issue Form F on the limited information provided on Form E. Although the Federation was consulted before the regulations were issued, they were not shown the proposed new Form E and were "astonished" when they found that the regulations had been made effective. Further representations made by the Federation to the Home Office have apparently been without result.

I agree with Dr. Maingay that both common sense and common courtesy demand that the medical referee should be given adequate information before issuing Form F, and this has been recognized by coroners themselves in some parts of the country. Although I have been unable to come to a satisfactory arrangement with the coroner for my own district, every Form E which I receive from the coroner of adjoining districts has the cause of death written on the back.

Let us hope that the Brodrick committee will recommend a satisfactory solution to this problem.—I am, etc.,

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Protein-bound Peptides in Human Serum

SIR,—We wish to report the detection of two peptide fractions, bound to proteins, in serum from normal subjects and from patients with rheumatoid arthritis receiving treatment with antirheumatic drugs. The fractions were isolated by applying the sera to Sephadex columns and collecting portions of the eluates containing the proteins and associated bound molecules. The proteins were removed by precipitation with trichloroacetic acid followed by centrifugation and the supernatants were concentrated and analysed for ninhydrin-positive substances using a Technicon Amino-acid Analyzer system.

Two fractions, appearing as narrow discrete peaks with maxima at 60 and 270 min running time, were found in each sample of serum. They behaved as homogeneous materials when passed through several types of Sephadex columns and after elution with a variety of salt solutions. Both fractions gave mixtures of amino-acids on acid hydrolysis. Over 90% of the 60 fraction and over 70% of the 270 fraction were bound to the circulating proteins. Their total concentrations (protein-bound plus free) in the sera were approximately 0.01% of the albumin in terms of the colour given with ninhydrin. Sera from patients with active rheumatoid arthritis receiving therapy with

one or more of the following drugs, aspirin, indomethacin, prednisolone, and gold salts, contained significantly more of fraction 60 and significantly less of fraction 270 than normal sera.

The behaviour of these peptides is that predicted for the hypothetical "protective" peptides of McArthur and co-workers (19 June, p. 677). They occur in human serum and are bound to circulating proteins. The higher concentration of fraction 60 in the serum of patients with rheumatoid arthritis receiving therapy shows that more of this peptide is bound to proteins in such patients. If this fraction is displaced by the anti-rheumatic drugs a higher proportion should be bound in untreated patients. We have observed that in one patient who for several days received paracetamol, which possesses analgesic but not clinical anti-inflammatory activity,¹ the total concentration of fraction 60 was not only above that found in the treated patients but also that it decreased by over 60% after subsequent treatment for seven days with full antirheumatic doses of aspirin.

Further investigation of the chemical structure and anti-inflammatory activity of this peptide are indicated, together with a search for similar compounds which are also displaced by the commonly used anti-rheumatic drugs and which are bound to a greater extent to serum proteins in rheumatic patients.—We are, etc.,

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¹ Boardman, P. L., and Hart, F. D., *British Medical Journal*, 1967, **4**, 264.

Chorea and Occlusion of Central Retinal Artery

SIR,—The association of chorea with occlusion of the central retinal artery has been reported 15 times since 1875.¹

A further case was a 15-year-old African girl who came to hospital during her second attack of chorea and was found to be blind in the right eye. She became blind overnight during her first attack two years previously. Apart from features of Sydenham's chorea, the only abnormality was in the right fundus. This consisted of a stark white disc, typical of optic atrophy, and retinal pallor. There was extreme attenuation of the central retinal artery and its branches. The branches on the temporal side were represented by white streaks, the "ghosts" of occluded arteries. Slightly increased pigmentation surrounded the macula. The heart was normal. Blood count, cerebrospinal fluid, chest x-ray, and E.C.G. were normal.

This association of central retinal artery occlusion with chorea, though rare, must be more than coincidence. It may provide a clue to the pathogenesis of Sydenham's chorea. Possible mechanisms of the occlusion are embolism, arterial spasm, and thrombosis.^{2,3} Embolism seems unlikely because most reported cases had no endocarditis. It would be an odd coincidence by which emboli, when they occur, consistently reach the central retinal artery and no other arteries. It is more likely that the chorea syndrome results from arteritis and thrombosis specific to certain arteries. The only

analogous condition is systemic lupus erythematosus which has been reported in association with chorea⁴ and is known to cause arterial occlusion and endocarditis.—I am, etc.,

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Natal, South Africa

¹ Ling, W., Oftedal, G., and Simon, T., *American Journal of Diseases of Children*, 1969, 118, 525.

² Hearn, G. W., and Roper-Hall, M. J., *British Medical Journal*, 1961, 2, 684.

³ Willetts, G. S., *British Medical Journal*, 1961, 2, 688.

⁴ Greenhouse, A. H., *Archives of Internal Medicine*, 1966, 117, 389.

Leukaemia on Myeloma

SIR,—Acute myeloblastic leukaemia is seen rarely as a terminal event in patients with multiple myeloma. There has recently been a minor epidemic of cases (20 in all)¹⁻³ and there has been speculation about the possible aetiological role of melphalan, since the majority of the myeloma patients who developed leukaemia had had long-term treatment with this drug. A direct relationship between melphalan and leukaemia is by no means established; in order that the possibility can be investigated adequately, it is important that all cases of this triad—multiple myeloma, acute myeloblastic leukaemia, and melphalan—should be recorded. We would like, therefore, to report the details of another case (which, so far as we can ascertain, is the first to be reported in Britain).

A woman born in 1904 presented in April 1965 at another hospital with a seven-week history of cough and increasing dyspnoea. On examination she was anaemic with the signs of a chest infection but no lymphadenopathy or hepatosplenomegaly. The findings then were: Haemoglobin 11.0 g/100 ml; W.B.C. 5,800/mm³ with a normal differential; platelets 185,000/mm³; E.S.R. 110 mm in the first hour; blood urea 35 mg/100 ml; serum calcium 9.9 mg/100 ml.

Bone marrow showed large numbers of plasma cells including primitive forms, and there were multiple punched out translucencies on the skull x-ray. Total serum protein was 9.8 g/100 ml (albumin 4.7 g/100 ml); IgA—4,300 mg/100 ml (K paraprotein); IgG—420 mg/100 ml; and IgM—8 mg/100 ml. There was a trace of Bence Jones protein in the urine.

She was transferred to St. Bartholomew's Hospital, and in June 1965 started melphalan 4 mg daily; this was stopped after a month because of pancytopenia. Over the succeeding two years she received melphalan intermittently in a daily dose of 1-2 mg, controlled according to her blood count. On this treatment the concentration of paraprotein in the serum fell to 1.5 g/100 ml, with a total protein of 9.3 g/100 ml in October 1967. From November 1967 to May 1971 she was given continuous melphalan 1 mg daily (total melphalan dose—June 1965 to May 1971=1,617 mg).

In May 1971 she was admitted again with a history of three months increasing dyspnoea and tiredness and three weeks cough. She was anaemic with bilateral bronchopneumonia and pleural effusions. Her blood count was then Hb 7.9 g/100 ml; W.B.C. 3,600/mm³ with 6% myeloblasts, 1% myelocytes, 6% metamyelocytes, 59%

neutrophils, 2% basophils, and 26% lymphocytes. Platelets were 9,000/mm³.

The bone marrow showed persistent infiltration with abnormal primitive plasma cells and, in addition, there was hyperplastic granulopoiesis with an increase in primitive cells (blasts 12%, promyelocytes 23%). The erythroid precursors were also morphologically abnormal. The results of lysozyme assays were:^{4,5} Serum lysozyme 44 µg/ml (normal 10) and urine lysozyme 30 µg/ml (normal 1) by micrococcus lysis method.

The melphalan was stopped and she was given blood transfusion and antibiotics. Her chest infection failed to resolve and she subsequently developed a coliform urinary infection. Her clinical condition deteriorated with a rapidly rising white cell and blast count in the peripheral blood (to W.B.C. 38,200/mm³ with 22% blasts on 18 June) and a rising blood urea until her death three days later.

The findings at postmortem were: (1) The bone marrow, which contained plasma cell myelomata, was invaded by myeloid leukaemia cells; (2) bilateral bronchopneumonia; (3) fibrinopurulent pericarditis; (4) abscesses in the liver, left kidney, and femoral marrow; and (5) obsolete apical pulmonary tuberculosis (with no evidence of local reactivation or dissemination).

We would like to thank Sir Ronald Bodley Scott for permission to report details of this case and Dr. Ralph Carmel of St. Mary's Hospital (Experimental Haematology Unit) for performing the lysozyme assays.

—We are, etc.,

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¹ Videbaek, A., *British Medical Journal*, 1971, 2, 326.

² Osserman, E. F., *British Medical Journal*, 1971, 2, 327.

³ *British Medical Journal*, 1971, 1, 568.

⁴ Perillie, P. E., Kaplan, S. S., Lefkowitz, E., Rogaway, W., and Finch, S. C., *Journal of the American Medical Association*, 1968, 203, 317.

⁵ Wiernik, P. H., and Serpick, A. A., *American Journal of Medicine*, 1969, 46, 330.

Side Effects of Intermittent Rifampicin

SIR,—Dr. G. Poole and others (7 August, p. 343) have reported a high incidence of unusual and sometimes serious adverse reactions to rifampicin 1,200 mg twice-weekly, and as a result they have terminated their investigation of the intermittent use of this drug. In contrast, Decroix and others¹ in France encountered no serious toxicity when giving 900 mg twice a week for a year to 62 patients, and Verbist and others² gave the very high dose size of 30 mg/kg once a week to 100 patients in the Congo without encountering any toxicity. Our own experience, which will be reported in full elsewhere, has been that when side effects do occur during intermittent treatment with this drug, most patients can still continue on a rifampicin-containing regimen.

This unit is currently collaborating with the Tuberculosis Treatment Services of Hong Kong in a controlled clinical trial of reserve regimen chemotherapy for failure patients in which daily, twice-weekly, once-

weekly, and once-weekly preceded by 2 months daily treatment with rifampicin and ethambutol is being studied. The rifampicin dosages are 450 mg in the daily regimen, and 900 mg, 1,050 mg, and 1,200 mg, according to body weight, in the twice-weekly and once-weekly regimens. The dosages of once-weekly rifampicin were originally higher (1,200, 1,500, and 1,800 mg for the three weight classes), but were reduced to the 900, 1,050, 1,200 mg schedule 7 months after the intake had begun because of the occurrence of adverse conditions. Over 250 patients have already completed at least six months of treatment on the rifampicin-containing regimens. The standard reserve regimen, ethionamide, pyrazinamide, and cycloserine has been included as a control group.

We recognize five symptom complexes which occur with intermittent rifampicin treatment: (1) the "flu" syndrome, consisting of attacks of fever, chills, headache, malaise, and bone pains, of which the last mentioned can be very severe; (2) cutaneous episodes, namely flushing and/or itching, with or without urticaria, involving particularly the face and scalp; (3) the abdominal syndrome, consisting of attacks of abdominal pain and nausea sometimes associated with vomiting and/or diarrhoea; (4) the respiratory syndrome (uncommon), consisting of dyspnoea with or without wheezing; and (5) purpura (uncommon). The first four syndromes usually come on two to three hours after a dose of rifampicin and are gone by the evening of the same day.

Cutaneous episodes tend to occur early in treatment and the "flu" syndrome later. More than one syndrome can occur in the same patient and it is not uncommon for a patient to have cutaneous or gastrointestinal symptoms during the first weeks of treatment, and then develop the "flu" syndrome in the third or fourth month. A patient may also have more than one syndrome, particularly the abdominal and "flu" syndromes, at the same time. The episodes may be very mild and there may be only a single one, so that, for example, the occurrence of a cutaneous episode within a few days of starting treatment does not mean that a patient may not then continue the regimen for many months uneventfully. Attacks of the abdominal syndrome or the "flu" syndrome have in many cases stopped completely or become so mild or infrequent as to be of no further concern to the patient or staff, simply after lowering the dose of rifampicin.

A procedure for the management of episodes in the intermittent rifampicin regimens which is satisfactory in clinical practice has now been in use for several months in Hong Kong. If purpura occurs (only two cases), rifampicin is stopped immediately and is not given again. For the other syndromes the following procedure has been evolved: (1) if an episode severe enough to need clinical action occurs, the effect of lowering the dose of rifampicin by one capsule (150 mg) at a time, to a minimum of 600 mg a dose is tried; (2) if symptoms persist, an attempt to induce tolerance to rifampicin is made by giving daily doses, usually starting with 150 mg, a dose which in most patients produces no symptoms, and increasing by 150 mg a day up to a dose of 450 mg which is then continued daily. Only in the uncommon event of these procedures failing to terminate the episodes is the rifampicin discontinued.