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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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.

When given in conventional daily dosage, rifampicin is highly effective but very expensive, costing well over £200 a year for one patient. This makes the use of daily rifampicin regimens unrealistic in nearly all the developing countries and indeed in many technically advanced countries too. If an intermittent regimen containing a smaller total weekly dosage of rifampicin which is both therapeutically effective and of low toxicity could be found the applicability of this very valuable drug would be much increased. It would indeed be a great pity if the report of Dr. Poole and others were to be interpreted as discouraging further investigation along these lines.

In the final analysis the aim must be to evaluate rifampicin-containing regimens in terms of efficacy, safety, convenience, cost and applicability, in comparison with the alternative regimens available for the treatment of the same type of disease, in the same population.—We are, etc.,

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1 Decroix, G., et al., *Revue de Tuberculose et de Pneumologie*, 1971, 35, 39.

2 Verbist, L., et al., *Proceedings of the Symposium on Rifampicin*, Prague, 5-9 October, 1970, p. 104, Prague, Czechoslovak Medical Press, 1971.

Undescended Testis

SIR,—I feel it is time that the term orchidopexy was abandoned for the more rational operations to correct undescended testes.

Pexis (πηξις) means nailing or pegging, with the general implication of a rather rough job. Surgeons who take this operation seriously know the vital necessity to place the testis in the scrotum without the slightest hint of tension, no matter how extensive a procedure is necessary to achieve this end. If stitches to the thigh, or Torek or Ombrédanne procedures, or elastic bands, or scrotal pouches have to be done to keep the organ in the scrotum after operation, then it will surely die.

Chalasis (χαλασις) means essentially loosening, untying, lowering gently into its natural position. The descriptive term orchiochalasis is therefore offered for what we are trying to do.—I am, etc.,

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Prophylaxis of Wound Infection

SIR,—The results reported by Mr. T. A. M. Stoker, and Professor H. Ellis (25 September, p. 769) from the Westminster Hospital prompted us to review the effect of powdered noxythiolin on our own wound infection rate. The results are part of a wound infection trial in which, after a wound swab was taken, nothing, saline, aqueous chlorhexidine, or noxythiolin are instilled into the wound at the end of the operation in a random manner. The wounds are inspected up to 10 days postoperatively by an observer who does not know the nature of the solution or powder used. The result in the first 176 wounds are:

	No. of Wounds	No. of Wound Infections
Nothing	47	7
Saline	41	6
Chlorhexidine	44	3
Noxythiolin	44	11

From these results it appears that neither chlorhexidine or noxythiolin is significantly better than nothing or saline in the prevention of wound infection. Secondly, the lower infection rate in the chlorhexidine group leads us to believe that there may be a significant reduction when more patients have been included. On the other hand, the results with noxythiolin suggest an increase in wound infection rate, and although there is no significant difference between the control group and the noxythiolin group, there is a significant difference at the 5% level ($\chi^2=5.4$) between noxythiolin and aqueous chlorhexidine.

These results have led us to abandon the use of topical powdered noxythiolin in attempts to prevent wound infection, since there may even be an increase in wound infection associated with its use. The trial continues using aqueous chlorhexidine.—We are, etc.,

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Epitaph for the M.C.H.C.

SIR,—We were interested to read the letter by Dr. Rose (16 October, p. 169), who cited some of our own unpublished work.¹

We are not sure that our observations have been interpreted correctly. Perhaps we could clarify this matter by briefly describing our results. We have found that when the microhaematocrit method is used significant quantities of plasma are trapped between the centrifuged red cells. This produces a falsely high value for the packed cell volume (P.C.V.) and a falsely low value for the mean corpuscular haemoglobin concentration (M.C.H.C.). The error due to trapped plasma is smallest with blood samples from normal people. Here plasma trapping accounts for 3% of the packed red cell column. In iron deficiency, however, trapped plasma may account for 5-6% of the red cell column, and in blood with sickled red cells the plasma trapped may account for over 20% of the red cell column. The microhaematocrit method can therefore seriously overestimate the P.C.V. and seriously underestimate the M.C.H.C., especially in iron deficiency and in bloods with red cell sickling.

Anaemia per se is not responsible for the increased plasma trapping seen in iron deficiency, because if plasma is aspirated from sedimented blood samples so that the "haemoglobin" level becomes normal, increased plasma trapping is still evident.

We have concluded that the fall in M.C.H.C. in iron deficiency is to some extent artefactual. If allowance is made for trapped plasma in the microhaematocrit then the recalculated values of M.C.H.C. in iron deficiency are often within the accepted

normal range. Under these circumstances it is not surprising that electronic counters, such as the Coulter S, produce normal estimates of the M.C.H.C. These machines do not centrifuge the sample, so there can be no error due to plasma trapping. The Coulter "S", for example, simply calculates the M.C.H.C. from direct measurements of the haemoglobin, the red cell count, and the mean cell volume.

In severe iron deficiency there appears to be a genuine fall in the M.C.H.C. even after correction for trapped plasma, and we have also found that these samples give a low M.C.H.C. on the Coulter "S". Our data emphasize the findings of Conrad and Crosby² that the prime abnormality in hypochromia is the production of a small red cell with a normal haemoglobin concentration. Only in more severe deficiency does the haemoglobin concentration within the cell fall.

Like others, we have found a low mean corpuscular haemoglobin together with a low mean cell volume to be of great value in the diagnosis of iron deficiency and thalassaemia, and obviously these measurements now replace conventional M.C.H.C. in diagnosis.—We are etc.,

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¹ England, J. M., Walford, D. M., and Waters, D. A. W., *British Journal of Haematology*, 1971, in press.

² Conrad, M. E., and Crosby, W. H., *Blood*, 1962, 20, 173.

Accidents at Work

SIR,—In your leading article on the above subject (25 September, p. 722) reference is made, discussing the *Annual Report of H.M. Chief Inspector of Factories, 1970*,¹ to "some notoriously hazardous occupations such as coal mining now employ fewer men. . . ." The accidents incurred by coal miners are not reported under the Factories Act but rather under the Mines and Quarries Act, and receive separate comment in the *annual Report of H.M. Chief Inspector of Mines and Quarries*.²—I am, etc.,

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¹ *Annual Report of H.M. Chief Inspector of Factories, 1970*, Cmnd. 4758. London, H.M.S.O., 1971.

² Ministry of Power. *Report of H.M. Chief Inspector of Mines and Quarries for 1968*. London, H.M.S.O., 1969.

Iododeoxyuridine and Trachoma

SIR,—In my review of Burnet's *Genes, Dreams and Realities* (18 September, p. 712) I stated, in reply to Burnet's claim that no human benefit whatever had yet been derived from the study of molecular biology, that a programme of fundamental research in this subject had yielded iododeoxyuridine, which was an effective chemotherapeutic agent in a number of severe virus infections of the eye, including trachoma. I am grateful