Board of Medical Examiners (USA) testing material has been introduced into the undergraduate curriculum on an experimental basis and it is hoped that by doing this the strengths and weaknesses in the curriculum—at least within the American context of medical education—will become apparent and that, furthermore, graduates who wish to go to the United States and Canada either for postgraduate training or to settle there permanently will find it easier to take the requisite American examinations. Many postgraduate activities enamate from the college—the Irish Surgical Postgraduate Training Committee in association with the Joint Committee of the Surgical Colleges co-ordinates postgraduate surgical training in Ireland, and the Faculties of Anaesthetists, Radiology, and Dentistry organise postgraduate training in their respective subjects. With the recent inauguration of the Faculty of Nursing, the college has given overdue recognition and status to this branch of the profession.

The future

The college now enters a new era in its development and, while recognising that the new school is a considerable achievement, the academic staff are only too aware that the departments within the college must be developed so as to produce not only competent doctors but through its hospitals and postgraduate institutions to consolidate its position firmly on the stage of world medicine. The emphasis must now be on intellectual rather than further structural development. A prerequisite for this must be the removal from its graduates of the archaic semantic handicap of a licence as distinct from a degree; the college for almost 200 years has awarded a diploma of licence to its students at graduation and, now that this qualification is recognised in EEC countries as being of degree status, it is to be hoped that soon the title and basic qualifications of the college will be declared a primary degree so that college graduates may enter the academic arena on an equal footing with their university colleagues.

To the staff, students, and graduates of the college, the medical school extension must serve as a stimulus to future development; to those sceptical of the survival of a private medical school it must be seen as the college's vote of confidence in its own future; and to the medical profession it is an example of what can be achieved through private enterprise.

Nam et ipsa scientia potestas est.

Clinical Topics

Myelotoxicity of gold

APRIL G L KAY

British Medical Journal, 1976, **1**, 1266-1268

Summary

Of 55 patients who developed blood dyscrasias attributable to gold treatment 15 with bone marrow hypoplasia died. A few of the dyscrasias, occurring in patients who had taken a low total dose of sodium aurothiomalate, may have resulted from immune hypersensitivity, but most, occurring in patients who had taken a higher total dose, were due to cumulative toxicity. All patients receiving gold treatment should undergo frequent blood counts. Any pronounced or continuing fall in the counts is a warning of toxicity, and gold treatment should be stopped. Treatment should be resumed only with caution, and in some patients already in remission lower doses may be just as effective in controlling the disease.

Introduction

Gold has been used in the treatment of rheumatoid arthritis for nearly 50 years, but its true value was first established more recently,[1 2] since when it has remained a standard treatment. Adverse consequences of chrysotherapy include damage to the haemopoietic system, which is sometimes fatal.[3-5] Seventeen deaths from blood dyscrasias attributed to gold were reported to the Committee on Safety of Medicines between 1965 and 1971.[6] These and more recent observations[7] led to the present study.

Arthritis and Rheumatism Council Epidemiology Research Unit and Guy's Arthritis Research Unit, Guy's Hospital, London SE1

APRIL G L KAY, MB, BS, medical officer

Patients and methods

The records of 55 patients who developed blood dyscrasias while on gold treatment were collected from two sources: from rheumatology units in response to personal requests (42) and from the Committee on Safety of Medicines (13). Initially the patients were included if they had developed thrombocytopenia of less than 100×10^9/l (100 000/mm^3) or leucopenia of less than 2×10^9/l (2000/mm^3) during or within a few months of chrysotherapy. These criteria were subsequently extended to include patients with selective polymorph neutropenia of less than $0{\cdot}5 \times 10^9$/l (500/mm^3). Marrow biopsies were reviewed in 14 cases.

Of the 55 patients, 45 were women and 10 were men. The mean age at the time of the reaction was 45 years (range 13-74 years). All the reactions except one occurred in the years 1965-71.

Results

All patients had received initial test doses of 2·5-20 mg sodium aurothiomalate (Myocrisin), and in most (47) the weekly dose thereafter was 50 mg. Abnormalities in the blood count were noted after an average of 23 weeks of treatment (range 3-104 weeks) and after a mean dose of 682 mg (range 40-2040 mg). Fourteen of the 15 patients with pancytopenia who died had not reached the conventional full course

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dose of 1 g. The patients fell into two main groups: those developing reactions at a total dose of less than 200 mg sodium aurothiomalate (low-dose group) and a larger group in whom the reactions developed at a dose of greater than 200 mg; in this high-dose group only three patients had taken less than 400 mg.

LOW-DOSE GROUP

Of the nine patients who had received less than 200 mg sodium aurothiomalate, six developed thrombocytopenia only; eosinophilia was noted in one of these. All six recovered two to 12 weeks after the gold was withheld, and the apparent benefit from dimercaprol in one case[8] must remain doubtful. The other three patients in the low-dose group developed neutropenia (fig 1), which was associated in two cases with skin irritation or a rash, fever, and eosinophilia. A marrow biopsy in one case showed poor overall cellularity and leucopoiesis represented entirely by blast cells. Recovery in all these cases was rapid and complete, possibly helped by fresh (irradiated) blood transfusion or dimercaprol and prednisolone.

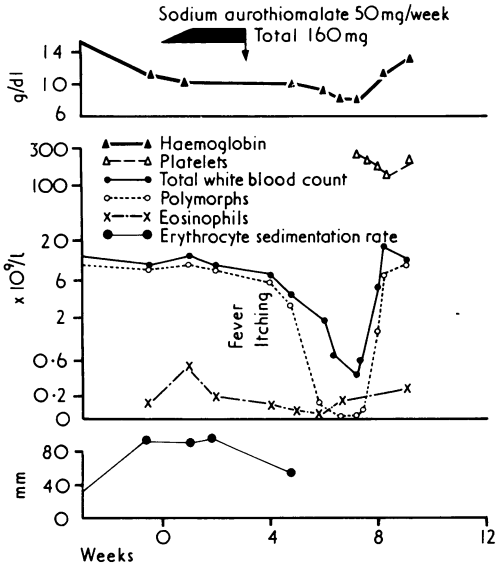

FIG 1—Neutropenia developing at a low total dose of gold.

Conversion: SI to traditional units—Blood counts: 1 × 10^9/l = 1000/mm^3.

HIGH-DOSE GROUP

Twenty-six patients developed thrombocytopenia at doses of sodium aurothiomalate ranging from 280-2050 mg. In most of these patients (15) there was no record of a platelet count performed before clinical evidence of thrombocytopenia developed. In eight patients platelet depression developed suddenly, but in three others a gradual fall was observed, which continued after the gold was stopped. Two patients developed eosinophilia before, and leucocytosis as, they became acutely thrombocytopenic. Marrow biopsies were performed in only six of these patients: in three the appearances were normal, in one there was general hypoplasia, and in two there was a reduction in the number of megakaryocytes. All 26 patients recovered, 10 of them without specific treatment. The period of recovery varied from a few weeks to over a year, but the rate of recovery did not seem to be related to the dose of gold received. Nor, with the possible exception of an effect from corticosteroids in a few cases, was it influenced by the treatment given.

By contrast, only five of the 20 patients who developed pancytopenia recovered. The 15 deaths were directly due to marrow aplasia; the immediate cause was haemorrhage in nine, infection in two, and a combination of both in the remaining four. There was a small difference in dosage between the fatal and the non-fatal cases, with mean totals of 744 mg in 18·6 weeks and 598 mg in 15·2 weeks respectively.

All five patients who recovered were attending rheumatology units familiar with chrysotherapy and were treated with various combinations of corticosteroids, dimercaprol, and penicillamine. A girl aged 13 years

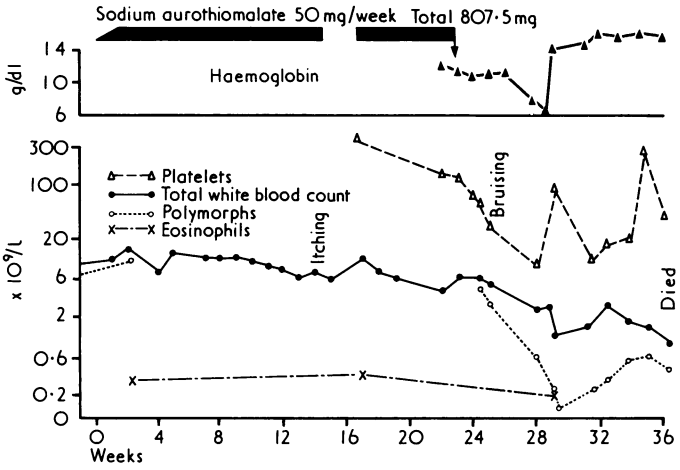

FIG 2—Fatal pancytopenia. White cell count fell steadily; it was at first within the normal range. Erythrocyte sedimentation rate was not recorded.

developed eosinophilia preceding leucopenia and thrombocytopenia and recovered rapidly after the gold was stopped. Two other patients who recovered were found to have severe marrow hypoplasia several months after gold treatment had ceased.

All those who died had received more than 400 mg sodium aurothiomalate, and eight out of 13 patients on whom sufficient information was available had already experienced remission of their arthritis at the time of onset of marrow depression. Eleven patients were receiving 50 mg and one 100 mg sodium aurothiomalate weekly. One patient was taking phenylbutazone concurrently with gold, and four had been on this drug before starting chrysotherapy. Five of the patients were being given gold by their general practitioners, and in all but one of these blood counts were infrequent.

The course in one patient (fig 2) was of some interest because a downward trend of leucocyte and platelet counts, though still within the normal range, could be seen in retrospect to have been a danger signal. When gold was stopped because of skin irritation there was a temporary rise in the white count, which then fell again after the gold was restarted. This patient was one of the two who died in whom there was evidence of early marrow recovery. Combinations of dimercaprol, penicillamine, corticosteroids, and supportive treatment with fresh blood and platelet concentrates were given in an attempt to save these patients.

Discussion

Girdwood[7] estimated that the incidence of fatal reactions to gold is about 1·6 per 100 000 prescriptions and is over five times that of any other drug. Since gold remains valuable in the treatment of rheumatoid arthritis it is important to understand the precise circumstances in which bone marrow toxicity occurs and how fatal overdosage can be avoided.

Reviewing the available information on these 55 patients, I looked for premonitory signs and symptoms: rashes were observed in 12 and stomatitis in two; two of the patients complained of sore throats and six of malaise.

Eosinophilia, traditionally regarded as a warning sign and recently observed to occur often in patients on gold,[9] particularly before or with skin reactions,[10] was noted in only five cases. The low incidence was partly accounted for by the infrequent recording of differential white counts. The mechanisms producing these blood dyscrasias remain uncertain. Howell *et al*[11] have shown that colony formation in normal marrow is inhibited by sodium aurothiomalate in a dose-dependent manner. Most of the cases of aplasia in patients who had had substantial doses of sodium aurothiomalate (400 mg or more) and whose white cell counts showed a steady decline were probably due to direct bone marrow toxicity. In a minority of patients a small dose of sodium aurothiomalate (<200 mg) produced either neutropenia or thrombocytopenia. The onset was sudden and they recovered quickly, and some type of hypersensitivity may have been the pathological mechanism.[12,13] This has not so far been

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proved,[8 14 15] but positive lymphocyte transformation[16] and the occurrence of eosinophilia in these cases is suggestive.

The prevention of direct toxicity depends above all on monitoring by frequent blood counts: these must include platelet as well as leucocyte counts, and preferably the results should be charted on a flow sheet with the dose of gold given. Any pronounced fall or continued falling trend is a danger signal even if the blood count is still within the normal range. Gold should then be stopped and resumed only with great caution. All the dose schedules were within the accepted safe range, but all but nine of the dyscrasias occurred before 1 g of sodium aurothiomalate had been given; some of these patients were already in remission and still receiving 50 mg weekly. Lower or less frequent dosage may be safer and just as effective in maintaining disease control.

Treatment of established aplasia depends on vigorous supportive measures, and possibly in rare circumstances bone marrow transplantation may be considered. There is little positive evidence that specific measures such as treatment with dimercaprol or penicillamine are of benefit, but doubtless they will continue to be used, as will corticosteroids, which seem to help in some cases of thrombocytopenia.[10]

I thank Dr W H W Inman and the Committee on Safety of Medicines; all the clinicians and haematologists who generously allowed me to include their cases; the late Dr H J A Richards, of May and Baker Limited; and Dr H E M Kay for reviewing the marrow specimens and for advice and criticism.

References

1 Research Sub-Committee of the Empire Rheumatism Council, *Annals of the Rheumatic Diseases*, 1960, **19,** 25.
2 Research Sub-Committee of the Empire Rheumatism Council, *Annals of the Rheumatic Diseases*, 1961, **20,** 315.
3 Forestier, J, *Journal of Laboratory and Clinical Medicine*, 1934-5, **20,** 827.
4 Meyer, W, *Medizinische Klinik*, 1970, **65,** 949.
5 Tuel, J, *Ugeskrift for Læger*, 1973, **135,** 1639.
6 Committee on Safety of Medicines, *British Medical Journal*, 1971, **1,** 471.
7 Girdwood, R H, *British Medical Journal*, 1974, **1,** 501.
8 England, J M, and Smith, D S, *British Medical Journal*, 1972, **2,** 748.
9 Jessop, J D, *et al*, *Rheumatology and Rehabilitation*, 1974, **13,** 75.
10 Davis, P, and Hughes, G R V, *Arthritis and Rheumatism*, 1974, **17,** 965.
11 Howell, A, Gumpel, J M, and Watts, R W E, *British Medical Journal*, 1975, **1,** 432.
12 Horowitz, H, and Nachman, R L, *Seminars in Hematology*, 1965, **2,** 287.
13 Davis, P, *et al*, *British Medical Journal*, 1973, **3,** 17.
14 Deren, B, *et al*, *Archives of Internal Medicine*, 1974, **134,** 1012.
15 Stavem, P, Stromme, J, and Bull, O, *Scandanavian Journal of Haematology*, 1968, **5,** 271.
16 Denman, E F, and Denman, A M, *Annals of the Rheumatic Diseases*, 1968, **27,** 582.

Problems of Childhood

Infant feeding: a current view

D P ADDY

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The recent report[1] by the Department of Health and Social Security (DHSS) has emphasised the superiority of breast milk and advocated renewed efforts in promoting breast-feeding by educating schoolchildren, parents, and mothers-to-be and by the appropriate instruction of medical students and student nurses. In this respect, and in noting the possible dangers associated with bottle-feeding, the report agrees with recent trends.[2-7]

Superiority of breast-feeding

Infant feeding is an emotive subject and advocates of breast-feeding have sometimes relied more on a personal belief in its naturalness, and therefore rightness, than on the evidence, and there has consequently been a widespread belief, even among paediatricians, that artificial milks are just as good.[8] Recently, however, evidence showing the unique character of human milk in the nutrition of the human infant has accumulated to an extent where it is now difficult to deny that "breast is best."

Some of the reasons for advocating breast feeding are listed in table I, in which an attempt is made to assess the reliability of the evidence incriminating artificial feeding for each of the conditions listed.

TABLE I—*Factors incriminating artificial feeding*

Sound evidence:	
Infection	— gastrointestinal
	— other
Chemical disturbance	— hypocalcaemia
	— hypernatraemia
Obesity	
Cows' milk allergy in infancy	
Necrotising enterocolitis	
Some evidence—not conclusive:	
Cot death	
Atopic diseases	
Equivocal evidence:	
Ulcerative colitis	
Coronary vascular disease	
Multiple sclerosis	

Dudley Road Hospital, Birmingham B18 7QH
D P ADDY, MRCP, DCH, consultant paediatrician

INFECTION

Gastroenteritis

Over 14 000 infants were admitted to hospital in England and Wales in 1972 with gastroenteritis.[9] Of these, 306 died[10] and the infant mortality rate from this cause was 0·4 per 1000 live births or about 1 in 40 deaths in the first year of life.[10] The disease is much more common in bottle-fed babies.[11 12] In a recent hospital series from Manchester[13] only one of 339 infants, of whom 170 were under 6 months, was breast-fed. The opportunity for bacterial contamination during the preparation of the feeds is a constant risk with bottle-

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