roidism, which must have contributed to the pathogenesis of hypocalcaemia. The hyposecretion of iPTH in these patients is probably secondary to several factors including hypomagnesaemia, which inhibits the secretion of iPTH both in vivo and in vitro.²⁻⁹ Antimicrobial and cytotoxic drugs may also have an inhibitory effect on iPTH secretion. Vinblastine, for instance, disrupts the morphology of the parathyroid gland.¹⁰ Aminoglycosides have been incriminated in the pathogenesis of hypoparathyroidism,³ but in our series two patients developed the syndrome in the absence of aminoglycoside treatment. All nine patients, however, had been taking doxorubicin (or daunorubicin) and cytarabine; these drugs may have contributed to the suppression of parathyroid secretion.

In conclusion, we have described a syndrome that consists of a combination of hypocalcaemia, hypomagnesaemia, and a state of absolute or relative hypoparathyroidism in patients receiving treatment for acute leukaemia. In our series the syndrome was common and led to profound clinical problems, including tetany. The condition appears to be multifactorial and requires further investigation. Awareness of this metabolic problem allowed us to intervene therapeutically and to reduce morbidity. We subsequently prevented any appreciable decrease in plasma calcium and magnesium concentrations by giving appropriate supplements and 1α -hydroxycholecalciferol. Despite this concentrations of parathyroid hormone remained low (unpublished data).

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References

- 1 Mir MA, Delamore IW. Metabolic disorders in acute myeloid leukaemia. *Br J Haematol* 1978;**40**:79-92.
- 2 Rude RK, Oldham SB, Singer FR. Functional hypoparathyroidism and parathyroid hormone end-organ resistance in human magnesium deficiency. *Clin Endocrinol (Oxf)* 1976;**5**:209-24.
- 3 Keating MJ, Sethi MD, Boden GP, Sa Maan NA. Hypocalcaemia with hypoparathyroidism and renal tubular dysfunction associated with aminoglycoside therapy. *Cancer* 1977;**39**:1410-4.
- 4 Levi J, Massry SG, Coburn JW, Llach F, Kleiman CR. Hypocalcaemia in magnesium-depleted dogs; evidence for reduced responsiveness to parathyroid hormone and relative failure of parathyroid gland function. *Metabolism* 1974;**23**:324-35.
- 5 Lifshitz F, Harrison HC, Harrison HE. Response to vitamin D of magnesium deficient rats. *Proc Soc Exp Biol Med* 1967;**125**:472-6.
- 6 Chase CR, Slatopolsky E. Secretion and metabolic efficacy of parathyroid hormone in patients with severe hypomagnesaemia. *J Clin Endocrinol Metab* 1974;**38**:363-71.
- 7 MacManus J, Heaton FW. The influence of magnesium on calcium release from bone in vitro. *Biochim Biophys Acta* 1970;**215**:360-7.
- 8 Hillyard CJ, Oscier DG, Foa R, Catovsky D, Goldman JM. Immuno-reactive calcitonin in leukemia. *Br Med J* 1979;iii:1392-3.
- 9 Targovnik JH, Rodman JS, Sherwood LM. Regulation of parathyroid hormone secretion in vitro: quantitative aspects of calcium and magnesium ion control. *Endocrinology* 1971;**88**:1477.
- 10 Reaven FP, Reaven GM. A quantitative ultrastructural study of microtubule content and secretory granule accumulation in parathyroid glands of phosphate and colchicine treated rats. *J Clin Invest* 1975;**56**:49.

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Therapeutic control of anticoagulant treatment

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Abstract

Control of anticoagulant treatment was studied in 250 patients. One hundred and fifty patients receiving long-term anticoagulant treatment (group 1) were studied for 52 weeks and the remaining 100 (group 2) for 12 weeks after discharge from hospital. The desired British corrected ratio range was 2.5-3.3, and a range of 2.3-3.5 was classified as satisfactory. In group 1 a satisfactory ratio was obtained for 70% of the study period and 120 of the 150 patients were maintained within this range for over 60% of the time. In group 2 only half of the patients were maintained within the satisfactory range and for 50% of the study period or less. The time and effort expended in therapeutic control were more than most clinics could afford, and the results for group 2 were disappointing.

The standard of long-term anticoagulant treatment should be improved by continuous review of control and by "therapeutic quality control."

Introduction

In the early days of anticoagulant treatment haemorrhage was a real danger owing to the variable sensitivities of thromboplastins, and as a result most patients received insufficient treatment. In his historical review of anticoagulant treatment Loeliger¹ stated that a ratio range of 2.0-2.5 was recommended by the American Heart Association based on the earlier work of Allen *et al*^{2,3} and Wright *et al*,⁴ who had suggested ranges of 1.5-3.0 and 2.0-3.0 respectively. At the time this was considered to be adequate and safe. With the standardisation of thromboplastins by the introduction of British comparative thromboplastin by Poller^{5,6} and the "external quality assessment scheme"⁷ that followed, anticoagulant treatment was placed on a safer foundation.

Higher ratio ranges are now recommended, especially for patients who have had open-heart surgery. Blackburn⁸ recommended a British corrected ratio (BCR) of 2.0-4.0 based on clinical experience, but Poller⁹ found that haemorrhage was rare in hospitals using British comparative thromboplastin as a reagent and suggested that a BCR of 5.0 was a safe upper limit for hospital patients with active thrombosis. Loeliger¹ proposed that the optimum therapeutic range should be 3.0-5.0 for inpatients and 2.5-4.5 for outpatients. For patients with artificial heart valves Boekhout-Mussert *et al*¹⁰ advised a higher range, equivalent to a BCR of 3.0-5.0.¹ The range adopted for the "Dutch trial"¹¹ in elderly patients after myocardial infarction was 2.7-4.5.

The effectiveness of attempting to achieve higher ratio ranges therefore requires confirmation.

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Patients and methods

I reviewed anticoagulant ratios in 250 patients. A third of the patients had received heart-valve replacements or coronary artery grafts. The others suffered from multiple myocardial infarctions, recurrent pulmonary embolism, heart-valve disease, atrial fibrillation, recurrent deep-vein thrombosis, and arterial vascular disease, and so were an average selection of patients attending anticoagulant clinics. For this investigation all were anticoagulated to the same degree to see how the ratio range could be maintained.

The patients were divided into two groups: group 1 consisted of 150 long-term patients, who were reviewed for 52 weeks (1980), and group 2 consisted of 100 patients treated for three months after discharge from hospital.

As British comparative thromboplastin consistently gave a control time of 12 ± 0.5 s when Quick's test was performed with a prothrombin-time meter (Clotek; Hyland) the defined ranges were based on prothrombin times in seconds as in table I.

TABLE I—Defined ranges of British comparative ratio

Prothrombin time (s) (control value 12 s)	British ratio	Classification	Range score
30-40	2.5-3.3	Aimed for range	
28-42	2.3-3.5	Satisfactory	A
43-50	3.6-4.2	Overanticoagulation	B
> 50	> 4.2	Potentially dangerous	C
23-27	2.0-2.3	Insufficient anticoagulation	D
< 23	< 2.0	Inadequate	E

The control achieved was recorded as the number of weeks for which the defined ranges were obtained. When the range changed between visits the range "score" was considered to have lasted for half the interval between the visits. The figure shows the record card of one patient whose ratio was unstable and passed through all the ranges.

Date	Prothrombin time (s)		Brit ratio	Daily dose (mg)	test	Subdivided dose
	Patient	Control				
4-4-80	49	12	4.08	3 1/2	28-4	But...mg (.....) on each Mon Tues Wed Thur Fri Sat Sun 2 wks
28-4	32	12	2.66	3 1/2	12-5	But...mg (.....) on each Mon Tues Wed Thur Fri Sat Sun 2 wks
12-5	22	12	1.83	3 1/2	2-6	But...4...mg (.....) on each Mon Tues Wed Thur Fri Sat Sun 3 wks
2-6	37	12	3.08	3 1/2	23-6	But...4...mg (.....) on each Mon Tues Wed Thur Fri Sat Sun 3 wks
23-6	41	12	3.42	3 1/2	7-7	But...3...mg (.....) on each Mon Tues Wed Thur Fri Sat Sun 2 wks
7-7	36	12	3.00	3	28-7	But...3 1/2...mg (.....) on each Mon Tues Wed Thur Fri Sat Sun 3 wks
28-7	55	12	4.58	3	11-8	But...3 1/2...mg (.....) on each Mon Tues Wed Thur Fri Sat Sun 2 wks
11-8	27	12	2.25	3	25-8	But...3 1/2...mg (.....) on each Mon Tues Wed Thur Fri Sat Sun 2 wks

Record card of one patient receiving anticoagulant treatment showing range scores attained.

Though overanticoagulation is not advisable for the safety of patients, it is nevertheless satisfactory for inhibition of thrombosis, and so there was some bias in group 2 and a BCR range of 2.3-4.2 was considered to be satisfactory (ranges A + B).

Results

Group 1—Table II shows the average percentage of time for which the defined ratio ranges were recorded in the 150 patients over 52 weeks. The satisfactory range (BCR 2.3-3.5) was attained for nearly 70% of the time; the range indicated insufficient or inadequate anticoagulation for 25% of the time. Sixty-three patients (42%) were maintained within the satisfactory range for 60-70% of the time and 57 (38%) for over 75% of the time, so that 120 patients (80%) were maintained in the satisfactory range for more than 60% of the time. Thirty (20%) patients were maintained in the satisfactory range for only 50% or less of the time.

Group 2—Just over half (51) of the 100 patients given anticoagulant treatment for three months after discharge from hospital were maintained in the satisfactory range for only 50% or less of the time; 34 were maintained in this range for 60-75% of the time and 15 for over 75% of the time. Table III shows the number of patients whose ratio was maintained in the satisfactory range during each week of the three months: more patients were adequately controlled during the first week of each month, after which dose requirements altered and it took the remainder of the month to bring the patients back in control. Even in the good week of the month, however, only 40 of the patients were under adequate control. Some patients were brought under control only during the last month, just before treatment was due to be stopped.

TABLE III—Analysis of time for which ratio in patients in group 2 was maintained in satisfactory range

Weeks:	First month				Second month				Third month			
	1	2	3	4	1	2	3	4	1	2	3	4
No of patients maintained in satisfactory range	40	22	25	13	43	15	13	29	39	19	16	26

Discussion

The figures for the patients who received anticoagulant treatment over 52 weeks were better than was originally predicted in the preliminary report.¹² To obtain these results, however, it was necessary to determine patients' prothrombin times every two to three weeks and at weekly intervals when there were appreciable changes in prothrombin time or dose. The time and effort required is much more than most anticoagulant clinics can afford.

The standard of anticoagulant control in patients treated for only three months after discharge from hospital was poor and probably of no clinical value, but the cost and effort entailed were considerable, for most of the patients had to be seen weekly and many of them required ambulances.

In past years, when a BCR range of 2.0-2.5 was accepted as satisfactory, patients could be seen at intervals of four to six weeks without any appreciable danger. With the dangers of overdosage due to variable sensitivity of thromboplastins diminished by national and international standardisation and quality assessment of methods, a higher BCR range of 2.5-4.5¹ is now advised. Maintaining this higher range without danger of overanticoagulation is more difficult since this is on the steep portion of the dose-prothrombin time curve.

Another difficulty is that the response to anticoagulants is affected by so many factors (for example, patient non-compliance, individual resistance or sensitivity,¹³ dietary change,¹⁴ and drug interactions¹⁵⁻¹⁷), which thwart the maintenance of good

TABLE II—Proportion of time for which ratio was maintained in each range in patients in group 1

					British ratio				
					<2.0 (Inadequate)	2.0-2.3 (Underanticoagulated)	2.3-3.5 (Satisfactory)	3.6-4.2 (Overanticoagulated)	74.2 (Potentially dangerous)
Time for which ratio maintained as % of year	..	..	..	..	5.4	19.3	69.6	4.3	1.4
(No of weeks)	..	..	..	..	(3)	(10)	(36)	(2)	(1)

therapeutic control. Because of these difficulties patients must be seen more often to maintain good therapeutic control: this is expensive in manpower and time and more than most hospitals can afford. Harries *et al*¹⁸ and McInnes¹⁹ confirmed that junior staff always play for safety when prolonged intervals are in use, and as a result underanticoagulation is the most common defect of control.

Mitchell²⁰ pointed out that so many statistical errors were made in the early trials of anticoagulant treatment, and the quality of thromboplastins was so poor and variable then, that the findings of most of these trials must be considered to be invalid.

The findings of the early Medical Research Council trials of anticoagulant treatment after myocardial infarction²¹⁻²³ were equivocal except for a reduction of the secondary effects of intramural thrombi. The value of anticoagulant treatment in this condition has therefore fallen into disrepute recently, and few now continue anticoagulant treatment for long after patients are discharged from hospital. The recent "Dutch trial,"¹¹ avoiding the errors of early trials and maintaining the therapeutic ratio range within close limits, showed that intensive and stable anticoagulant treatment substantially reduced the risk of recurrent myocardial infarction. This suggests that early trials failed due to inadequate control of treatment.

Over the next few years the number of patients receiving long-term anticoagulant treatment will increase owing to the reassessment of these new trials and the increased number of patients undergoing cardiac surgery.

Recommendation—Anticoagulant treatment is expensive and is not cost effective. It is invariably delegated to rotating junior staff, who may not have had previous experience, and so there is no consistent control. Medical assessment of anticoagulant treatment should be started. The method described here is simple and may be recorded in the patients' record cards after each visit. The "score" may then be evaluated annually. British comparative thromboplastin and the associated quality assessment scheme has given anticoagulant treatment a safe foundation. With the higher therapeutic BCR ranges now being advocated therapeutic quality control is required so that this expensive and potentially dangerous treatment may be used to the greatest effect.

References

- Loeliger EA. The optimal therapeutic range in oral anticoagulation. *Thromb Haemostas* 1979;**42**:1141-52.
- Allen EV, Barker NW, Waugh JM. A preparation from spoiled sweet clover which prolongs coagulation and prothrombin time of the blood: a clinical study. *JAMA* 1942;**120**:1009-15.
- Allen EV. The clinical use of anticoagulants. *JAMA* 1947;**134**:323-9.
- Wright IS, Marple CD, Beck DF. Anticoagulant therapy of coronary thrombosis with myocardial infarction. *JAMA* 1948;**138**:1074-9.
- Alderson MR, Poller L, Thomson JM. Validity of the British system for anticoagulant control using the national reagent. *J Clin Pathol* 1970;**23**:281-5.
- Poller L. The British national thromboplastin. *Br J Haematol* 1971;**20**:359-62.
- Poller L. The British system for anticoagulant control. *Thromb Diath Haemorrh* 1975;**33**:157-62.
- Blackburn EK. Long-term anticoagulant therapy. *Prescriber's Journal* 1977;**17**:73-4.
- Poller L. British comparative thromboplastin therapeutic range. *Thromb Haemostas* 1976;**36**:485.
- Boekhout-Mussert MJ, Briët E, van Brummelen P, Lemkes HHPJ, Loeliger EA. Arterial thromboembolic complications with aortic ball valve prostheses. *Am Heart J* 1978;**95**:270-1.
- The Sixty Plus Reinfarction Study Research Group. A double-blind trial to assess long-term oral anticoagulant therapy in elderly patients after myocardial infarction. *Lancet* 1980;ii:989-94.
- Duxbury BMCD. Control of anticoagulant therapy. *Lancet* 1981;ii:1001.
- Breckenridge AM. Interindividual differences in the response to oral anticoagulants. *Drugs* 1977;**14**:367-75.
- Goodman LS, Gilman A, eds. *The pharmacological basis of therapeutics*. 5th ed. New York: Macmillan, 1975.
- Mackie MJ, Douglas AS. Anticoagulants. *Br J Hosp Med* 1976;**16**:118-23.
- Fenech A, Winter JH, Douglas AS. Individualisation of oral anticoagulant therapy. *Drugs* 1979;**18**:48-57.
- Kelly JG, O'Malley K. Clinical pharmacokinetics of oral anticoagulants. *Clin Pharmacokinet* 1979;**4**:1-15.
- Harries AD, Birtwell AJ, Jones DB. Anticoagulant control. *Lancet* 1981;ii:1320.
- McInnes GT. Efficacy of anticoagulation in the UK. *Lancet* 1981;ii:88.
- Mitchell JRA. Anticoagulants in coronary heart disease—retrospect and prospect. *Lancet* 1981;ii:257-62.
- Medical Research Council. An assessment of long-term anticoagulant administration after cardiac infarction. *Br Med J* 1959;ii:803-10.
- Medical Research Council. An assessment of long-term anticoagulant administration after cardiac infarction. *Br Med J* 1964;iii:837-43.
- Medical Research Council. An assessment of short-term anticoagulant administration after cardiac infarction. *Br Med J* 1969;ii:335-42.

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SHORT REPORTS

Lhermitte's sign in Behçet's disease

The neurological manifestations of Behçet's disease may resemble those of multiple sclerosis. The most common patterns in Britain are transient or persistent episodes of brain-stem dysfunction and focal cerebral or spinal cord disease.¹ The diagnosis of Behçet's disease is clinical and may be difficult, particularly when neurological disease precedes the more easily recognisable systemic features.

Lhermitte's sign consists of a sudden tingling or sensation of electric shock in the limbs on flexion of the neck and was originally thought to be pathognomonic of multiple sclerosis.² It is now recognised as occurring in various conditions affecting the cervical cord and cervicomedullary junction.^{3,4} We observed this sign to be a prominent feature in two patients with Behçet's disease.

Case reports

CASE 1

An 18-year-old Cypriot developed shock-like sensations "like a flash of blood or electricity" in his legs and arms on flexion of the neck. This persisted and was followed by left-sided hypoesthesia, leg weakness, and incoordination. He had suffered arthritis of the hands at the age of 15 and subsequently episodes of erythema nodosum.

On examination he had bilateral jerk nystagmus, left-sided cerebellar signs and sensory impairment with impaired joint position and vibration sense, and a spastic paraparesis. Lhermitte's sign was present. Ocular examination showed old anterior uveitis with active inflammation of the vitreous and periphlebitis. There were no other notable abnormalities. The clinical impression was of multiple sclerosis, but ocular inflammation and distinct inflammatory changes in the cerebrospinal fluid suggested an alternative such as sarcoidosis or Behçet's disease. A myelogram was normal.

Six months later he developed painful crops of oral ulcers and occasional painful penile ulcers, which subsequently recurred. His neurological condition gradually deteriorated despite corticosteroids and immunosuppressives. The clinical diagnosis was Behçet's disease, dominated by neurological symptoms. The original complaint of Lhermitte's sign persisted.

CASE 2

A 45-year-old woman developed neurological disease. Behçet's disease had been diagnosed nine years earlier on the basis of longstanding painful mouth and genital ulcers, polyarthralgia, and uveitis. She had been treated intermittently with steroids and immunosuppressives. She later complained of right-sided weakness and "brisk electric shocks" down her right side on flexion of the neck. These were momentary, shooting from the neck to the fingers and toes.

She was mildly cushingoid with active arthritis, orogenital ulceration, and anterior and posterior uveitis. Neurological examination showed reduced sensation on the right, including joint position and vibration sense. There was mild pyramidal weakness on the right but no evidence of incoordination or nystagmus. Lhermitte's sign remained present. Investigations showed an