No circulatory or metabolic changes were found which might account for the severity of symptoms in accidental hypothermia in persons who have walked to the point of exhaustion. Blood volume normally falls by 5 to 15% during the first 10 to 15 minutes of muscular exercise (for references see Pugh, 1969), and we had expected to find a further decrease in blood volume associated with exhaustion in hill-walkers. This, however, appears not to be the case, at any rate in persons who have free access to fluid and take occasional short rests. According to recent catheter studies (Ekelund, 1967), the rising heart rate and tendency to postural hypotension in persons working to exhaustion are due essentially to failure of vasomotor regulation and not to changes in blood volume. They found reduced cardiac stroke output, reduced peripheral resistance, and altered distribution of blood in the capacitance vessels.

The only positive observation bearing on fatigue was ketonuria. Subject S. H., who finished in a state of partial collapse on Edale I, showed the greatest degree of ketonuria, and there was less ketonuria on Edale II, when the subjects seemed less tired. Two months later urine samples were collected on 250 participants in a 50-mile (80-km.) walking competition in the same area. The leading teams that completed the course at a run showed no ketonuria. Slower teams showed ketonuria roughly in proportion to their times. Some participants who were exhausted showed obvious mental changes in spite of the fact that the competition took place in warm weather. This was an important observation, since mental change is a common early finding in "exposure" accidents, and is usually attributed to hypothermia.

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Vincristine and Prednisone for the Induction of Remissions in Acute Childhood Leukaemia

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Summary: A total of 65 children with acute lymphoblastic leukaemia and seven with other types of acute leukaemia received treatment with a combination of vincristine and prednisone. In all 122 courses of treatment were given. Of 22 patients with acute lymphoblastic leukaemia who received this as their first treatment, all achieved complete remission. The complete remission rates were 82% for patients with acute lymphoblastic leukaemia in their first relapse, 63% in the second relapse, and much lower in subsequent relapses and in the patients with other types of acute leukaemia. Alopecia and gastrointestinal and neuromuscular toxicity occurred respectively in 51%, 29%, and 21% of instances, only the last of these side-effects of vincristine being dose-related. Most of the complete remissions were obtained with a total dose of vincristine which carried only a low risk of neurotoxicity.

Introduction

It is now well established that combinations of certain anti-leukaemic drugs are superior to the same drugs used singly for

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the induction of remissions in acute leukaemia (Acute Leukemia Group B, 1965 ; Frei *et al.*, 1965 ; Krivit *et al.*, 1966 ; Karon, 1968). Vincristine sulphate (Oncovin), for example, is now generally accepted as a valuable remission-inducing agent in acute lymphoblastic leukaemia, both at the onset of the disease and during relapse (Karon *et al.*, 1962 ; Evans *et al.*, 1963 ; Heyn *et al.*, 1965 ; Karon *et al.*, 1966 ; Howard, 1967 ; Haggard *et al.*, 1968), but its effectiveness has been shown to be greatly enhanced by combination with prednisone, when remission rates of over 80% can be achieved (Acute Leukemia Group B, 1965 ; Hananian *et al.*, 1965). It is less useful as a maintenance agent, both on account of its cumulative toxicity and because the length of remissions maintained with vincristine compares unfavourably with those maintained with other agents (Karon *et al.*, 1966 ; Haggard *et al.*, 1968).

Many of the previously reported results of treatment with vincristine have referred to groups of patients treated at various stages of their disease. In this paper we analyse our experience with vincristine and prednisone as a remission-inducing combination in previously untreated acute lymphoblastic leukaemia in children, and show that the results compare favourably with those of other reported regimens, including, for example, the triple therapy with prednisone, vincristine, and Rubidomycin described by Mathé *et al.* (1967). We also show that the efficacy of this combination diminishes progressively with succeeding relapses, and that neurotoxicity can be largely avoided by confining the dose of vincristine to the minimum necessary to induce remission. No evidence is presented on the effect of vincristine and prednisone on the duration of remissions, as these were all subsequently maintained by the use of other drugs.

Patients

During the past four years 65 patients with acute lymphoblastic leukaemia, aged 10 months to 11 years, and seven with other types of acute leukaemia, aged 3 to 12 years (Table I) have received a total of 122 courses of treatment with vincristine and prednisone at the Hospital for Sick Children. Of the lymphoblastic group 31 patients have received a single course so far, 22 have received two courses each, 10 have received three, and two have received four separate courses.

TABLE I.—*Case Material*

Type of Acute Leukaemia	No. of Patients	No. of Courses of Treatment
Lymphoblastic	65	113
Myeloblastic	5	6
Myelomonocytic	1	1
Plasma cell	1	2

Dosage

Prednisone was given to all patients at about 60 mg. per sq. m. body surface per day, in divided dosage, for two to four weeks, and then tailed off over about another 10 to 14 days in most instances. Vincristine was given intravenously weekly: individual doses varied from 1 to 3·3 mg./sq. m., but were within the range of 1·5–2·0 mg./sq. m. in 80% of instances. Up to seven weekly doses were given, but 90% of courses consisted of two to four doses of vincristine. Patients received supportive therapy with red cell and platelet transfusions, and with antibiotics whenever this was indicated.

Criteria of Remission

Patients were considered to be in *complete remission* when bone-marrow smears showed not more than 5% of blasts in a cellular marrow, when the peripheral blood contained no leukaemic cells and not less than 1,500 neutrophils and 100,000 platelets per cu. mm., and when there was no clinical evidence of enlargement of liver, spleen, or lymph nodes, or of infiltration of other organs—for example, kidneys or gonads. Evidence of meningeal leukaemia was not held to disqualify from complete-remission status, since this complication occurs independently of the state of the leukaemia in other sites, and is not amenable to most forms of systemic therapy. In fact none of the patients had evidence of meningeal involvement at the time of achieving complete remission, though 10 had such evidence at the time of haematological relapse (one during two relapses) and were therefore treated with intrathecal methotrexate concurrently with the vincristine and prednisone.

Patients showing significant clinical and haematological improvement (diminution in organ size and marked reduction in total peripheral blood and/or marrow blast cell count, with symptomatic improvement), but without reversion to complete-remission status (see above), were considered to have achieved *partial remission*.

Results

In Table II the results in acute lymphoblastic leukaemia are subdivided into those achieved in previously untreated patients at the time of diagnosis and those achieved in subsequent relapses. The small number of other types of acute leukaemia are considered as a single group, irrespective of the stage of disease at which the treatment was given ; three of these were treated at diagnosis, two in the first, three in the second, and one in the third relapse.

TABLE II.—*Results of Treatment with Vincristine and Prednisone*

Type of Leukaemia	Stage of Disease	Total Courses of Treatment	Remissions			
			Complete		Complete + Partial	
			No.	%	No.	%
Acute lymphoblastic	Initial treatment	22	22	100	22	100
	1st relapse	22	18	82	18	82
	2nd relapse	30	19	63	27	90
	3rd relapse	24	6	25	13	54
	4th-6th relapse	15	1	6	5	33
Other acute	All stages	9	1	11	5	56
Totals ..		122	67	55	90	74

In 22 consecutive patients with acute lymphoblastic leukaemia who received vincristine and prednisone as their first treatment we have so far had no failure to achieve complete remission with this regimen, and all but two of these results were achieved within four weeks of starting treatment. The lower 95% confidence limit of an observed 100% remission rate in a series of this size is 87%, and the 99% confidence limit is 81%.

There was a slight diminution in complete remission rate at the first relapse, and again at the second relapse, and a much poorer response in patients in third or subsequent relapses. The time from diagnosis of acute lymphoblastic leukaemia to first, second, third, and subsequent relapses in this series is indicated in Table III. Since only 8 of the 39 courses given for third or subsequent relapses were the first the patient had received, and since there were only seven failures and eight partial remissions among the 52 courses given for first and second relapses, whether or not the patient had previously received vincristine and prednisone, it was not possible in this series to determine whether the diminishing probability of response with successive relapses was chiefly attributable to the development of acquired resistance to the drugs or whether it was an inherent function of the stage of advancement of the disease. Of the 34 patients with acute lymphoblastic leukaemia who have received more than one course, 18 have achieved two remissions (six of these patients are still alive in the second of these, and will eventually receive a third course), four have

achieved three remissions each, and one has achieved four successive complete remissions on this treatment.

TABLE III.—*Time from Original Diagnosis of Acute Lymphoblastic Leukaemia to Successive Relapses*

Relapse No.	Time Since Diagnosis of Leukaemia (Weeks)		
	Mean	Median	Range
1	44	31	7–218
2	74	61	17–257
3	86	69	28–264
4–6 inclusive	97	87	52–174

Vincristine Dosage

The total number of weekly doses of vincristine in each course of treatment is shown separately in Table IV for those cases in which complete remission was achieved and for the remainder. In three-quarters of all courses, three or four weekly doses were used and in only 2 out of the 69 instances in which complete remission was achieved were more than four doses required.

TABLE IV.—*Total Number of Weekly Doses of Vincristine*

	Doses of Vincristine						
	1	2	3	4	5	6	>6
Complete remissions ..	0	8	42	17	2	0	0
Partial remissions and failures	0	9	15	18	4	6	1

The total dose of vincristine given during each course, in relation to body surface area, is shown in Table V. In the whole series the total dose ranged from 3 to 14 mg./sq. m., and 62% of the courses (76/122) totalled 6 mg./sq. m. or less. Three-quarters of the complete remissions (52/59) fell into this low-dose group ; the only complete remission requiring more than 10 mg./sq. m. was achieved in a 12-year-old boy with acute plasma-cell leukaemia, at the onset of his disease.

TABLE V.—*Total Dose of Vincristine*

	Total Vincristine (mg./sq.m.)					
	2–	4–	6–	8–	10–	12–
Complete remissions	8	44	11	4	2	0
Partial remissions and failures ..	8	16	15	5	8	1

Vincristine Toxicity

The incidence of the three chief types of side-effect of vincristine in this series in relation to the total dose administered in individual courses is shown in Table VI. Bulk-producing laxatives were used routinely to prevent constipation and intestinal colic so far as possible. It is obvious from Table VI that the incidence of alopecia was not dose-related, and that of gastrointestinal toxicity was at least not significantly so in this series. Neuromuscular toxicity, on the other hand, is clearly dose-related. It should be stressed, however, that the figures in Table VI relate solely to *symptoms* of toxicity ; loss of deep tendon reflexes alone, for example, or minor degrees of muscular weakness detected on examination but unnoticed by the patient or his parents, have not been included, as such findings are reversible and of little clinical significance. Among the neuromuscular symptoms observed were pains in the jaw and limbs, ptosis, foot-drop, weakness of limbs, and (in three cases) generalized convulsions without apparent alternative cause. Most of these, including all those which developed in the lowest dosage group, were only transitory.

Table VI also shows that most of the complete remissions were achieved with a dose of vincristine which carried a low risk of neurotoxicity. In general it would seem fair to conclude from these figures that if remission has not occurred before serious neurotoxic effects are seen it is unlikely to be achieved if further doses of vincristine are given.

TABLE VI.—*Relation Between Total Dose of Vincristine, Toxicity, and Remission Rate*

Total Dose (mg./sq.m.)	No. of Courses	Complete Remissions	Symptoms of Toxicity		
			Alopecia	Gastro-intestinal*	Neuro-muscular†
→6	70	48 (69)	34 (49)	19 (27)	9 (13)
>6→10	34	14 (41)	19 (56)	9 (26)	10 (29)
>10	11	1 (9)	6 (55)	5 (46)	5 (46)
All courses	115	63 (55)	59 (51)	33 (29)	24 (21)

Percentage remission rate and toxicity for each dosage group shown in parentheses.
Seven courses have been excluded from this analysis, as follow-up was not long enough for assessment of toxicity.
Significance of dose relationship:
* χ^2 (2 d.f.) 1·18; $P > 0·5$.
† χ^2 (2 d.f.) 6·51; $P < 0·05$.

Discussion

Our experience with vincristine and prednisone confirms the observation of others (Acute Leukaemia Group B, 1965 ; Hananian *et al.*, 1965) that this is an extremely effective drug combination for the induction of remissions in acute lymphoblastic leukaemia, and shows that it is often capable of inducing two or more successive remissions in the same patient, though remission rates diminish progressively throughout the course of the disease. A complete remission rate of 100% in 22 consecutive previously untreated cases compares very favourably with previously reported series, though it is closely comparable to the best of them. In the great majority of these patients complete remissions were achieved within one month.

The chief disadvantage of vincristine is its neurotoxicity, but this is known to be dose-related (Karon *et al.*, 1962 ; Carbone *et al.*, 1963), and, like Karon *et al.* (1966), we have been able to show that the therapeutic and neurotoxic effects of the drug can be largely dissociated by confining the dose of the drug to the minimum necessary to induce remission, and by stopping it as soon as remission has been achieved. In practice three or four weekly doses, each of 1·5–2 mg./sq. m., are usually sufficient for the purpose ; persistence beyond this point is progressively more likely to cause neurotoxicity and less likely to induce a complete remission. For reasons of toxicity, of course, adrenocortical steroids should also be withdrawn as soon as a remission has been achieved.

In recent years vincristine and/or prednisone have also been used in the treatment of patients during remission, whether in the course of a cyclical chemotherapy regimen (Australian Cancer Society's Childhood Leukaemia Study Group, 1968 ; Krivit *et al.*, 1968) for so-called "reinduction" in patients during maintenance with other antileukaemic drugs (Acute Leukaemia Group B, unpublished) or as components of intensive combined chemotherapy (Henderson, 1967). A possible theoretical objection to their use in these ways would be the risk of development of resistance, so that patients were deprived of their benefit during subsequent relapses. Unless any of these approaches to treatment are clearly shown to improve the quality and duration of total survival, it may be thought that vincristine and prednisone should be reserved for the treatment of relapses.

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Type III Hyperlipoproteinaemia

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Summary: Eighteen patients with type III hyperlipoproteinaemia, diagnosed on the basis of skin lesions, serum lipids, and lipoprotein electrophoresis, have been fully investigated over a period of 15 years. The incidence of coronary artery disease was only slightly increased, and was not increased at all among first-degree relatives. Peripheral occlusive arterial disease was probably more common. An increased incidence of carbohydrate intolerance was found in neither the patients nor their relatives. The effects of treatment on the skin were uniformly good.

Introduction

The clinical features of the various types of xanthomatosis have remained curiously ill-defined over the years. This is partly because the syndrome has presented in and been studied by a number of separate disciplines. Dermatological, cardiac, and metabolic departments have independently studied their own group of patients. Possibly more important than this, however, has been the undue emphasis given to the biochemical and genetic features of the condition, so that it has become little more than a series of lipid levels, a lipoprotein electrophoretic pattern, or a family tree. For instance, Fredrickson *et al.* (1967) studied the plasma lipids and electrophoretic pattern in 24 cases of type III hyperlipoproteinaemia, but described the individual clinical features in only eight (Fredrickson and Lees, 1966). Even so, this remains the largest series to date.

The present paper describes the clinical and biochemical features in 18 cases of type III hyperlipoproteinaemia observed over a number of years. Cases 1, 11, and 13 were reported in a previous communication (Cases 4, 6, and 5 respectively in Borrie, 1957) as being examples of idiopathic hypercholesterolaemic xanthomatosis associated with triglyceridaemia.

Clinical Features

The clinical features are summarized in Table I. There were 14 men and 4 women, the ages at onset varying from 24 to 53. All were referred to hospital on account of their skin lesions, which in every case were the first manifestations of their disease. During the same period of time only eight other cases of primary hyperlipoproteinaemia were seen in the skin department. The duration of the disease to date varies from 1 to 30 years, four patients having suffered for less than five years, two for from 5 to 10 years, nine from 11 to 20 years, and three for more than 20 years.

TABLE I.—*Clinical Features*

Case No.	Sex	Age at Onset	Duration (Years) in 1968	Xanthomata				Arcus	Diabetes	Cardiovascular Involvement
				E	P	T	TN			
1	M	40	20	+	+	+	–	+	–	Cardiac and peripheral arterial
2	F	34	30	+	+	+	+	–	–	Cardiac
3	F	53	1	+	+	+	–	–	–	—
4	M	28	2	–	+	+	–	–	–	—
5	M	28	19	–	–	+	–	–	–	—
6	M	30	30	–	+	+	+	+	+	(E.C.G. not performed)
7	M	38	4	–	+	+	–	–	–	—
8	M	25	16	–	–	+	–	–	–	—
9	M	28	18	–	–	+	–	–	–	—
10	M	26	14	+	+	+	+	–	–	—
11	M	28	21	+	+	+	–	–	–	—
12	M	29	9	–	–	+	–	–	–	Rheumatic heart disease. Peripheral arterial
13	M	41	18	–	+	+	–	–	–	Cardiac
14	F	53	14	–	+	+	–	–	–	Cardiac
15	F	48	13	–	+	+	–	–	–	(E.C.G. not performed)
16	M	37	12	–	–	+	–	–	+	—
17	M	37	8	–	+	+	–	–	–	Cardiac
18	M	24	4	–	+	+	–	–	–	—

E = Eruptive. P = Plane on fingers or hands. T = Tuberose. TN = Tendinous.

All types of xanthomata were found, eruptive xanthomata occurring in five patients, plane xanthomata of the palmar aspect of the fingers or hands in 13, and tuberose xanthomata in all. These latter, as well as affecting the more usual sites of the elbows, knees, and buttocks, also involved the fingers and hands in nine cases. The frequent involvement of the fingers and hands was one of the most characteristic features of the series, and the types of lesions are illustrated in Fig. 1. Only three patients had tendon lesions and one (Case 1) had xanthelasma. One patient had a corneal arcus before the age of 45. One patient (Case 10) had gout, beginning at the age of 39, 13 years after the onset of the hyperlipoproteinaemia.

One patient had diabetes mellitus beginning at the age of 46, nine years after the onset of the hyperlipoproteinaemia. The glucose tolerance test was performed in 13 other cases (see Table IV), in all of which it was normal.

Six patients had cardiovascular disease, and the details are shown in Table II. Case 12 also had rheumatic heart disease at the age of 14 and a successful mitral valvotomy at the age of 27, but this was not thought to be associated with the hyper-

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