Four of these 25 patients were included in the original report* and are included in this report. Our 25 patients were older than those described by Weinstein et al. and thus may be more representative of the normal adult population. We are reporting our results to help physicians who wish to apply this protocol to their patients over 50 years old.

The therapeutic protocol was as described* except that patients over 50 were included. The criteria for response and the supportive care given were similar.

Fourteen women and 11 men with ages ranging from 20 to 72 (mean, 49.4; median, 52) were treated. Fourteen of the 25 were over 50 years old. A 20-year-old patient was treated for first relapse from a prior complete remission established by other treatment. A 31-year-old patient had blast crisis from a previously unrecognized case of chronic myelocytic leukemia. Twelve (48 per cent) of the patients had complete remissions, three (12 per cent) had partial remissions, and the others had no remission. Four patients died of sepsis before a second bone-marrow examination. Two patients died of sepsis while in complete remission. Six of the 25 patients were still alive at eight, 20, 60, 88, 208, and 252 weeks as of March 7, 1981. However, the two with the longest remissions had relapses after 144 and 204 weeks.

Seven of the patients did not receive the prescribed doses. As experience with toxicity accumulated, Days 6 and 7 of cytarabine and Day 3 of doxorubicin were excluded in five patients over 55 years old. Days 6 and 7 of cytarabine were dropped in two other patients because of the acute onset of sepsis and neutropenia during therapy. Three of these seven patients had partial remissions. The others died of sepsis and thus would have had the same outcome had they received the full dose. It is conjectural whether the three partial responders would have had complete remissions had they received the full course of therapy, or whether they too would have died of sepsis.

Patients 50 years old or younger had better response rates and improved durations of survival as compared with those over 50 years old (Table 1).

Table 1. Results of Chemotherapy in Acute Nonlymphoblastic Leukemia.

Characteristic	Age	
	<50 yr	>50 yr
No. of patients	11	14
No response (no. of patients)	1	9
Partial response (no. of patients)	0	3
Complete response (no. of patients)	10	2
Mean duration of survival (mo) *	>17.4	3.2 †
Range	1–58.6	0.5–9.3
Median duration of survival (mo) *	10.7	1.6
No. of patients with continued remission	3	1
Mean duration of continued remissions (mo)	12	4.6

*From the first day of therapy, calculated until March 7, 1981. †P = 0.05.

Thus, the protocol described by Weinstein et al.* had activity in acute nonlymphoblastic leukemia, with no differences in response rates between patients younger than 17 years and those 18 to 50. However, in accord with the authors' original contention, the patients over 50 had more morbidity and lower rates of response to the program.

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ASYMPTOMATIC DIGOXIN TOXICITY

To the Editor: A healthy two-year-old boy was admitted after accidental ingestion of an unknown quantity of digoxin (Lanoxin). He did not seem to be in any acute distress, and he had an unremarkable physical examination. The cardiogram revealed sinus tachycardia at 100 beats per minute, with a PR interval varying from 0.16 to 0.18 second. Ipecac emesis was followed by administration of charcoal and magnesium sulfate. The initial laboratory studies showed that the hemoglobin level was 12.1 g per deciliter, the red-cell count 6600 per cubic millimeter, the sodium 144 mmol per liter, the potassium 4.4 mmol per liter, the blood urea nitrogen 10.3 mg per deciliter, and the blood digoxin 13.0 ng per milliliter (MDS Laboratories, Olean, N.Y.; confirmed by reassay).

Two hours later, the cardiac monitor first showed intermittent sinus bradycardia and sinus pauses. These persisted for three days. The child had no symptoms and remained well throughout the hospitalization. The blood digoxin level decreased to 1.3 ng per milliliter 40 hours after ingestion.

This child tolerated very high digoxin blood levels without any untoward effects. We are not aware of any previous reports of asymptomatic persons with such high blood digoxin levels.

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PROLONGED ADVERSE EFFECTS OF HALOPERIDOL IN NORMAL SUBJECTS

To the Editor: Haloperidol is being used increasingly for the treatment of various psychiatric conditions, producing well-known side effects. However, its effects in normal persons have not been studied systematically. We report adverse effects of unexpected duration and severity in normal volunteers.

Three men 28 to 32 years old volunteered to participate in a double-blind experiment to determine the effect of oral haloperidol (5 mg) on plasma levels of beta-endorphin. Levels of haloperidol were assayed as well. All three subjects had pronounced akathisia (a desire to keep moving), which lasted from 36 hours to five days. They also had dysphoria. Subject 1 had a panic attack associated with akathisia three hours after receiving haloperidol; he also experienced blurred vision, dry mouth, and nausea. The anxiety and akathisia subsided spontaneously — but not completely — after about an hour. On the next day he was very agitated and could not concentrate. Diphenhydramine reduced his discomfort for the next three days. For the following six weeks he reported recurrence of the anxiety and dysphoria whenever he drank coffee.

Subject 2 reported akathisia, dysphoria, and anxiety starting approximately six hours after he took 5 mg of oral haloperidol. Benztropine mesylate (2 mg) produced temporary relief. Akathisia recurred, and then subsided at four days, and dysphoria lasted two weeks. He also had difficulty commencing micturition for 10 days, unusual fatigue, increased sleep time for one month, and decreased libido for two weeks.

Subject 3 had considerable akathisia for about 36 hours. Subjects 1, 2, and 3 had peak plasma drug levels of 3.7, 4.4, and 2.4 ng per milliliter, respectively, within two hours after drug administration. Beta-endorphin levels were not consistently affected.

Independently of our three subjects, a 28-year-old psychiatrist took 5 mg of oral haloperidol to test for dysphoria, a frequent report of her patients. For 36 hours she had dysphoria, sedation, blurred vision, and difficulty with fine motor coordination. Akathisia lasted four to five days.

Kendler[1] and Belmaker and Wald[2] have reported akathisia after administration of 1 mg of intramuscular haloperidol and 5 mg of intravenous haloperidol, respectively, with the effect lasting five hours and 36 hours, respectively. Akathisia and dysphoria after the use of neuroleptic drugs in psychiatric patients may be more common than is generally realized. Van Putten et al.[3] have suggested that these dysphoric effects may be responsible for noncompliance with treatment. These symptoms may be overlooked if they are erroneously linked with psychopathology or not clearly described by the patient.

Haloperidol was found to persist in the rat brain for at least 48 hours after a single dose.[4] The half-life of haloperidol in the brain was about 30 hours. Should these data be extrapolated to human beings, they might explain the first three or four days of effect. The effects lasting several weeks may be due to modification of receptor sensitivity.

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1. Kendler KS. A medical student's experience with akathisia. Am J Psychiatry. 1976; 133:454-5.
2. Belmaker RH, Wald D. Haloperidol in normals. Br J Psychiatry. 1977; 131:222-3.
3. Van Putten T, May P, Werder S, Wittman L. Subjective response to antipsychotic drugs. Arch Gen Psychiatry. 1981; 38:187-90.
4. Ohman R, Larsson M, Nilsson IM, Engel J, Carlsson A. Neurometabolic and behavioral effects of haloperidol in relation to drug levels in serum and brain. Naunyn Schmiedebergs Arch Pharmacol. 1977; 299:105-14.

VITAMIN E THERAPY IN HOMOZYGOUS β-THALASSEMIA

To the Editor: In a recent issue of the *Journal*, Corash et al.[1] reported that high-dose oral vitamin E supplementation improved red-cell survival in Mediterranean-type glucose-6-phosphate dehydrogenase deficiency. This effect is due to the prevention of lipid peroxidation of the red-cell membrane. We have administered vitamin E to 30 subjects with homozygous β-thalassemia, in which there is a peroxidation of erythrocyte-membrane lipids.[2,3] Vitamin E was given orally to 10 patients and parenterally to 20 patients at a dose of 300 mg per day during the intertransfusional period. Serum and red-cell vitamin E was measured before and after the treatment. Red-cell malonyldialdehyde, an intermediate product of lipid peroxidation, was also determined. In the orally treated group, no statistically significant variation was observed. In the parenterally treated group, a significant increase in serum and red-cell vitamin E levels and a significant decrease in malonyldialdehyde levels were noted (Table 1). The intertransfusional period was also significantly prolonged ($P<0.001$). These data suggest that vitamin E may also be useful in homozygous β-thalassemia to reduce the transfusion requirement. The vitamin should be given parenterally, since oral administration is ineffective. This finding seems to indicate poor intestinal absorption of the vitamin in homozygous β-thalassemia.

Table 1. Tocopherol and Malonyldialdehyde Levels (Mean ±S.D.) before and after Parenteral Treatment with Vitamin E in 20 Patients.

VARIABLE	BEFORE THERAPY	AFTER THERAPY	P VALUE *
Serum tocopherol (μg/ml)	3.6±1.3	7.5±2.4	<0.001
Red-cell tocopherol (μg/ml packed red cells)	3.1±2.3	6.8±2.3	<0.001
Red-cell malonyldialdehyde (μmol/ml packed red cells)	5.7±2.3	2.5±2.2	<0.001

*By Student's t-test.

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1. Corash L, Spielberg S, Bartsocas C, et al. Reduced chronic hemolysis during high-dose vitamin E administration in Mediterranean-type glucose-6-phosphate dehydrogenase deficiency. N Engl J Med. 1980; 303:416-20.
2. Maggioni G, Castro M, Donfrancesco A, Spano B, Giardini O. Haemolysis and erythrocyte lipids in thalassaemia major. Acta Haematol (Basel). 1974; 52:207-13.
3. Rachmilewitz EA, Lubin BH, Shohet SB. Lipid membrane peroxidation in beta-thalassemia major. Blood. 1976; 47:495-505.

CIMETIDINE AND THE CONTROL OF PAIN IN CHRONIC RELAPSING PANCREATITIS

To the Editor: There is no conclusive evidence that cimetidine has any therapeutic benefit in acute pancreatitis.[1] Indeed, in laboratory animals, cimetidine has been implicated in the development of this condition.[2] In chronic pancreatitis, the use of cimetidine has largely been limited to patients with pancreatic insufficiency who are receiving oral enzyme supplements.[3]

Recently we have been impressed with the efficacy of cimetidine in relieving pain in patients with the acute phase of chronic relapsing pancreatitis. From July to December 1980, we treated eight consecutive patients with this condition with intravenous cimetidine, 800 mg every six hours. The chief etiologic factor in six patients was alcohol, but in two patients no cause was found. No analgesics were used and all patients were free of pain within four hours of starting treatment. This relief of symptoms was not paralleled by an equally rapid decline in the serum amylase level, which remained abnormally elevated for five to 10 days in all patients. A pseudocyst developed in one patient who was relatively asymptomatic during cimetidine treatment.

Adequate pain relief in patients with chronic pancreatitis is hampered by the risk of drug dependence. Hence, a therapeutic role for cimetidine would be of great value, even if the drug could not be shown to reduce pancreatic damage. Controlled studies are needed. It is hoped that this report will stimulate interest in the problem and its possible remedy.

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1. Meshkinpur H, Molinari MD, Gardner L, Noeler FK. Cimetidine in the treatment of acute alcoholic pancreatitis. Gastroenterology. 1979; 76:1201.
2. Joffe SN, Lee FD. Acute pancreatitis after cimetidine administration in experimental duodenal ulcers. Lancet. 1978; 1:383.
3. Dobrilla G, Bonoldi MC, Chilovi F, Bertaccini G. Effects of cimetidine on pancreatic function and disease. In: Torsoli A, Lucchelli PE, Brimblecombe RW, eds. Further experience with H_2-receptor antagonists in peptic ulcer disease and progress in histamine research. Amsterdam: Excerpta Medica, 1980:140-51.

ORAL CIMETIDINE DOES NOT CAUSE FALSE-POSITIVE TEST FOR BLOOD IN STOOL

To the Editor: The testing of gastric aspirates for occult blood by the Hemoccult test (SmithKline Diagnostics) after oral ingestion of cimetidine suggested to Norfleet and his colleagues that cimetidine taken orally causes false-positive Hemoccult tests.[1] Furthermore, Schentag did not observe false-positive Hemoccult-reactions in gastric juice after intravenous administration of cimetidine, and he concluded that the false-positive Hemoccult-test induced by oral cimetidine was caused by FDC blue lake No. 2, a component representing 0.004 per cent of the tablet's weight.[2]

Subsequently, Hauser and his co-workers demonstrated that false-positive Hemoccult tests were caused by cimetidine itself.[3] Chemical cimetidine, cimetidine injection solution, cimetidine tablets, and the liquid preparation yielded false-positive Hemoccult tests in vitro under various conditions.

The percentage of intestinal absorption of 400 to 800 mg of 2-^{14}C-cimetidine administered orally is high. The recovery of orally ingested radiolabeled cimetidine in the feces ranged from 7.1 to 12.8 per cent, whereas only 1.8 to 2.9 per cent of an intravenous dose was detected in the feces.[4] A substantial biliary excretion and an enterohepatic circulation of the drug have not been demonstrated.[1]

We investigated whether cimetidine provokes a false-positive