The above letters were referred to the authors of the article in question, who offer the following reply:

To the Editor: We agree with Dr. Pini and colleagues that subcutaneous heparin (3500 IU every eight hours) is probably not optimal for prophylaxis. The dosage dilemma has been well reviewed by Bergqvist.1 After elective hip surgery, using 5000 IU of heparin every 12 hours, there was a 27 per cent incidence of deep-vein thrombosis in the treated patients. None of the exclusions or included patients died during the 10-week observation period.

Although we agree with Dr. White that giving adjusted heparin dosages followed by routine oral anticoagulation therapy is something cumbersome, it is worth the effort in high-risk patients. Hampson et al. demonstrated that in 7 of 22 patients deep-vein thrombosis developed after prophylactic heparin had been discontinued.2 We have adopted the policy of keeping our patients on oral anticoagulation until they are well mobilized. A recent study by Hull et al. demonstrated the control of oral anticoagulation.3 Eleven of 49 patients (22 per cent) in whom thromboplastin times were controlled with the Simplastin reagent (desired therapeutic ratio, 1.6 to 2.0) had hemorrhagic complications. Eight of these had ratios over 2.0, and all of them were grossly overcoagulated when the Manchester comparator reagent was used for determination of thromboplastin time. We use the Meazza Dade reagent for the control of thromboplastin time (desired therapeutic ratio, 1.5 to 2). In a recent series of 40 orthopedic patients followed over a two-month period, the mean ratio of some 350 thromboplastin determinations was 1.66, and 95 per cent of all values remained between 1.4 and 2.25. One of the 40 patients had a hemorrhagic complication (2.5 per cent). At present we cannot identify which patients may have deep-vein thrombosis after subcutaneous heparin has been stopped.

We disagree with Dr. Hoaglund. In most studies, using tilt-table bilateral phlebography, the majority of deep-vein thrombi are either in the operated leg or bilateral,4,6,7 and our own experience using bilateral venography has revealed an 11 per cent incidence of deep-vein thrombosis in the unoperated limb (unpublished data). The study by Moskowitz et al. does not provide an authoritative answer to the question.8 These authors used 125I fibrinogen scanning and flat-table venography for the diagnosis of deep-vein thrombosis. In patients with "deep-vein thrombosis," the correlation between these two tests was only 30 per cent. In our study all patients underwent bilateral Doppler scanning every second day (not mentioned in the article), and phlebography of the nonoperated leg would have been performed in patients with positive ultrasound scanning in the nonoperated limb. Since this did not occur, we did not think it was in the interest of the patients to perform bilateral venography.


DIET AND SLEEP PATTERNS IN NEWBORN INFANTS

To the Editor: In their study of diet and sleep patterns (Nov. 10 issue)* Yomgan and Zeisel attempt to examine the effects of two amino acids, tryptophan and valine, on sleep patterns in newborns. From their methodologic description it cannot be ascertained whether the three formulas (tryptophan in 10 per cent glucose, valine in 5 per cent glucose, and Similac 20, the standard) were isocaloric or whether they were consumed in equal amounts. Not only is the caloric density an important consideration in feeding studies, but doubling the sugar concentration of the tryptophan formula in contrast to the valine formula might affect other metabolic factors in addition to the total caloric load.

These workers also chose observers and parents to assess the latency of sleep and its duration. Since polygraphic techniques are available to monitor not only the presence of sleep but its stages, such techniques might increase objectivity and add new dimensions to future studies.

Experimental design modification is certainly required to test whether tryptophan itself is responsible for the modification in sleep reported in these healthy newborns. However, of those who recall last winter's holiday fasting (turkey is a good source of tryptophan) are unlikely to claim that diet does not influence sleep behavior.

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The above letter was referred to the authors of the article in question, who offer the following reply:

To the Editor: Dr. Strain's letter emphasizes our finding that the combination of tryptophan and additional glucose, as compared with a valine solution, influenced sleep onset in newborns. Our stated rationale for this design was that "[t]he combination of tryptophan and high-glucose treatment . . . maximized the carrier transport of tryptophan across the blood-brain barrier by directly increasing blood tryptophan levels while insulin secretion acted to decrease the levels of competing large neutral amino acids." Future studies are required to separate the effects of glucose and dietary tryptophan on the onset of sleep.

Although we indicated that there were no differences in amount of modified formula consumed (60 ml of tryptophan and additional glucose vs. 53 ml of valine solution), Dr. Strain is correct in pointing out that the feedings were not isocaloric (0.34 kcal of tryptophan, 0.17 kcal of valine solution, and 0.66 kcal of Similac per milliliter). Since Similac had the highest caloric density and yet had intermi-
ate effects on the onset of sleep, it is unlikely that caloric density itself produced the effect on sleep onset.

Dr. Strain incorrectly suggests that we chose parents to assess infant behavior. In fact, all observations were conducted by five research assistants who had received extensive training in behavioral observations before the study, who were blind to the infant's treatment group, and whose reliability (interobserver) was monitored and maintained at greater than 90 percent agreement.

Previous studies in infants have compared the coding of states of consciousness and sleep stages based on behavioral observations with coding based on polygraphic techniques (including the electroencephalogram, electromyogram, and electro-oculogram and measurements of respiration and heart rate) and found them highly correlated. We chose to code sleep stages on the basis of behavioral observation because previous research had suggested an initial stress effect on infant state from manipulations associated with polygraphic techniques, and we thought we should avoid this first-night stress effect on sleep stages.

Finally, we wish to point out and correct a calculation error regarding the amount of tryptophan and valine actually ingested. Infants actually ingested a mean of 13.4 mg of tryptophan (not 19.8 mg) and a mean of 18.7 mg of valine (not 27 mg). The second sentence of the results section should have read: "The infants in the tryptophan group ingested a feeding containing a mean of 13.4 mg of tryptophan (60 ml), whereas those in the valine group ingested a mean of 18.7 mg of valine (53 ml)."

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**MERCAPTOPURINE "BIOAVAILABILITY"**

To the Editor: On the basis of pharmacokinetic data, Zimm et al., have questioned whether an optimal amount of mercaptopurine is currently being given in maintenance chemotherapy regimens for acute lymphoblastic leukemia (April 28, 1983, issue). They suggest that giving mercaptopurine intravenously, rather than orally, and monitoring the dose by determining blood levels might increase the effectiveness of this agent and reduce the relapse rate in acute lymphoblastic leukemia, which is still about 50 percent.

The biochemical pharmacology of mercaptopurine may be more important than the pharmacokinetic data. Mercaptopurine is a prodrug that becomes active only after conversion to the nucleotide level. The first nucleotide formed, thioinosinic acid, requires phosphoribosylpyrophosphate and the enzyme hypoxanthine-guanine phosphoribosyltransferase. Once formed, thioinosinic acid is converted intracellularly to other cytotoxic nucleotides. The antileukemic effect of mercaptopurine thus depends ultimately on the amount and persistence of thiopurine nucleotides in the target cells. Since patients vary considerably in their enzymatic characteristics, an assay of intracellular thiopurine nucleotides would be required to evaluate the effect of different amounts of plasma mercaptopurine in different patients.

Zimm et al. found that the fraction of free drug in plasma was variable when oral doses of mercaptopurine (75 mg per square meter of body surface area) were given to children with acute lymphoblastic leukemia. We measured the plasma concentration–time curve (AUC), it appeared that the mean "bioavailability" of the oral drug was only 16 percent. These data do not differentiate between drug absorption and drug metabolism. The AUC for intravenous mercaptopurine also varied enormously (from 246 to 1707, with a mean of 993±493.3 [S.D.J]. The fate of mercaptopurine obviously varies in different persons, independently of the route of administration.

Human leukemic cells exposed to 50 μM mercaptopurine in vitro varied greatly in their ability to convert mercaptopurine to thioinosinic acid. The rate of conversion appeared to be closely related to the phosphoribosylpyrophosphate content of cells. Little correlation was observed between the dose of oral mercaptopurine and the amount of thioguanine nucleotide formed in the erythrocytes of children with leukemia. The thioguanine nucleotide levels, however, correlated well with the absolute neutrophil count after two weeks of therapy and may be a better measure of the ability of a patient to form thio purine nucleotides than the plasma level of free mercaptopurine.

When [3H]thioguanine was given intravenously, the amount of thio guanine nucleotides formed in the bone marrow of different patients varied widely, as did the incorporation of thioguanine into DNA.

Early experience with intravenous mercaptopurine given at different doses and schedules was not encouraging. In view of the available information, it is premature to recommend the intravenous administration of mercaptopurine in standard maintenance regimes. It may be particularly hazardous to give intravenous mercaptopurine to patients who have been on oral maintenance therapy with the drug, or to those in whom allopurinol is given concomitantly. For clinical safety, the optimal dose of mercaptopurine should still be monitored by the serial determination of neutrophil and platelet counts, supplemented when necessary by examination of the bone marrow.

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**HOW MANY MILES TO THE VA DOCTOR?**

To the Editor: Williams et al. (Oct. 20 issue) have convincingly shown that 80 percent of the U.S. population lives less than 10 miles from a physician and that 98 percent of Americans are within a 25-mile range of a doctor. In some areas, including northern New England, only a minuscule proportion of the population (0.2 percent) lives beyond this range. On the basis of these findings, the authors thought that they could "confidently predict that market forces will improve geographic access to medical care during the next decade." We believe that this conclusion, probably true in a general, nationwide sense, does not apply to population subgroups.