absorbed in sufficiently large quantities to reverse hypoglycemic coma in diabetic subjects would involve first intestinal hydrolysis and then absorption.

We are indebted to Dr Rosenbaum and his colleagues for providing their experience using instant glucose at the Cleveland diabetic camp. Since most carbohydrate in instant glucose is disaccharides and oligosaccharides, which require disaccharidases for hydrolysis and absorption, and since these enzymes are found only in the mucosal brush border of the small bowel, it seems highly improbable that absorption of large quantities of carbohydrates from instant glucose could occur in any site other than the small bowel. Because of this, we agree with the correspondents that when swallowed orally, this preparation appears to increase glucose levels. Nevertheless, the question raised relates to the rapidity of action of instant glucose as a therapy for comatose hypoglycemic subjects. Instant glucose may not necessarily work long before a diabetic patient could obtain intravenous glucose, and clearly, intravenous glucose is not the only alternative for the therapy for hypoglycemic coma. It is also unclear as to why the slower appearance of glucose in the blood, as provided by instant glucose, would be advantageous for the treatment of hypoglycemic coma as Rosenbaum et al suggest, because prolongation of hypoglycemia has been shown to be harmful in clinical studies on therapeutic insulin shock.

The observations in patients treated with instant glucose at the Cleveland summer camp notwithstanding, the potential remains substantial for aspiration or for irregular absorption from puddling in the oropharynx. It therefore seems prudent to conclude that instant glucose, although efficacious when swallowed in the awake diabetic subject, may not be the most appropriate therapy for the treatment of insulin-induced hypoglycemic coma.

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Cyanide Production From Laetrile in the Presence of Megadoses of Ascorbic Acid

To the Editor.—As previously reported in THE JOURNAL (240:1139, 1978), the "antineoplastic diet" of laetrile proponents calls for megadoses of ascorbic acid (vitamin C) among other dietary requirements. We performed a series of experiments designed to see if ascorbic acid would increase the hydrolysis of laetrile (amygdalin) to benzaldehyde and hydrocyanic acid (HCN), and therefore increase the probability that the patient would suffer from cyanide poisoning while receiving laetrile therapy.

Cyanide Released From Amygdalin in Vitro—37 °C Incubation for One Hour

Cell	Inner Well	Outer Well, μg of Cyanide (2 mL 0.1 Mole of Potassium Hydroxide)
1	Amygdalin, 100 mg; blood, 1 mL	0.03
2	Amygdalin, 100 mg; water, 1 mL	0.00
3	Amygdalin, 100 mg; stomach contents, 5 mL	0.04
4	Amygdalin, 100 mg; ascorbic acid, 100 mg	0.30
5	Amygdalin, 100 mg; ascorbic acid, 100 mg; blood, 1 mL	4.40
6	Amygdalin, 100 mg; ascorbic acid, 100 mg; stomach contents, 5 mL	1.80

Six Conway microdiffusion cells were prepared as shown in the Table. A plastic cover was sealed in place with a water-soluble starch-glycerol paste. The sealed cells were incubated at 37 °C for one hour and then left an additional hour at room temperature. The potassium hydroxide solutions were then analyzed for cyanide levels by the method of Valentour.[1] The results are also shown in the Table.

The Table shows that the presence of ascorbic acid did increase the amount of HCN liberated in blood but that the total cyanide level was only 0.073% of the available amount (6% of the total weight of amygdalin). Furthermore, animal studies of amygdalin oral toxic reactions, with and without ascorbic acid, have shown no major differences in observed toxic reactions or measured cyanide levels (Hill HZ et al, unpublished data). The amount of cyanide released from amygdalin and blood incubation without ascorbic acid was 0.001% of the total available HCN. The small amount of cyanide released is consistent with the recovery of close to 100% of unchanged amygdalin observed in a recent study of parenterally administered doses to humans,[2] indicating little effect of the enzymes systems within blood on the dissociation of amygdalin.

The incubation of the amygdalin-ascorbic acid-stomach contents (Table, cell 6) also showed increases in the level of cyanide released when compared with that of the amygdalin-stomach contents incubations alone (Table, cell 3). While the total cyanide released was only a small percentage of that available, it will add to the well-established total body cyanide burden that is produced by orally administered amygdalin (Hill et al) (239:943, 1978).

In summary, in vitro amygdalin released more cyanide in the presence of ascorbic acid, but the amounts produced were very small when compared with those of total available cyanide. Animal studies[2] tended to show no notable increased toxic reaction in oral administration of amygdalin and ascorbic acid and insignificant increases in the level of total cyanide produced. However, such large individual animal variations in cyanide concentrations were observed that minor changes would not have been noted. Therefore, one would conclude from the limited studies performed that megadoses of ascorbic acid with oral doses of amygdalin could have a small additive effect on the total body burden of cyanide. Similarly, any trace amounts of cyanide produced in blood by concomitant parenteral administration of amygdalin and ascorbic acid will add to any existing body cyanide burden and possibly worsen an undesirable situation.

We used unadulterated amygdalin; however, all injectable amygdalin seized as contraband by the Food and Drug Administration has been found to be adulterated when tested. Thus, it is possible that the amount of free cyanide released from amygdalin by ascorbate and blood in the current study is substantially less than would be released from contraband amygdalin.

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Drs Helene Z. Hill and George J. Hill II, Marshall University School of Medicine, Huntington, WVa, provided the amygdalin and ascorbic acid for the experiments and contributed to these studies.

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Valproic Acid in Epilepsy

To the Editor.—We are writing in regard to the article "Valproic Acid (Depakene): A New Anticonvulsant Agent" (240:2190, 1978), in which Lewis presented a succinct review of the literature relative to the efficacy and toxicity of this drug. His conclusion that valproic acid "is most effective in absence seizures (simple and complex)" and "has produced improvement in tonic-clonic seizures, mixed absence with tonic-clonic seizures, and myoclonic epilepsy" may lead the reader, especially in view of the publicity in the public media before Food and Drug Administration approval, to believe that valproic acid may well be the long-sought "ideal anticonvulsant."

Since our experience with valproic acid does not parallel the findings described by Lewis and conflicts with the advance enthusiasm relative to efficacy, we would like briefly to present our results in 48 patients treated with this drug. To avoid the inherent complexities and nosologic confusion associated with the International Classification of Seizures, we have used conventional and traditional terminology in our communication.

The distribution of seizure patterns in our series was grand mal, six; psychomotor, 14; myoclonic epilepsy of older children (Lennox-Gastaut syndrome), 21; and petit mal, seven. Most of the patients with myoclonic, some with psychomotor, and four with petit mal epilepsy also exhibited or had a history of grand mal seizures.

All of the patients with grand mal, myoclonic, or psychomotor seizures were refractory to the standard anticonvulsants, administered singly and in combination. Four of the seven children with petit mal spells had been treated with ethosuximide (Zarontin), two with clonazepam (Clonopin), ethosuximide, and trimethadione (Tridione) concurrently, and the other patient had received no previous therapy. In 47 patients, valproic acid was added to the earlier therapeutic regimen in a dosage of 15 mg/kg/day, and this dosage was maintained for two weeks. The daily dose was subsequently increased as indicated by clinical response or signs of toxicity by 5 to 10 mg/kg each week to a maximum of 50 mg/kg.

Maximal daily doses of valproic acid were of little or no value in our six patients with grand mal epilepsy or in the 14 with psychomotor seizures. Of our 21 patients with myoclonic attacks who were treated with valproic acid in maximal dosage, 19 failed to show any improvement; one child experienced a 75% reduction in seizure frequency; the number of seizures in the other patient was initially reduced by 50%, but two months later, the attacks recurred and persisted at a frequency that surpassed the rate before valproic acid was used. Of the seven patients with petit mal epilepsy, two derived no benefit from valproate sodium therapy, and five were controlled of their seizures.

The only notable untoward reactions observed in our series were one case of thrombocytopenia and marked drowsiness in some patients also receiving barbiturate therapy, principally phenobarbital.

Our experience with the use of valproic acid in the treatment of epileptic seizures indicates that it is of little or no benefit in grand mal, psychomotor, or myoclonic epilepsy of older children (Lennox-Gastaut syndrome), but is of substantial value in petit mal epilepsy.

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Possible Teratogenic Hyperthermia and Marathon Running

To the Editor.—The article by John D. Cantwell, MD (240:1409, 1978), extolled the many benefits of running. I would like to add a note of caution for women runners; namely, that marathon running may pose a teratogenic risk during early pregnancy. This warning seems warranted on the basis of the following evidence: First, marathon runners experience sustained increases of core temperature into the "high fever" range.[1,2] Second, recent studies[3-5] have shown an association between birth defects and episodes of maternal hyperthermia.

Because the first half of gestation is apparently the period of greatest risk for hyperthermia-induced birth defects,[4] a substantial number of women may already have trained for and run the marathon during this critical period, either because they were unaware of or unhindered by their pregnancy. A study of the outcomes of such pregnancies might be informative in regard to the relationship between high maternal body temperature and birth defects or spontaneous abortions.

It would be sadly ironic if the great pain and effort invested by these women in conditioning their bodies were at the same time causing tragic and irreparable malformations in their babies. Since exercise-induced hyperthermia undoubtedly occurs in other sports and in certain occupations, I hope that efforts will soon be made to evaluate the teratogenic risk associated with exercise-induced hyperthermia during the various stages of pregnancy.

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Exercise-Related Hematuria

To the Editor.—The provocative study by Siegel et al (241:391, 1979) found that after running the Boston Marathon, subjects with hematuria had no RBC casts in their urine. The authors suggested that absence of formed elements argued against a glomerular origin. They further cite 21 cases of exercise-related hematuria in which no upper urinary tract cause was found.

The following case demonstrates that the appearance of bloody urine after running may arise from the upper urinary tract.

Report of a Case.—A 17-year-old high school cross-country runner ran a 3.2-km race at a local golf course. He ran his best time ever (11 minutes, 23 s), and for the first time in his life, he ran barefoot. Three hours later he painlessly voided dark red, burgundy-colored urine. Sixteen hours later an intravenous pylelogram showed a large filling defect in the right renal pelvis, which suggested a blood clot. No other kidney lesion was identified. Gross hematuria cleared within 24 hours. Numerous urinalyses have since been normal. The subject had lost 16 kg during the preceding year (68 kg to 53 kg) as a result of endurance training.

Comment.—The case demonstrates that the occurrence of hematuria