sion of isotonic amino acids, the basic principles of body fuel regulation need not be altered to explain these findings. Firstly, in postoperative patients infused only with saline, peak rates of urinary nitrogen loss (observed on the second to fourth days) coincide with fivefold to 10-fold increments in blood ketones.[9,10] Secondly, administration of glucose alone (100 g per day) reduces nitrogen losses by 30 to 60 per cent in the postoperative period, despite suppression of ketosis and stimulation of insulin secretion.[9,10] Thirdly, a nitrogen-sparing effect of ketone infusions has been observed only after prolonged fasting, a condition in which basal nitrogen losses are well below those observed in the postoperative state.[11] Fourthly, as shown elsewhere in this issue of the *Journal* by Greenberg et al., addition of 5 per cent dextrose to isotonic amino acids fails to impair their nitrogen-sparing action. Fifthly, these authors also find that accentuation of fat utilization by addition of a hypocaloric lipid emulsion to the amino acid mixture fails to improve nitrogen balance beyond that observed with amino acids alone. Nitrogen balance was identical in patients given only amino acids, amino acids plus lipid, or amino acids plus glucose. Noteworthy is the fact that in all three groups, administration of isotonic amino acids resulted in protein sparing well in excess of that observed with glucose alone.

An interesting question raised by the observations of Greenberg et al. is the precise metabolic signals responsible for improved nitrogen metabolism in patients receiving amino acid infusions. Two factors that warrant consideration are hyperaminoacidemia and hyperinsulinemia. In subjects fed protein meals, postprandial hyperaminoacidemia involves primarily the branched-chain amino acids, leucine, isoleucine and valine.[12] These amino acids are unique in their ability to escape hepatic uptake while dominating nitrogen repletion in muscle tissue.[12] They are also particularly effective in their ability to stimulate protein synthesis in muscle.[13] Interestingly enough, the hyperaminoacidemia observed by Greenberg et al. in the patients infused with amino acids alone or amino acids plus lipid involved the branched-chain amino acids, suggesting that the mechanism of muscle nitrogen repletion may be analogous to oral protein feeding. In contrast, plasma amino acid levels did not rise in the group given amino acids and glucose. However, plasma insulin concentration was highest in the latter group. Hyperinsulinemia induced by addition of glucose to protein meals has recently been demonstrated to blunt the hyperaminoacidemia caused by protein feeding while stimulating muscle uptake of branched-chain amino acids.[14] The intracellular availability of these amino acids for protein synthesis is thereby increased. Thus, perhaps insulin alternates with the branched-chain amino acids as the circulating signal enhancing nitrogen retention in muscle. In subjects fed pure protein meals,[12] or infused with amino acids in the absence of glucose, hyperaminoacidemia (involving leucine, isoleucine and valine) may have a major role in improving nitrogen balance. On the other hand, in subjects given glucose or glucose plus amino acids, hyperinsulinemia may effect a reduction in nitrogen catabolism in the absence of hyperaminoacidemia.

Regardless of the mechanism involved, it is now clear that improvement in nitrogen balance induced by amino acid infusions in the face of caloric deficiency requires neither ketosis nor hypoinsulinemia. The theory attributing a catabolic effect to insulin or glucose (or both) thus cannot be sustained. Abandoning this scheme should not, however, detract from the clinical importance of the demonstration that isotonic amino acid infusions result in protein sparing in the postoperative period and in other catabolic states.

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"PROPPER" USE OF DESFERRIOXAMINE

ALTHOUGH clinical problems involving iron are usually associated with a deficiency of this essential element, an appreciable number of patients suffer from iron overload. This accumulation of iron can result from increased absorption, as in primary hemochromatosis and thalassemia intermedia, or from multiple blood transfusions, as in β-thalassemia major and hypoplastic anemia. Excess iron is deposited in body stores as ferritin or hemosiderin and can eventually amount to several hundred grams. The pathophysiology of iron deposition in tissues — e.g., the heart and liver — is believed to be due to free radicals generated by the iron. Damage caused by such radicals leads to fibrosis, necrosis and eventual organ failure.

The lack of an effective excretion mechanism for iron in man forces the physician to intervene either through phlebotomy or by the use of specific iron chelators. Phlebotomy

is particularly effective in treating primary hemochromatosis since the removal of 1 unit of blood removes approximately 250 mg of iron. When phlebotomy is contraindicated, chelation therapy has been attempted. Unfortunately, the use of chelators has met with limited success. Several, such as ethylenediaminetetra-acetate (EDTA) and diethylenetriaminepenta-acetate (DTPA), have been abandoned because of toxicity. One chelator that has attracted intermittent interest since its introduction in 1960 is desferrioxamine.[1] This chelator, which is isolated from *Streptomyces pilosus*, has a very high affinity for iron and is without serious toxicity in man. However, after an initial flurry of investigative activity, it was realized that intramuscular administration of desferrioxamine on a chronic basis failed to bring all patients into iron balance (or negative iron balance). The drug was able to chelate only a very small fraction of the iron in total body stores. Moreover, the daily intramuscular injections of the drugs were not well accepted by the children or their parents, and, thus, its use was greatly curtailed in the United States.

A small clinical trial of prolonged desferrioxamine therapy was continued in England.[2] After six years it was apparent that the rate of accumulation of iron in the desferrioxamine-treated group was less than that in the control group. This study prompted a re-evaluation of desferrioxamine in the United States. The paper in this issue of the *Journal* by Propper et al. attempts to define conditions to improve the response to desferrioxamine. These workers have found that the slow continual infusion of desferrioxamine substantially increases the amount of excreted iron in patients with β-thalassemia major. Presumably, this increased excretion occurs because the drug has access to a replete chelatable pool that is slowly filled from otherwise inaccessible body stores. This observation should stimulate further studies of the pharmacology and potential toxicity of continual desferrioxamine infusions and eventually lead to the development of new drug delivery systems and depot forms of this and other chelators. The next few years, one may hope, will see an improvement in the understanding and funding of chelator therapy that will parallel the recent advances made in understanding the molecular pathology of thalassemia.

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VIRUS MARKERS IN MULTIPLE SCLEROSIS

OVER the past 20 years, many diagnostic tests for multiple sclerosis have been described. However, none of them have proved to be specific for the diagnosis, which still rests on varied neurologic symptoms and signs occurring in char-

In the present issue of the *Journal*, Levy and Auerbach describe a blood test based on the adherence of peripheral blood lymphocytes to measles virus-infected tissue culture cells. Purified populations of lymphocytes from patients with multiple sclerosis formed rosettes in vitro when mixed with measles-virus-infected epithelial cells. Similarly prepared lymphocytes from control populations showed much less rosetting activity; in fact, there was no overlap of patient and control values, suggesting that the assay may be of diagnostic importance. The positivity of the test in patients with multiple sclerosis was not affected by the severity, duration or activity of the disease.

However, several reservations must be kept in mind before the authors' conclusions are accepted too readily. A wider range of control patients, including those with viral diseases, subacute sclerosing panencephalitis and immunologic disorders (e.g., systemic lupus erythematosus) should be tested. The specificity of the reaction for measles virus should be analyzed by use of target cells chronically infected with other viruses, and by an attempt to block the rosetting by measles-specific antiserum. An effort should also be made to determine whether the measles-receptor-bearing cells are T lymphocytes, B lymphocytes or still other cells. Although Valdimarsson et al.[1] have found that only T lymphocytes have measles receptors, others have shown replication of measles virus in both human T and B lymphocytes, as well as in monocytes.[2-4] In patients with multiple sclerosis the numbers of B lymphocytes in peripheral blood are slightly increased, whereas T-lymphocyte numbers are slightly reduced,[5] and there are no data concerning monocytes.

Levy and Auerbach wisely avoid drawing any conclusions concerning the role of measles virus in the pathogenesis of multiple sclerosis. A wide variety of viruses have been suggested as possible causes of the disease since Poskanzer et al. suggested that it may result from exposure to an infectious agent during childhood.[6] Evidence suggesting a viral role has come from epidemiologic, serologic and histologic studies and from rare reports of virus isolations from brain tissue.[7-15] The viruses receiving the greatest attention have been members of the paramyxovirus group, particularly measles and parainfluenza-1[7-11] and a recently described transmissible agent referred to as the multiple-sclerosis-associated agent.[12-15]

Over 20 different studies have demonstrated that patients with multiple sclerosis have slight but consistently elevated serum measles antibody titers as compared with controls.[7,8] A few studies have also indicated that there may be local production of measles antibody in the central nervous system, as reflected by elevated levels in the cerebrospinal fluid.[8,9] However, Arnason et al. have demonstrated that the small increases in measles antibody levels observed by some groups may be related to the unusual distribution of histocompatibility types in patients with multiple sclerosis.[16] Persons with HLA-3 had increased measles antibody titers whether or not they had multiple sclerosis; since patients with the disease have a disproportionate prevalence of HLA-3, the elevated measles antibody titers may reflect histo-