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AMINO ACID SOLUTION AND PROCESS FOR PREPARING THE SAME

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This invention relates to amino acids and particularly to amino acid mixtures of the type intended for parenteral, rectal, and oral use in therapy requiring the administration of large amounts of amino acids, and to the preparation of such mixtures. Amino acid mixtures of this sort are finding wide-spread use in medicine to restore and maintain the proper nitrogen balance and the necessary nutritional state of the body in the treatment of conditions where a large protein loss exists as, for example, after injury, post-operative shock, severe malnutrition, damage to the alimentary canal, and the like.

Amino acid mixtures previously available in the form of acid, basic, or enzymatic hydrolysates are not entirely satisfactory because they cause certain undesirable side reactions when administered in large doses and at a fast rate. There is, for example, a marked tendency to produce nausea and vomiting when such hydrolysates are administered at rates or in amounts exceeding very low limits. In most cases where administration of amino acids is necessary or desirable, side reactions of this type can not be tolerated because of the weakened condition of the patient; and administration of the hydrolysates at rates which will not cause these reactions greatly reduces the effectiveness of the treatment as a means for restoring and maintaining proper protein balance.

Recently, Madden et al., J. Exptl. Med. 79, 607-624 (1944), has shown that mixtures of eleven pure amino acids containing 60% of natural essential amino acids are definitely superior to protein hydrolysates in being tolerated, maintaining nitrogen balance, and in regenerating blood protein. The mixtures of pure amino acids thus have the advantage that they can be infused into patients more rapidly and in larger amounts. There are also marked disadvantages in such mixtures. Foremost of these is the high cost of pure amino acids and the unavailability of large quantities required for widespread therapy. Secondly, these mixtures contain approximately 25% of d-amino acids (the unnatural form) a large part of which probably can not be utilized by the human body (see Rose, Physiological Reviews, 18, 109 (1938); Albanese, Bulletin of Johns Hopkins Hospital, 75, 175 (1944)) and which undoubtedly limits the usefulness of the mixture.

It is now discovered in accordance with the present invention that by a new procedure, fully hereinafter described, it is possible to prepare from inexpensive protein material an amino acid mixture consisting predominantly of the natural essential amino acids which is superior nutrition-

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ally and toxicologically to any protein hydrolysate or mixture of amino acids prepared previously and which can be administered in oral, rectal, and parenteral therapy at rates and in amounts heretofore impossible with existing amino acid preparations.

The striking increase in the rate at which our amino acid mixture may be administered parenterally is clearly demonstrated by the following tabulation based upon an extended comparison of the rates at which various preparations are tolerated when a total of 220 mgms. of N/kgm. of body weight is infused into the normal dog.

TABLE I

Preparation	Lowest rate in mgm. N/kgm./min. which will produce vomiting
Our mixture.....	30
Madden—mixture of pure amino acids.....	6
Enzymatic hydrolysate.....	4
Acid hydrolysate.....	2

A further advantage of our mixture over the Madden mixture is that there is less spillage into the urine. When both solutions are infused at 6 mgms. of N/kgm./min. and a total of 200 mgms. of N/kgm. is given, 19% of the amino acids of the Madden solution is lost into the urine in 24 hours whereas only 13% of those of our mixture is lost in an equal period of time.

Speed of infusion would be of no great advantage if there were a corresponding increase of spillage of amino acids into the urine. Experiments have shown this not to be the case with our solution; the loss into the urine is the same at rates of 6 and 12 mgms. of N/kgm./min.

Regarded in certain of their broader aspects, novel features of the present invention include, as new products, balanced mixtures of the natural essential amino acids in substantially pure form, characterized as being free of dicarboxylic acids and substantially free of physiologically inactive isomeric amino acids, and the process of preparing such mixtures that comprises isolating from a protein acid hydrolysate a fraction consisting of substantially pure natural essential monoamino monocarboxylic acids, and adding to said fraction substantially pure tryptophane, essential basic amino acids, and fortifying amounts of essential monoamino monocarboxylic acids present but deficient in said fraction.

In carrying out the process in accordance with the present invention, any protein which is high