In the Matter of

CERTAIN AMINO ACID FORMULATIONS

Investigation No. 337-TA-127

Unreviewed Initial Determination

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United States International Trade Commission / Washington, D.C. 20436

UNITED STATES INTERNATIONAL TRADE COMMISSION

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This is an initial determination issued by a Commission administrative law judge (presiding officer) that was not reviewed by the Commission. The initial determination has, therefore, become the Commission determination in this investigation on the issue of violation of section 337. See section 210.53(h) of the Commission's Rules of Practice and Procedure, 47 Fed. Reg. 25134, June 10, 1982 and 48 Fed. Reg. 20225, May 5, 1983; to be codified at 19 C.F.R. § 210.53(h).

UNITED STATES INTERNATIONAL TRADE COMMISSION
Washington, D.C.

P U B L I C V E R S I O N

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INITIAL DETERMINATION

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PROCEDURAL HISTORY

On July 12, 1982, American Hospital Supply Corporation and Massachusetts General Hospital filed a complaint with the U.S. International Trade Commission alleging violations of Section 337 of the Tariff Act of 1930, as amended. 19 USCA §1337.

The Commission issued a notice of investigation which was published in the Federal Register on August 20, 1982. An investigation was instituted to determine whether there is a violation of Section 337 in the unauthorized importation of certain amino acid formulations into the United States, or in their sale, by reason of the alleged direct infringement by said formulations of claims 1, 5, or 14 of U.S. Letters Patent 3,950,529, and by reason of the alleged contributory infringement and induced infringement in the sale by respondents of said formulations of claims 1, 5, 6, 7, 9 or 14 of the '529 patent, the effect or tendency of which is to destroy or to injure substantially an industry which is efficiently and economically operated in the United States.

American Hospital Supply Corporation is an Illinois corporation with its principal place of business in Evanston, Illinois. Massachusetts General Hospital is a non-profit corporation under the laws of Massachusetts, with its principal place of business in Boston, Massachusetts.

The two respondents are Travenol Laboratories, Inc., a Delaware corporation with its principal place of business in Deerfield, Illinois, and Pfrimmer & Company, a West German corporation with a place of business in Erlangen, West Germany.

The parties have entered into the following stipulations, among others:

Complainants own the '529 patent in issue (the Fischer patent), and Massachusetts General has licensed its rights in the Fischer patent to American. American is the exclusive licensee.

American produces and sells an amino acid formulation for liver diseased patients as an enteral or food product under the trademark "Hepatic-Aid," and a product for parenteral or intravenous administration under the trademark "HepatAmine." Hepatic-Aid has been on the market since approximately May, 1979, and HepatAmine has been on the market since late October 1982. Only Hepatic-Aid is in issue here.

Travenol introduced its product, an enteral amino acid formulation for nutritional support of liver diseased patents, in the U.S. market in September, 1981, under the trademark "Travasorb Hepatic."

A hearing commenced on February 22, 1983, and was completed on March 9, 1983. All parties have filed briefs, and have consented to the jurisdiction of the Commission.

The overall issue in this case is whether either respondent has engaged in an unfair method of competition or unfair act under Section 337 falling within the scope of the notice of investigation. The specific issues are:

1. Whether the '529 Fischer patent is valid.
2. Whether the patent was infringed by either respondent.

3. Whether the patent is enforceable.

4. Whether there is a domestic industry under the patent, and if so, whether that domestic industry is efficiently and economically operated.

5. Whether complainants have shown the amount of injury to the domestic industry required by Section 337.

Under Section 210.14 of the Commission's Rules, the Commission reserves to itself all consideration of the public interest factors and the appropriate form of relief if a violation of Section 337 is found. No findings are made on these issues.

FINDINGS

1. The Background of the Fischer Patent

The '529 Fischer patent was issued on April 13, 1976, based on a patent application filed on February 3, 1975. The inventors are Josef E. Fischer, Norman N. Yoshimura, Thomas L. Westman, and Fred H. Deindoerfer. The patent was issued and all claims allowed, without discussion, rejection or revision of any claim. Travenol Ex. 10, American Ex. 1.

Complainants allege that claims 1, 5, 6, 7, 9 and 14 of the '529 patent have been infringed by Travenol's Travasorb Hepatic product, an enteral amino acid preparation used in the treatment of patients with liver disease. Travenol contends that all of the claims in issue are invalid, unenforceable, and if found to be valid and enforceable, they are not infringed.

The subject matter of the '529 patent is certain amino acid formulations for administration to human patents with liver disease, formulations which

may be adapted for either intravenous (parenteral) or oral (enteral) administration. The formulations are intended to provide nutritional support for liver diseased patients, to reduce the incidence of hepatic encephalopathy, and to treat those suffering from hepatic encephalopathy (coma caused by severe liver disease).

The level of ordinary skill of those in the pertinent art at the time of the alleged invention, in the early 1970's, was high. Those studying liver disease from various points of view in the early 1970's included animal scientists, physiologists, biochemists and physicians. TR 484. These people generally had college degrees and many had advanced degrees. TR 484-485.

By the early 1970's extensive knowledge about amino acids was available to one with ordinary skill in the art.

There are approximately twenty amino acids used by the liver to manufacture protein. By 1949, Dr. William C. Rose had published studies establishing minimum amounts of certain amino acids needed by healthy persons. These amounts are referred to as the "Rose pattern." Dr. Rose identified eight of the twenty amino acids as essential. The essential amino acids cannot be synthesized by the human body. They have to be provided either by the diet or by other products which can be broken down into these essential amino acids. TR 102. The essential amino acids are valine, leucine, isoleucine, threonine, phenylalanine, tryptophan, methionine, and lysine. TR 103, American Ex. 75.

Of the remaining 12 amino acids, two are sometimes called "semi-essential," (histidine and arginine), and the rest are called non-essential amino acids, because the human body can synthesize them if it is given the precursors to these compounds. TR 103. Products such as ammonia, carbohydrates, other nitrogen sources, and essential amino acids can be converted into non-essential amino acids. TR 104.

If the human body is not given sufficient amounts of non-essential amino acids, or the precursors to make them, there may be less than optimum protein synthesis, a condition sometimes described as a state of "negative nitrogen balance." A negative nitrogen balance shows that the patient is breaking down more protein than he is synthesizing. A positive nitrogen balance shows that the patient is synthesizing more protein than he is breaking down. Most healthy human adults are in a state of nitrogen equilibrium, where synthesis is occurring at the same rate as catabolism. TR 104, 105. If a human body is in a neutral or positive state of nitrogen balance, it can be assumed that all 20 amino acids are being provided in adequate amounts either from outside sources or through synthesis by the body itself. Stipulation.

In the normal human body, the liver receives virtually all the blood flowing from the digestive tract, after enrichment by products of the digestive process. A principal function of the normal liver is to regulate the levels of some amino acids in the blood. This is accomplished within fairly narrow tolerances primarily through complex metabolic processes, using about 5000 enzymatic pathways in the liver. TR 1012-1013. Some amino acids are converted

into others. Excessive amounts of certain amino acids are oxidized. Combustion products (CO_2, H_2O, urea) are diverted from the blood to other organs and are eliminated from the body.

Some amino acids, particularly the branched chain amino acids, are not substantially affected or regulated by the liver at all. These are metabolized through pathways independent of the liver. Stipulation.

The liver's control of certain amino acid levels has been compared to a lawnmower, controlling the height of growing grass; after a protein rich meal, the liver may fall behind in its regulating function, but normal levels are attained within about 90 minutes. TR 1031-1537.

Proteins are essential to man and animals and, in normal subjects, are obtained from food. Patients who, because of illness, surgery or injury, are unable to take in nutritionally adequate quantities of protein through the alimentary tract quickly develop malnutrition, evidenced by wasting of the body stores of protein (i.e., muscle mass, nerve tissue, etc.). Stipulation.

Proteins usually are not administered directly to a patient's bloodstream for nutritional purposes, because at the cellular level, the body can only utilize the individual amino acids. The body's means for breaking proteins down to individual amino acids are located primarily in the gastrointestinal tract. In the 1940's, it was discovered that protein such as milk protein (casein) and hen's egg protein (ovalbumin) could be broken down chemically to the individual amino acids by the process of hydrolysis, and the resulting protein hydrolyzates could be provided to patients intravenously. Intravenous

administration of protein hydrolyzate solutions provided a means to compensate partially for a patient's inability to consume protein orally. Stipulation.

Although the availability of protein hydrolyzates was a significant medical advance, these solutions were impure, they contained byproducts of the hydrolysis reaction, and the pattern of amino acids in the hydrozylates was related to the patterns of amino acids occurring in the proteins from which the hydrolyzates were made. TR 1623.

By the mid-1960's, all of the individual amino acids had become available in a pure form at reasonable cost. Synthetic solutions with any pattern of amino acids desired could be prepared from them. American Ex. 179, TR 1623.

In the mid-1960's, Dr. Stanley Dudrick perfected a surgical technique for inserting a cannula (delivery tube) for administering concentrated nutritional solutions into deep veins, such as the subclavian vein. Because of the small blood flow in peripheral veins, such as those in the arm, before that technique beame available it was virtually impossible to administer nutritionally adequate quantities of amino acids and carbohydrates (glucose) through catheters inserted into those veins. Because of the large blood flow in deep central veins, Dr. Dudrick's technique permitted the administration of larger amounts of solutions that were concentrated in amino acids and glucose. This technique became known as "hyperalimentation." Stipulation.

Malnutrition was a serious problem for a patient with a liver disease such as cirrhosis. The feeding of protein to a patient with cirrhosis often led to hepatic encephalopathy or coma. Hepatic encephalopathy is generally

characterized by a depressed mental state with impaired consciousness, decreased intellectual performance and altered personality. Both acute and chronic liver disease are associated with the series of neuropsychiatric changes known as hepatic encephalopathy. By restricting protein intake, the tendency of a cirrhotic patient to develop hepatic encephalopathy or coma could be reduced, but limitation of protein intake contributed to malnutrition. 'Stipulation.

About 98% of people with liver disease can be treated by a careful diet, avoiding alcohol and meat in order to lessen the demand on the diseased liver. TR 1025-30, 1495-96. Hepatic encephalopathy is not present in most people with liver disease, whether the disease is mild or severe. TR 373. Patients with severe liver disease may or may not have hepatic encephalopathy. TR 373-74; 1027-29.

Physicians in the early 1970's recognized that there was an abnormally high ratio of ammoniagenic amino acids in the plasma of patients with certain liver diseases such as cirrhosis. At that time, physicians treating liver diseased patients conventionally could limit protein intake, or they could give the patent lactulose, or neomycin (an antibiotic), or they could try all three. Lactulose and neomycin were intended to reduce the amount of ammonia passing from the gut into the bloodstream. Lactulose (or casein) was quickly absorbed, so that it would not spend a long time in the intestines where ammonia was formed. Ammonia was formed in the gut from proteins. Ammonia was thought to be a principal cause of hepatic encephalopathy, and this theory is still widely accepted today. TR 388-393, American Ex. 78, pp. 245, 248. The theory

is that when the liver is not functioning properly, more ammonia is formed than the body can get rid of, and that the excess ammonia causes hepatic encephalopathy.

In a 1973 paper of Dr. Rudman (Travenol Ex. 45), the amino acids in proteins were classified for ammonia-generating tendencies when the amino acids were metabolized in patients with liver disease. The amino acids threonine, serine, glycine, histidine and lysine were shown to be the most ammoniagenic of the amino acids.

Dr. Rudman made physicians aware of which amino acids tended to generate ammonia. The conventional treatments for controlling the level of ammonia in the plasma, however, were not always successful. They sometimes caused malnutrition if the patient was deprived of adequate protein over a long period of time, and they did not always prevent hepatic encephalopathy.

In an article published in 1971, Dr. Fischer hypothesized that hepatic encephalopathy could be caused by the abnormally high levels of certain amino acids in the plasma of liver diseased patients. He suggested that the aromatic amino acids (phenylalanine, tyrosine and tryptophan) were precursors for "neurotransmitters" and "false neurotransmitters" synthesized in the brain. The normal neurotransmitters (called "putative" neurotransmitters) were those compounds released by nerve cells which carry an impulse from one nerve to another across the junction or "synapse." American Ex. 115. These normal neurotransmitters were thought to be the compounds dopamine and norepinephrine. In addition to the normal neurotransmitters, closely related false neurotransmitters (compounds known as "octopamine" and "tyramine") were also produced in brain tissue of patients exhibiting hepatic encephalopathy. Stipulation.

Dr. Fischer's hypothesis is that there is a transport mechanism which carries the aromatic and branched chain amino acids from the bloodstream to the brain. The location of this transport mechanism is called the "blood-brain barrier." Dr. Fischer suggested that competition exists between the branched chain amino acids and the aromatic amino acids for passage across the blood brain barrier. If he increased the level of branched chain amino acids in the bloodstream he could lower the amount of aromatic amino acids which can enter the brain using the same transport mechanism. Dr. Fischer had the idea that increased amounts of aromatic amino acids in the plasma of patients with liver disease and dimished amounts of branched chain amino acids in their plasma resulted in increased concentrations of the aromatic amino acids passing into the brain. Since aromatic amino acids might be the percursors of "false neurotransmitters," this might result in the synthesis of relatively greater amounts of false neurotransmitters and the sleep-inducing agent, serotonin, and relatively lower amounts of normal neurotransmitters. Dr. Fischer's 1971 article indicated that these abnormalities in brain chemistry might be the cause of the neurological disturbances (hepatic encephalopathy) observed in liver diseased patients. American Ex. 123.

The "branched chain" amino acids are isoleucine, leucine and valine. The "aromatic" amino acids are tryptophan, phenylalanine and tyrosine.

Dr. Fischer's 1971 article suggesting that hepatic encephalopathy might be caused by the relative amounts of branched chain and aromatic amino acids in the plasma was based on the abnormal patterns of amino acids in the plasma of liver diseased patients which were known to those skilled in the art at that

time. American Ex. 28. In the early 1970's, several articles had reported that the plasma amino acid patterns of patients with severe liver disease were distorted. TR 1037-1038. These articles indicated that the levels of certain amino acids, such as the aromatic amino acids and methionine, were elevated in liver diseased patients, while the levels of other amino acids, such as the branched chain amino acids, were decreased.

In liver disease, the function of the liver in regulating certain amino acid levels is disrupted. Branched chain amino acids apparently are not regulated by the liver, but the levels of aromatic amino acids are. In a patient with severe liver disease, the low level of branched chain amino acids is not due to the liver's failure to regulate branched chain amino acids, but there is some relationship between a damaged or cirrhotic liver and the low level of branched amino acids compared to a higher than normal level of aromatic amino acids in the plasma.

In advanced stages of liver disease, blood leaving the intestines in the portal vein often bypasses the liver through enlarged collateral veins. TR 1021. This bypass circulation results from increased pressure in the portal vein arising from blockage or restriction of portal blood flow through the liver. TR 367-68, 1021. If blood from the intestines bypasses the liver entirely this may alter the normal amino acid patterns in the plasma. Even blood entering a diseased liver may not be broken down into a normal amino acid pattern because of the poorly functioning liver.

It was known prior to 1974 that certain amino acids were elevated in patients with specific liver diseases such as phenylketonurics (PKU), maple

syrup urine disease (MSUD) patients, and tyrosinemia patients. TR 1038-39. The technique of "normalization" of abnormal levels of amino acids in the blood plasma by varying the diet was known before 1974. Normalization was used in treating liver diseases involving specific enzyme deficiency defects such as PKU (toxic elevation of phenylalanine), MSUD (toxic elevation of branched chain amino acids), and tyrosenemia (toxic elevation of tyrosine). TR 410-14, 1037-38, 1580, 1037-44. Dr. Tucker had designed specific amino acid diets for patients with liver enzyme defects, such as an inability to metabolize valine. TR 1329-30. In each case, the treatment was to give diets abnormally low in certain amino acids to patients whose levels were abnormally high in those amino acids prior to treatment, and vice versa. TR 1321. Normalization was not one of the conventional treatments for patients with severe liver disease like cirrhosis,, but it was used for patients with a specific enzyme deficiency.

In the late 1960's, McGaw Laboratories, a division of complainant American Hospital Supply Corporation, became interested in formulating amino acid nutritional solutions for patients with specific diseases. Oral nutritional products (foods) can be introduced to the market more quickly than parenteral solutions which are considered to be drugs, because the lengthy process of clinical testing of drugs prior to registration and approval by the Food and Drug Administration is not required for foods. Stipulation. McGaw started with FreAmine, an amino acids product for patients with kidney disease.

In the late 1960's and early 1970's, McGaw decided to try to formulate an amino acid product for patients with liver disease. McGaw's scientists were aware of Dr. Fischer's interest in the causes of hepatic encephalopathy

and in 1972 they entered into a collaborative research arrangement with him. Dr. Fischer collected plasma samples from a reasonably large number of liver diseased patients and transmitted them in a frozen state to McGaw's laboratories for analysis. Stipulation. TR 750-751.

Dr. Fischer and three McGaw scientists then selected an experimental animal model with simulated liver failure and an amino acid pattern similar to those observed in human patients with chronic liver disease. TR 128, 759; American Ex. 116.

First, they measured the plasma amino acid levels in liver diseased human patients and test animals. Then, two intravenous amino acid solutions were given to human patients with liver disease, and the resulting amino acid plasma levels were measured. The two solutions used were FreAmine and an experimental solution called FreAmine E. The research up to this point (early 1973) was reported in an article entitled "Plasma Amino Acids in Patients with Hepatic Encephalopathy," written by Dr. Fischer, Dr. Yoshimura, Dr. Deindoerfer, and others, presented in May of 1973, and published in the American Journal of Surgery, 127: 40-47 (January, 1974). Stipulation. This is referred to as the 1974 Fischer article. American Ex. 119, Travenol Ex. 26.

These experiments with FreAmine and FreAmine E confirmed the known differences between the plasma amino acid profiles of patients with liver disease and those of healthy people. Travenol Ex. 60, pp. 105-106.

The 1974 Fischer article then suggested that normalization of plasma amino acid levels should be tried in patients who had alcoholic cirrhosis with hepatic encephalopathy. Dr. Fischer suggested varying the amounts of

the amino acids in the formulation to be administered to the patient to provide more of the amino acids where the plasma levels were below normal, and less of the amino acids where the plasma levels were above normal.

The 1974 article included research in administering FreAmine and FreAmine E amino acid solutions to patients with advanced liver disease and hepatic encephalopathy, and it summarized much of the prior art as of the early 1970's relating to plasma amino acid patterns of patients with liver disease. The article notes that there was a characteristic plasma amino acid pattern in patients with advanced cirrhosis and experimental animals with no liver function. Travenol Ex. 26, p. 40.

In one group of patients with hepatic encephalopathy, protein intake was restricted to less than 40 grams and generally less than 25 grams per day, which was considered to be nutritionally insufficient. The blood plasma amino acid patterns of these patients showed abnormally high levels of methionine, phenylalanine, tyrosine, ornithine, aspartic acid and glutamic acid. The levels of valine, leucine, isoleucine, and tyrosine were abnormally low. The hepatic encephalopathy conditions of one half of these patients cleared during the time that their protein intake was restricted. Travenol Ex. 26, p. 43, Fig. 1.

These patients then were divided into two groups, one of which received FreAmine, while the other received FreAmine E. FreAmine is a parenteral amino acid solution in which the profile of essential amino acids reflects that of hen's egg protein. TR 1620. FreAmine E is a parenteral amino acid solution containing only the eight essential amino acids. The pattern of essential

amino acids in FreAmine E follows the Rose pattern. The blood plasma amino acid patterns of the FreAmine patients remained essentially the same: methionine, phenylalanine, tyrosine, ornithine, aspartic acid and glutamic acid remained high, while valine, leucine, isoleucine and tyrosine were below normal. Travenol Ex. 26, p. 44, Fig. 3. In the FreAmine E patients, blood plasma amino acid patterns also showed high levels of methionine, phenylalanine, aspartic acid and glutamic acid. Valine, leucine, isoleucine and several of the nonessential amino acids were abnormally low. Travenol Ex. 119, p. 44, Fig. 2. Dr. Fischer was "somewhat surprised" at the failure of FreAmine E "to increase the persistently low concentrations of the branched chain essential amino acids, this despite the fact that two and a half times the minimal daily requirements recommended by Rose et al... were being administered." Travenol Ex. 119, p. 44.

A comparison of Figures 1 and 2 in the 1974 article shows that the plasma levels of the three branched chain amino acids were lower in the patients recei these amino acids in FreAmine E than in those who were protein restricted. It was clear that adding branched chain amino acids in a formulation reflecting th normal ratio of branched chain amino acids in ordinary protein did not raise th level of branched chain aminoacids in the plasma. The fasting patient had a hi ratio of branched chain amino acids in the plasma than the patient receiving no patterns of amino acids.

The 1974 article (at p. 46) suggested modification of normal amino acid mixtures to normalize the pattern of amino acids in the plasma of patients with liver disease:

> Since parenteral nutrition in patients with severe hepatic impairment is desirable, it is suggested from these studies that current amino acid mixtures be modified. As a first approximation, an attempt should be made to normalize plasama amino acid levels. Once plasma amino acid levels are normalized, it might be possible to infuse larger amounts of calories and protein than has heretofore been possible (in this study, approximately 45 to 55 gm of protein per twenty-four hours was possible at the most). Furthermore, normalization of plasma amino acid patterns may enable a more beneficial balance of amino acids as they enter the brain, with more efficient synthesis of the aforementioned neutrotransmitters, norepinephrine and dopamine. If this is true, perhaps greater amounts of amino acids may be infused in patients without recurrence of hepatic encephalopathy, provided a sufficient caloric amount is infused as well.
>
> It is acknowledged that such studies are somewhat crude and uncontrolled, that the exact relation between plasma amino acid imbalances and hepatic encephalopathy is unknown at the present time, and that those possibilities suggested herein are only theoretic. As a first approximation however, the approach to total parenteral nutrition in patients with hepatic disease should include the normalization of plasma amino acid patterns. Experimentally, when dogs with end to side portacaval shunts have spontaneous improvement in hepatic function because of the development of collaterals to the liver, normalization of the plasma amino acid pattern occurs (Aquirre, Westman, Yoshimura and Fischer: Unpublished observations). This further suggests that the plasma amino acid pattern seen in man and in dogs with liver disease is abnormal, that it serves no useful purpose in animals or patients, and that normalization of such a pattern would be beneficial.

The tests described in the Fischer article showed no improvement in the patients when FreAmine or FreAmine E was administered. The above quotation refers to a study made by Dr. Condon on dogs in which the time of survival in dogs with portacaval shunts) was increased when the diet was relatively high in branched chain amino acids. Later, Dr. Fischer learned that the foods resulting in a longer time of survival did not in fact have a higher ratio of branched chain amino acids, but this was not known when the 1974 Fischer article was published. TR 1566.

Table III of the article set forth the numerical deviations from "normal" levels of plasma amino acids which resulted from administering the FreAmine E and FreAmine solutions. Figures 2 and 3 showed the abnormal patterns of essential and non-essential plasma amino acids of patients treated with FreAmine E and FreAmine solutions, and they did show that the plasma amino acid levels in a patient with severe liver disease can be manipulated by altering the amounts of the amino acids in the diet fed to the patient. In concluding, the 1974 Fischer article suggested that FreAmine and FreAmine E solutions could be modified "... to normalize plasma amino acid levels." Travenol Ex. 26, p. 46. This suggested that altering the amino acid levels in plasma by administering amino acids in food could be accomplished in patients with severe liver disease. The level of branched chain amino acids in the plasma had not been raised by the branched chain amino acids given in FreAmine E, which suggested that altering the amino acid levels in plasma by adding branched chain amino acids in the food might not work.

It was not apparent why the levels of branched chain amino acids in the plasma were lower when a patient given FreAmine or FreAmine E, containing normal amounts of branched chain amino acids, than when a patient was given restricted protein. Why was the branched chain amino acid level remaining depressed, when they were not regulated by the liver? It was also not clear what effect the low level of branched chain amino acids had, or what the effect of normalizing those levels would be, or what effect the high level of aromatic amino acids had, or what the effect of normalizing those levels would be. Dr. Fischer suggested tests to find out what the effect of normalizing these amino acid levels would be.

Following Dr. Fischer's oral presentation in May 1973 of the report later published as the 1974 Fischer article, Dr. Yoshimura and Dr. Fischer independently reviewed the plasma amino acid data for the liver diseased patients. Each of them independently wrote down amino acid formulations which they proposed for giving improved nutrition to patients with liver disease. Travenol Ex. 61, Nov. pp. 114-115. Both proposals contained higher concentrations of branched chain amino acids and lower concentrations of phenylalanine and methionine than in FreAmine. Travenol Ex. 61, Nov. p. 115. Dr. Yoshimura's proposed increase in branched chain amino acids was based on his observation of the fact that in liver diseased patients to whom FreAmine was administered, the branched chain amino acid concentrations were low. The increase in the concentration of branched chain amino acids was intended to normalize the levels of these amino acids in the blood plasma. Travenol Ex. 61, Nov. pp. 115-117. The decrease in concentration of phenylalanine was for the same reason. Travenol Ex. 61, Nov. p. 119. Dr. Fischer and Dr. Yoshimura then agreed on a formula for the new amino acid solution and this formulation is known as "F080." TR 122, 170; Travenol Ex. 11, p. 278, column 2.

The principal difference between the F080 formula and FreAmine, which had been used previously as a nutritional supplement for kidney diseased patients, was that the ratio of the branched chain amino acids to the aromatic amino acids was much higher in F080 than in FreAmine. TR 147.

Following agreement on the formulation for F080, Dr. Yoshimura had experimental solutions prepared and a sample was sent to Dr. Fischer. In 1974 Dr. Fischer administered the solution intravenously to experimental

animals with simulated liver disease and hepatic encephalopathy. TR 147-148, 775-776.

The results were surprising to the inventors. Animals that were in coma or near comatose states awakened when given this experimental solution. TR 171-173, 775-776.

The animal experiments were described in an article co-authored by Dr. Fischer and published in 1975. Travenol Ex. 11. The 1975 Fischer article was prepared for presentation at a meeting in February, 1975, immediately after the application for the '529 Fischer patent was filed on February 3, 1975. In these experiments, dogs with simulated liver failure were divided into three groups. The first group was given dextrose and blood plasma, the second group was given a commercially available conventional amino acid formulation (FreAmine II), and the third group was given F080. Each group also received dextrose, vitamins and electrolytes. Two of the five dogs in the first group died in hepatic encephalopathy. All three dogs in the second group died in hepatic encephalopathy. All dogs given F080, although in hepatic encephalopathy, improved within 24 hours after being given F080. The 1975 Fischer article discusses these experiments and suggests that the neurological conditions of the test animals were directly related to their plasma amino acid patterns and that these plasma amino acid patterns could be normalized by the administration of F080. The question of what would happen to a dog with hepatic encephalopathy if the ratio of the branched chain amino acids (valine, leucine, and isoleucine) to the aromatic acids (phenylalanine and tyrosine) could be normalized was answered. American Ex. 117, TR 117,

776-779. The animal model closely simulated a human patient with a cirrhotic liver and hepatic encephalopathy.

The 1975 Fischer article was published after the application for the Fischer patent was filed on February 3, 1975, and it is not prior art to the Fischer patent. It contains a detailed description of the animal experiments which formed the principal basis for the Fischer patent application.

In about 1974, the McGaw scientists prepared a paper entitled "Disclosure of Invention" (American Ex. 147) for their counsel to use in preparing the Fischer patent application. TR 192-193. The disclosure was based on the experimental work on F080. The F080 formula was expanded to include "molar ranges" or "molar ratios." It also included enteral formulas, and another amino acid solution which differed from F080.

The Fischer patent application was filed on February 3, 1975, and the '529 patent was issued on April 13, 1976. All claims were allowed without change or discussion.

The question of whether the Fischer patent is valid or infringed must be considered in the context of the foregoing background.

2. Validity

Travenol argues that claims 1, 5, 6, 7, 9 and 14 of the patent are invalid under Sections 112, 102 and 103 of the Patent Act. These claims are attached hereto as Appendix A.

(a) Presumption of Validity

Section 282 of the Patent Act provides that a patent shall be presumed to be valid. Each claim of a patent is presumed to be valid regardless of whether other claims are found to be invalid. The burden of establishing invalidity rests upon the party asserting it. 35 U.S.C.A. 282.

Some courts have held that the presumption of validity may be weakened or destroyed if prior art more relevant to the alleged invention than that cited by the Patent and Trademark Office (PTO) was not presented to the PTO during the patent application process. See Baumstimler v. Rankin, 677 F.2d 1061, 215 USPQ 575 (5th Cir. 1982); 2 D. Chisum, Patents §5.06[2] (1982). In Solder Removal Co. v. USITC, 582 F.2d 628, 199 USPQ 129 (CCPA 1978), however, the CCPA noted that the burden of persuasion remained with the party asserting invalidity "whether the most pertinent prior art was or was not considered by the examiner," but that the burden "may be more easily carried by evidence consisting of more pertinent prior art than that considered by the examiner." 199 USPQ at 133. In this context the CCPA used "burden of persuasion" in the sense of the ultimate substantive burden of proof, rather than the burden of going forward. See E.W. Cleary, McCormick on Evidence, p. 785. The position of the CCPA will be followed here.

The parties stipulated that the most pertinent prior art was the Fischer 1974 article and the Ghadimi patent. Both were referred to in the specification of the Fischer patent. Neither is cited by the patent examiner, but the examiner had to be aware of their existence if he read the specification. There is no evidence that copies of the Fischer 1974 article and the Ghadimi patent were sent to the patent examiner or that he considered them. Another patent which was summarized in the specification, the Bergstrom patent, was cited by the examiner, presumably because he found it and read it. Mr. Moyer, who was a primary examiner in 1975, testified only that if he felt that a document as defined in the disclosure was pertinent, in general he would seek it out. Travenol Ex. 63, at 64. If Mr. Moyer had read and considered the Fischer 1974 article and the Ghadimi patent, however, there is no explanation as to why he did not follow the same practice as with the Bergstrom patent, and cite them as well.

Complainants allege that the presumption of validity is not weakened because the existence of the two most pertinent pieces of prior art was disclosed to the examiner. Respondents contend that the patent applicant misrepresented the prior art and failed to disclose important information in the Fischer article and the Ghadimi patent, with the result that the examiner, who had a limited amount of time, (Travenol Ex. 63 at 28), would not have thought it necessary to find the article and the patent and to read them. The Ghadimi patent probably would have been readily available to the examiner, if not in use by another examiner, and the Fischer 1974 article could have been requested without difficulty.

There is no persuasive evidence that the examiner did in fact read and consider the two most pertinent prior art references and it is found that it is unlikely that he did so. As indicated in Solder Removal, the burden of persuasion that the patent is invalid remains with respondents, but the burden may be more easily carried here since it is unlikely that the examiner read and considered the two most pertinent prior art references.

(b) Section 112

Section 112 states:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is mostly nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention.
>
> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention. A claim may be written in independent or dependent form, and if in dependent form, it shall be construed to include all the limitations of the claim incorporated by reference into the dependent claim.
>
> An element in a claim for a combination may be expressed as a means or step for performing a specified function without the recital of structure, material, or acts in support thereof, and such claim shall be construed to cover the corresponding structure, material, or acts described in the specification and equivalents thereof.

Travenol argues that the Fischer patent claims in issue are invalid under 35 U.S.C. §112 because they are vague, ambiguous and indefinite. Specifically, Travenol contends that the terms "liver disease," "proportion," and "molar," as used in the asserted claims, are vague, ambiguous, and indefinite.

The use of the term "liver disease" in the Fischer patent would not be vague, ambiguous or unclear to one skilled in the art reading the specification as a whole. It is clearly stated that liver disease may in some cases lead to hepatic encephalopathy leading to death; that protein restriction may reduce the tendency to develop hepatic encephalopathy; and that protein restriction may contribute to malnutrition of the patient. American Ex. 1, col. 1, lines 35-49. The specification also states, that the patented formulation is aimed at providing "more nearly adequate nutrition while avoiding the complications of encephalopathy and coma," and that "if the patient can be maintained over a sufficient period of time with adequate nutrition, the liver may repair and fully recover." American Ex. 1, col. 3, lines 8-23.

PKU, maple syrup urine disease and tyrosinemia are diseases involving single genetic enzyme deficiencies. No one is sure which one of the approximately 600 enzyme systems in the liver is responsible for hepatic encephalopathy in complex liver disease. TR 1580-1581. The patent clearly is not directed to treatment of patients with genetic liver enzyme deficiency diseases. In the diseases there is no expectation that the liver may "regenerate" and "fully recover" if adequate nutrition can be maintained over a period of time, in contrast to the liver disease described in the patent. One skilled in the art would know from a reading of the patent which patient conditions would indicate use of the patented formulation.

Use of the terms "in proportion" and "molar" in the patent is also clear enough if the whole specification is read to satisfy Section 112. The invention described in the specification is based on formulations which have a specific relationship between the branched chain amino acids and other amino acids.

These formulations are intended to provide adequate protein nutrition for liver diseased patients without precipitating or exacerbating hepatic encephalopathy. TR 193, 196-197. The patent also concerns methods of supplying these amino acid formulations to liver diseased patients.

Claim 1 of the Fischer patent reads as follows:

> 1. An amino acid formulation for administration to human patients with liver disease, comprising a mixture of the following essential and nonessential amino acids combined in proportions defined by the following interrelated molar ranges:

Amino Acids	Molar Ranges
L-isoleucine	0.0549-0.0823
L-leucine	0.0670-0.101
L-valine	0.0574-0.0861
L-tryptophan	0.000816-0.00441
L-phenylalanine	0-M
L-tyrosine	0-0.00300
L-lysine	0.0333-0.0500
L-methionine	0.00491-0.0147
L-threonine	0.0228-0.0454
L-alanine	0.0686-0.103
L-arginine	0.0275-0.0413
L-histidine	0.0124-0.0186
L-proline	0.0556-0.0834
L-serine	0.0152-0.0571
glycine	0.0451-0.144
L-aspartic acid	0-0.0451
L-glutamic acid	0-0.0702
L-ornithine	0-0.0382
L-cysteine	0-0.00228

> wherein M represents the upper limit of the range for phenylalanine and is equal to 0.009 minus the respective molar amount of tyrosine present in said mixture, the combined molar amounts of phenylalanine and tyrosine being at least equal to 0.002 on the same respective molar basis, the respective molar proportions of isoleucine, leucine, valine, tryptophan, phenylalanine, and

tyrosine being selected from the above molar ranges thereof so that the ratio of the combined molar proportions of isoleucine, leucine, and valine to (a) the molar proportion of tryptophan is within the numerical range from 40 to 300, and to (b) the combined molar proportion of phenylalanine and tryosine is within the numerical range from 15 to 135.

Claim 1 describes the proportions of essential and nonessential amino acids to one another in terms of "molar ranges." The term "mole" is a chemical term used to indicate quantities of chemical substances. "Mole" is defined as the quantity of a substance whose weight in grams is numerically equal to its molecular weight. Equal numbers of moles of two different chemical compounds will contain the same number of molecules, although the actual masses or weights of the two compounds might differ. For example, the molecular weight of hydrogen is 2.02, and the molecular weight of oxygen is 32.00. One mole of hydrogen molecules will weigh 2.02 grams and will contain the same number of molecules as one mole of oxygen which weighs 32.00 grams. Expressing quantities of materials in molar amounts is convenient, in that these amounts are proportional to the number of molecules. Stipulation.

The Fischer patent describes proportions of amino acids in terms of "molar" quantities rather than gram or mass quantities. The word "molar" has at least two possible connotations: it can represent concentration, as in "moles per liter" (the number of moles of a dissolved substance per liter of solution), or it can be used as the adjective of the word "mole," meaning a quantity proportional to the molecular weight of a substance.

Travenol argues that the patent is invalid under Section 112 because there are <u>three</u> possible interpretations of "molar," and the patent does

not clearly specify the meaning of "molar." Travenol take the position that "molar" means "moles per liter," while complainants argue that "molar" as used in the Fischer patent is the adjective of the word "mole," and that "molar ranges" refers to the range of quantities proportional to the molecular weights of the various amino acids in the product rather than to the concentration of these amino acids in a solution. In addition to these two meanings of "molar," respondents note that there is a third possible meaning for "molar." This meaning is not adopted as the proper meaning of "molar" in the Fischer patent by any of the parties. Respondents rely upon it only to show that the meaning of the word "molar" is not clear from a reading of the patent. This third meaning will not be adopted here.

If respondents' construction of the word "molar" is used, the Hepatic-Aid product sold by American would not be made under the patent (TR 1412, Travenol Ex. 53), and the Travasorb Hepatic product sold by Travenol would not infringe the patent claims either directly or under the doctrine of equivalents.

Travenol's molar concentration or moles per liter construction of "molar ranges" is based upon the common scientific definition of "molar" as moles per liter. TR 1083, 1435, Travenol Ex. 15. Travenol's reading of molar ranges as meaning moles per liter is consistent with ordinary scientific usage, and using this meaning a product could be made under the Fischer patent. This product, however, cannot be administered to patients in that concentration.

In the "disclosure of invention" given by the inventors to their counsel before the application for the patent was filed, the word "molar" is used. Dr. Yoshimura, testifying about the disclosure of invention, indicated that

the ranges of concentration of the 19 amino acids, stated in moles per liter, (Travenol Ex. 2, p. 6, Table III) were derived arithmetically from the "preferred" F080 formulation (Table II) primarily by using a plus and/or minus 20% range. Travenol points out that Dr. Yoshimura used the term "molar" in the disclosure of invention to refer to concentration, and that many statements in the disclosure were omitted from the patent application. (The patent examiner was not given the disclosure of invention.)

Complainants contend that the word "molar" has a second scientifically accepted definition which should be used here. Under this definition molar quantities are quantities proportional to the molecular weights of the substances concerned. TR 197-204, American Ex. 4. To give the patent meaning, "molar" must be construed as meaning a quantity proportional to molecular weight.

The use of the terms "moles per liter," "concentrations," and "molar" in the patent, however, is sometimes confusing. For example, the table in column 6 (American Ex. 1) refers to concentrations, but uses ranges of moles per liter which are identical to the molar ranges in claim 1. The paragraph above the table indicates that the oral formulation should have "the same amino acids in the same respective molar concentrations or ranges." Claim 10, which is not in issue here, refers to concentrations, yet the numbers are the same as the molar ranges in claim 1. The meanings of the terms are not always clear, but the overall context in which they are used in the specification usually indicates that where a concentration or solution is involved, the solution can be diluted as long as the quantities of amino acids are proportional to the molecular weight

of that amino acid in the original solution. Reading the patent in this way, complainants' definition of molar is consistent with the invention, and a useful product can be made under the patent claims.

The phrase "in proportions defined by" in claim 1 shows that the "molar ranges" are intended to refer to a pattern of amino acids rather than to their degree of concentration in a solution. This concept is stated another way in column 3 of the patent: "Desirable relative internal proportions are defined by the following molar ranges:". If "molar ranges" were read to mean "moles per liter," the discussion of concentration in the specification in columns 5 and 6 and in claim 3 would make no sense.

Two series of numerical values are in the same proportions if there is any factor which when multiplied by all of the values in one series will cause those values to equal the corresponding values in the other series. For example 2:3:4 are in the same proportions as 12:18:24. There is one factor (6) which, when multiplied by each of the values in the first series, causes them to be equal to the values in the second series. While there are other factors that will not cause the values to be equal, that does not change the proportionality. If there is <u>any</u> factor which makes the values equal, then the proportions are the same. This is the "common factor" approach. Using this approach to compare a given amino acid formulation with the patent claims, a factor is selected which brings the greatest possible number of the numerical molar values for each individual amino acid into the claim ranges. American Physical Ex. GG and TR 259-260.

Because there are many possible concentrations for a particular amino acid formulation as claimed in the Fischer patent, it is desirable to describe the amino acid pattern of the product in terms of interrelated molar proportions as opposed to particular concentrations. This was the practice followed in claim 8 of the Ghadimi patent. Claim 8 refers to the weight concentrations of each amino acid. Although claim 8 is dependent on claim 1, the concentrations in claim 8 do not fall within the numerical ranges for amino acids described in claim 1. For the ranges appearing in claim 8 to fall within the ranges of claim 1, a common factor must be applied to the ranges of claim 8. TR 209, 210, American Ex. 5.

Claim 1 teaches that the combined "molar proportions" of the branched chain amino acids (isoleucine, leucine, and valine) should be from 40 to 300 times the "molar proportion" of trytophan, and from 15 to 135 times the combined molar proportions of phenylalanine and tyrosine. Tryptophan, phenylalanine and tyrosine are aromatic amino acids.

The specification of the Fischer patent teaches that the formulation should have the same molar ratios of branched chain amino acids to aromatic amino acids in enteral and parenteral solutions. The oral formulations may include 80 to 100% of the recommended daily allowances of essential minerals and other items such as food flavors which form a palatable liquid drink or a semi-solid food, including an appropriate amount of fats and carbohydrates. It is clear that the amount of water or other nonprotein ingredients was not essential to the invention. The ratio of certain amino acids to certain other amino acids in the product was important to the invention, and the degree of

the dilution was not. "Molar ranges" define the pattern of amino acids, or the ratio of amino acids to one another, and not their concentrations in a solution. TR 208-209, American Ex. 1, col. 6, col. 8.

It is a common practice to define amino acid formulations in terms of their patterns or profiles because, within reasonable limits, it is their pattern which is of physiological importance, rather than their concentrations. For example, Travenol sells its standard amino acid solutions in various concentrations. Travenol's Travasorb products are available in 3.5% solutions, 5.5% solutions, 8.5% solutions and 10% solutions. The amino acid patterns of each of these solutions are identical, although the absolute concentrations of amino acid in these solutions varies. American Ex. 78, pp. 87-88; TR 240.

The molar ranges listed in claims 1 and 14 of the Fischer patent will not be construed as defining concentrations in moles per liter. They specify the proportions of amino acids relative to one another. In claim 14, for example, a solid formulation is defined, indicating that the molar ranges do not necessarily define concentrations in moles per liter.

While claim 1 read by itself is not especially clear, a reading of claim 1 within the context of the whole specification by one with ordinary skill in the art would require complainants' construction of "molar ranges" to give the patent meaning. Any ambiguity in claim 1 should be resolved by construing it to claim the invention rather than some useless product.

The patent discloses the importance of the ratio between branched chain amino acids and aromatic amino acids. It would be clear to one with ordinary skill in the art that the patent claims in issue use "molar ranges" to refer to the relative proportions of certain amino acids, expressed in moles, and not to the degree of concentration of the amino acids in a single formula. The Fischer patent is not invalid under Section 112.

(c) Section 102

Respondents contend that the Fischer patent is invalid for anticipation under Section 102(e) of the Patent Act in view of the Ghadimi patent because the subject matter of the asserted claims is identically disclosed in the Ghadimi patent.

Section 102(e) provides that a person shall be entitled to a patent unless the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for the patent. 35 U.S.C.A. 102(e). This is the novelty requirement of the Patent Act. If an invention is not new, it cannot be patented. Under Section 103, the invention may be new but the subject matter may be so obvious that the invention is not patentable. Thus, an invention must be new and nonobvious to be patentable.

To anticipate a patent claim, a single prior source must contain all the essential elements of the claim in issue, and anticipation cannot be shown by combining more than one piece of prior art. See In re Saunders, 444 F.2d 599, 170 USPQ 213 (CCPA 1971).

The classic test for anticipation is "that which will infringe, if later, will anticipate, if earlier." Knapp v. Morss, 150 U.S. 221 (1893). See D.S. Chisum, Patents, §3.02(1).

Although all the essential elements must be found in a single prior source, the CCPA has held that the knowledge of those skilled in the art can be considered with the single prior source in determining anticipation. In effect other prior art known to those with ordinary skill in the art is also

considered. Under this construction, the CCPA has narrowed the distinction between anticipation under 102(e) and obviousness under Section 103. For example, if someone with ordinary skill in the art knew that equivalent elements could be substituted or that certain elements in the claim in issue were not essential, the asserted claim could be anticipated. As the CCPA stated in In re Donohue, 632 F.2d 123, 207 USPQ 197 at 199 (CCPA 1980):

> For a publication to constitute an anticipation of an invention and, thus, to bar the grant of a patent under 35 U.S.C. 102, it must be capable, when taken in conjunction with the knowledge of those skilled in the art to which it pertains, of placing that invention in the possession of the public.

The standard for anticipation for the CCPA therefore is whether the prior source, read in the context of what one with ordinary skill in the art would have known, already placed the invention asserted in the later patent claim in the possession of the public. The CAFC has stated that it will follow the precedent of the CCPA. South Corp. v. United States, 690 F.2d 1368, 215 USPQ 657 (C.A. Fed. 1982).

The '465 patent to Ghadimi (Travenol Ex. 7 or American Ex. 5) discloses an amino acid formulation for providing nutritional support for adults and children by intravenous administration.

The Ghadimi patent teaches that the processing of amino acids received intravenously is different from that of amino acids resulting from the digestion of proteins in food, and that the patterning of synthetic amino acid solutions after the patterns of normal foods, such as eggs, is inappropriate.

The Ghadimi patent also teaches that branched chain amino acids are not metabolized by the major pathways of the liver. Travenol Ex. 7, TR 255, 469-470.

The Ghadimi patent discloses formulations using all of the 19 amino acids in the Fischer patent. Many of the amino acids in the Ghadimi patent claims are in ranges overlapping the ranges of the same amino acids in the Fischer patent, whether respondents' "molar concentration" theory or complainants' "mole proportions" theory is used to interpret the Fischer claims. The question is whether these overlapping ranges mean that the Fischer patent was "anticipated" by the Ghadimi patent under Section 102, and that the Fischer patent is therefore invalid.

Table I of the Ghadimi patent sets forth general ranges for amino acid formulas. Under complainants' interpretation of the Fischer claims in issue, 16 of the amino acid ranges disclosed in Table I of the Ghadimi patent overlap the ranges of the same 16 of the 19 amino acids listed in claim 1 of the Fischer patent. Both the molar ratio of the branched chain amino acids to tryptophan and the molar ratio of the branched chain amino acids to phenylalanine and tyrosine in Table I of the Ghadimi patent overlap the ratios in claim 1 of the Fischer patent.

The upper part of the ranges in Table I of the Ghadimi patent overlaps the lower ranges of the percentages of branched chain amino acids in the Fischer patent. Table VIII in the Ghadimi patent describes specific formulations rather than ranges. The molar ratios of branched chain amino acids to phenylalanine plus tyrosine in these tables range from 7.6 - 7.9. American Ex. 108-110.

The ratios or molar proportions of branched chain amino acids to the combined molar proportions of phenylalanine and tyrosine in the Ghadimi formulations are described generally in ranges that overlap the ratios specified in the claims of the Fischer patent and extend below those ranges. All of Ghadimi's specific formulations, however, have one or both ratios in the lower limits of these ranges. Travenol Ex. 7, cols. 13-16, 19-20; TR 250.

Claim 1 of the Fischer patent specifies that the ratio of the molar proportion of branched chain amino acids to the combined molar proportions of phenylalanine and tyrosine range from 15 - 135. In the Ghadimi patent this ratio can be as low as 3.78, and in the specific examples of formulas in the Ghadimi patent, it ranges from 4.42 - 9.32. American Exs. 1, 5, and 102-110.

When proteins or amino acid formulations in which the ratio of branched chain amino acids to phenylalanine and tyrosine are in the ranges of Ghadimi's specific formulas are given to patients with severe liver disease, they have a tendency to cause or to exacerbate hepatic encephalopathy. For example, this ratio for cow's milk and hen's eggs is 3, and for beef muscle it is 4. For protein hydrolyzates, the ratio is 5. This ratio in conventional amino acid solutions is also within the ranges of the Ghadimi patent. For example, Travenol's FreAmine products have a ratio of 5. The FreAmine products do not cause improvement in patients with severe liver disease. See Travenol Ex. 26. Other enteral amino acid formulations for nutrition also have ratios in the ranges described by the lower limits of the Ghadimi specific formulas. For

example, American McGraw's Traum-Aid product has a ratio of 6. Travenol Ex. 7, American Exhibits 94, 99-101, 119, p.41, and 78, pp. 368-369.

The Ghadimi patent is directed at giving parenteral nutrition to adults and children. Although it is not directed specifically to patients with liver disease, it does not exclude such patients from its scope. Ghadimi did not recognize that certain products falling within the upper ranges of his formulations, showing high ratios of branched chain amino acids, might have a special beneficial effect on patients with severe liver disease. If he had recognized this, he would have distinguished between products in the upper ranges and products in the lower ranges of his patent. The Fischer patent discloses a new use for products similar to (but not identical to) some of the products covered by the Ghadimi patent ranges.

Some patients with severe liver disease may need parenteral nutrition, but products in the lower ranges of the Ghadimi patent could precipitate or exacerbate hepatic encephalopathy in these patients. This was not recognized by Ghadimi or taught in the Ghadimi patent.

Anticipation is not necessarily avoided by the discovery of a new use for, or property of, an old product. See Mandel Bros. v. Wallace, 335 U.S. 291 (1948); D.S. Chisum, Patents, §3.02(3) and §1.03(8). If the product made under the Ghadimi patent were identical to the product made under the Fischer patent, the new use for the product which was not recognized by Ghadimi (benefitting patients with severe liver disease by not causing or aggravating hepatic encephalopathy) might not have saved the Fischer patent claims from anticipation.

The Fischer claims and Ghadimi claims do not overlap, however, with respect to three amino acids in the products which otherwise are covered by both patents.

Although other courts in the past have required a strict standard of identity of the prior art and the patent claim to support anticipation, the CCPA allows a single piece of prior art to be considered together with the knowledge of those skilled in the art, with the effect that prior art known to those skilled in the art is indirectly considered under anticipation. Additional references may be relied on to show that the claimed subject matter, every material element of which is disclosed in the primary reference, was in possession of the public. The standard of anticipation is whether the invention has been "placed in the possession of the public" by the prior art. In re Donohue, 632 F.2d 123, 207 USPQ 196 (CCPA 1980), and In re Samour, 571 F.2d 559, 197 USPQ 1, (CCPA 1978).

There is no evidence in the record to show that one with ordinary skill in the art at the time of the Fischer patent invention would have known that the three amino acids that were not in overlapping ranges in both patents were immaterial or not essential as far as patients with severe liver disease were concerned.

Even if the Ghadimi patent had disclosed the significance of a high proportion of branched chain amino acids to aromatic amino acids for patients with severe liver disease, the Fischer patent does not make it clear to the reader that what complainants describe as the "heart of the Fischer invention" (the high ratio of branched chain amino acids to the low ratio of aromatic

amino acids) is the only significant or essential part of the Fischer patent claims. This would not have been known by one with ordinary skill in the art at the time of the Fischer patent invention or the Ghadimi patent invention. While the importance of the branched chain amino acid/aromatic amino acid ratio is stressed in the Fischer specification and the claims, there is no indication in the rather complex claims of the Fischer patent that the relationships among the other amino acids in the formula are unimportant.

The Ghadimi patent ranges do not anticipate the Fischer patent ranges because three of the nineteen amino acids are not found in the overlapping ranges, and one with ordinary skill in the art would not have known whether these three amino acids were essential or had to be in a particular relationship to other amino acids to have a beneficial effect.

Even if the three amino acids outside the overlapping ranges in the two patents were considered to be insignificant or unessential by those with ordinary skill in the art, those with skill in the art still would not have understood the critical significance of using the upper range rather than the lower range of the ratios of branched chain amino acids in Ghadimi's claim ranges for patients with severe liver disease, unless they were aware of the Fischer patent invention. See p. 47-48 below. Although a new use for a product will not avoid anticipation, a person reading the Ghadimi patent alone would not know that only products in the upper ranges shown in the Ghadimi patent had this new use.

The Ghadimi patent therefore did not place the invention of the Fischer patent in the possession of the public, and the Fischer patent is not invalid as anticipated by Ghadimi under Section 102.

(d) Section 103

Section 103 of the Patent Act (35 U.S.C.A. 103) states:

> A patent may not be obtained though the invention is not indentically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

In Graham v. John Deere Company, 383 U.S. 1, 17 (1966) the Supreme Court set forth the steps which are necessary to determine whether a patent is invalid under Section 103. The scope and content of the prior art must be determined, differences between the claims in issue and the prior art are to be ascertained, and the level of ordinary skill in the pertinent art resolved. A determination then must be made as to whether the differences between the claims in issue and the prior art would have been obvious to a hypothetical person with ordinary skill in the pertinent art at the time the invention was made.

The hypothetical person with ordinary skill in the art at the time of the alleged invention would be deemed to have been aware of the prior art in this field of study published in the United States. The level of skill of such a person was extremely high. See p. 4, supra.

The parties have stipulated that the most pertinent prior art is the 1974 Fischer article and the Ghadimi patent. Both the Fischer article and the Ghadimi patent contained new ideas, contrasting with conventional teaching at that time. Conventional teaching in the early 1970's was that excess

ammonia caused hepatic encephalopathy, and that the appropriate treatment of severe liver disease in cirrhotic patients was to restrict protein as one way to restrict the production of ammonia in the intestines. Although this could result in malnutrition, in many cases patients regained liver function after protein was restricted for a short time, and were then able to tolerate protein, so that severe malnutrition over a long period of time would not occur. In cases where hepatic encephalopathy lasted a long time, malnutrition was a serious problem, but the alternative of giving adequate protein could cause death.

The response of patients with severe liver disease to parenteral and enteral amino acid formulations was not predictable in the early 1970's. TR 422-423, 425-426, 772, 789, Travenol Ex. 26.

The experimental evidence developed by the inventors named in the Fischer patent in the early 1970's and on which the Fischer patent invention is based showed that administration of amino acids in certain patterns could provide protein nutrition to dogs with simulated severe liver disease without precipitating or exacerbating hepatic encephalopathy. American Ex. 123, TR 782.

Reports describing abnormal plasma amino acid patterns in liver diseased patients had appeared in the literature prior to that time. The significance of low plasma levels of branched chain amino acids and elevated plasma levels of aromatic amino acids in liver diseased patients had been recognized in the 1974 Fischer prior art article. American Ex. 119, p. 1, TR 422.

The liver is one of the body organs that can regenerate. If a patient can be maintained over a sufficient period of time with adequate nutrition, in many cases the liver will repair itself. American Ex. 1, col. 3. The fact that in many instances the liver could repair itself was known in the prior art, but how to keep the patient with severe liver disease alive long enough for this to occur was not known.

The conventional treatments for complex liver disease or severe liver damage in the early 1970's were restricting protein, and/or the administration of poorly absorbable antibiotics to destroy ammonia-producing bacteria in the intestines, (TR 391-392), and/or giving lactulose, which provided some nutrition without producing much ammonia. TR 392-393. While these conventional treatments did not aggravate hepatic encephalopathy, they did not provide adequate nutrition.

"Normalization" of amino acid levels in the plasma by diet has been used successfully where individual enzyme deficiencies were found in an otherwise healthy liver. In these patients, protein in the diet was not threatening to the health of the patient. The problem was to provide the specific proteins which were lacking due to liver enzyme deficiency.

Dr. Fischer's 1974 prior art article suggested the theory of normalization of amino acids levels in the plasma of patients with severe liver disease and a tendency to hepatic encephalopathy, but it was not conventional at that time, and it had not been tried on patients, except to the extent that FreAmine and FreAmine E, which added some branched chain amino acids along with other amino acids to the diet of patients with severe liver disease, had been tried unsuccessfully. Travenol Ex. 27.

Prior to 1974, it was known that the amino acid patterns in the plasma of patients with diseased livers were abnormal. In diseases involving the lack of an enzyme in the liver, causing one or more amino acids to be out of balance, "normalization" of the amino acid patterns in the plasma was achieved by increasing the amount of the amino acids in the diet that were low in the amino acid pattern in the plasma, and decreasing the amount of amino acids in the diet that were high in the amino acid pattern in the plasma. These patients had normal functioning livers except for the single enzyme deficiency.

The 1974 Fischer article suggested that since patients with encephalopathy had a low ratio of branched chain amino acids to other amino acids, compared with the ratio in normal plasma, it would be a good idea to try to raise the level of branched chain amino acids to other amino acids in the plasma, to normalize the amino acid ratio, by giving the patient (either orally or directly into the plasma) a formula high in branched chain amino acids. Fischer clearly suggested in his 1974 article the general idea which was later patented in the Fischer patent, and the general outline of the experiments that he and the other inventors were about to make which resulted in the Fischer patent application.

The 1974 article did not disclose the exact formula which would be tried. That formula was developed by Dr. Yoshimura and Dr. Fischer shortly after the report that later became the Fischer 1974 article was first presented in May, 1973. Even when the exact formula was decided upon, no one could predict whether the high ratio of branched chain to aromatic amino acids would survive in the plasma of patients with severe liver disease, as the blood circulated repeatedly through a partially functioning liver. The Fischer article suggested that

someone should try to give patients with severe liver disease amino acids with a high ratio of branched chain amino acids to aromatic amino acids. What was not known was what a partially functioning or injured liver would do to the levels of amino acids circulating through the liver at frequent intervals. Would certain amino acids be absorbed into other organs deprived of their normal nutrient sources? Would the malfunctioning liver continue to manufacture excessive aromatic amino acids, regardless of what was added to the plasma? Was the lawn-mower effect of the healthy liver so damaged that the normalizing effect of adding needed amino acids to the plasma would last only until the blood circulated through the liver again? Could a normal pattern of amino acids in the plasma be maintained for more than an hour or two? The fact that normalization had worked with an otherwise healthy liver with an enzyme deficiency did not mean that giving the patient a compensating pattern of amino acids would normalize the abnormal pattern of amino acids in the plasma of a patient with a severely diseased liver. Raising the amount of branched chain amino acids given to patients with severe liver disease by administering FreAmine and FreAmine E had resulted in lower levels of branched chain amino acids in the plasma as compared to the plasma levels of fasting patients. Travenol Ex. 26.

It was not known whether normalization of the levels of amino acids in the plasma would benefit patients with hepatic encephalopathy. When a patient has an infection, an abnormally high level of white blood cells is desirable to fight the infection even though it does not reflect the normal blood pattern of a healthy person. There was a suspicion but no proof that an abnormal plasma amino acid pattern in a person with hepatic encephalopathy was harmful.

To anyone with ordinary skill in the art, the 1974 Fischer article made it obvious to try a formula with a high ratio of branched chain amino acids to aromatic amino acids. The CCPA, however, has held repeatedly that a chemical formulation is not necessarily obvious under Section 103 merely because it was "obvious to try" the formulation. See In re Pantzer, 341 F.2d 121, 144 USPQ 415 (CCPA 1965). Whether an invention is nonobvious under Section 103 depends upon the standards set out in Graham v. Deere.

Respondents argue that the independent development of similar formulas by Dr. Fischer and Dr. Yoshimura shows the obviousness of the F080 formulation. Shanklin Corp. v. Springfield Photo Mount Co., 521 F.2d 609, 187 USPQ 129 (1st Cir. 1975), cert. denied, 424 U.S. 914. Similar formulas were developed, however, only because both Dr. Fischer and Dr. Yoshimura wanted to try a high ratio of branched chain amino acids to aromatic amino acids in connection with hepatic encephalopathy. This idea was not obvious to others at that time, and the formula agreed upon was untried and speculative as to its effects upon patients with hepatic encephalopathy.

Travenol also argues that the Fischer claims were obvious because the patent formula reflects only the calculations which would have resulted from known normalization techniques which could have been followed by anyone using the information on abnormal plasma amino acid levels found in the Fischer 1974 article. Amino acid normalization techniques had not been tried with patients with encephalopathy, however, and this is not surprising because at that time many patients with incipient encephalopathy got worse when they were given protein, protein was known to create ammonia, and ammonia was thought to

aggravate encephalopathy. Efforts were being made to reduce the ammonia generated by certain types of proteins, but the concept that more branched chain amino acids might have a beneficial effect on encephalopathy was Dr. Fischer's idea, and it was extremely controversial. When the F080 formula was tried on dogs, the results were surprising even to the inventors. TR 775-776. The results were contrary to the expectations of Travenol's director. American Ex. 27. The problem of severe liver disease was complex, involving 600 enzyme systems, unlike single enzyme deficiency diseases (TR 415, American Ex. 78, p. 420-421), and the solution of the Fischer patent invention was unpredictable and surprising. TR 772, 775-776, 171-172.

In September 1972, Dr. Law made an oral presentation in Mexico City. This oral presentation did not constitute prior art under Section 102. At the time of his oral presentation, no written version had been prepared. Dr. Law sent one copy of a later written version to a representative of McGaw Laboratories. A written summary of the oral presentation was distributed, but it disclosed nothing about raising the ratio of branched chain amino acids to aromatic amino acids.

Even if Dr. Law's presentation had been prior art, he outlined what was already known and suggested areas for additional experiments. Dr. Law testified that his Mexico City presentation was less pertinent than the Fischer article to the Fischer patent. Dr. Law was interested in a nutritional approach, while Dr. Fischer was primarily interested in a formula that would prevent or treat hepatic encephalopathy by reducing the number of false neurotransmitters in the brain.

Although the 1972 presentation by Dr. Law is not prior art to the invention of the Fischer patent, it was information known to the inventors before the patent application was filed. It did not disclose the Fischer patent invention.

The Fischer 1974 article itself disclosed the concept of the high ratio of branched chain amino acids to aromatic amino acids, but it did not disclose a specific formula, or prove that the formula worked. There was enough mystery about how a severely diseased or damaged liver functioned so that it was not clear that the concept would work. The Fischer patent is not invalid as obvious based on the disclosures in the 1974 Fischer article.

The Ghadimi patent claimed amino acid formulations within ranges which overlapped the ranges of the Fischer patent. Where the products were in overlapping ranges, the Ghadimi formulations would have the same effect on liver-diseased patients as the Fischer formulations. Other formulations covered by the lower ranges of the Ghadimi patent could have made patients with severe liver disease worse rather than better, however, and the Ghadimi patent did not teach this distinction.

Where the prior art claims ranges of ingredients which overlap the ranges of the same ingredients in the patent in issue, the claims in the second patent are prima facie obvious under Section 103 unless there is evidence of criticality of the claimed ranges as opposed to the overlapping prior art ranges. In re Malagari, 499 F.2d 1297, 182 USPQ 549 (CCPA 1974), Application of Clinton, 527 F.2d 1226, 1228-29, 188 USPQ 365 (CCPA 1976), and

Application of Hoeschele, 406 F.2d 1403, 1406, 160 USPQ 809 (CCPA 1969). The criticality of the claimed ranges can be shown by showing unexpected properties in the ranges claimed in the second patent.

In In re Aller, Lacey and Hall, 220 F.2d 454, 105 USPQ 233 (CCPA 1955), it was held that the optimization of a condition by routine experimentation was not patentable, but where a critical range gives an improved result, the discovery of the range is patentable. The critical range is described as a previously unrecognized result-effective variable. In re Yates 663 F.2d 1054, 211 USPQ 1149 (CCPA 1981).

Respondents cite cases such as U.S. Industries, Inc. v. Norton Co., 210 USPQ 94 (N.D.N.Y. 1980) to support their position that the Fischer patent claim ranges were not critical. In the cases cited by respondents, however, the ranges claimed to be critical were already known to produce better results in the prior art. Carter-Wallace, Inc. v. Gillette Co., 675 F.2d 10, 214 USPQ 497 (1st Cir. 1982) is not in point.

Respondents also contend that the patentee must claim the exact range within which the improved results occur. In In re Waymouth and Koury, 499 F.2d 1273, 182 USPQ 290 (CCPA 1974), the CCPA held that a claimed range was critical even though a device might operate over a different range from that claimed. The court noted that there was a difference in kind rather than in degree. The failure of the Fischer patent to establish the precise point at which the higher ratio of branched chain amino acids will benefit patients with severe liver disease will not invalidate the patent claims. The research necessary to find this point would be endless. See In re Sarett, 327 F.2d 1005, 140 USPQ 474 (CCPA 1964).

The claimed ranges in the Fischer patent are different in kind from the Ghadimi ranges, and are not just different in degree.

Criticality can be shown here. Formulations falling within the lower ranges of the Fischer patent (like FreAmine and FreAmine E) can exacerbate hepatic encephalopathy. Formulations falling within the Fischer patent claim ranges (overlapping the upper Ghadimi ranges) are surprisingly beneficial in the treatment of hepatic encephalopathy, and this was an unexpected property not disclosed in the Ghadimi patent.

The Ghadimi patent mentions "liver disease" in column 7, line 40, where it is noted that in mild parenchymal liver disease, the first abnormal finding is often increased blood tyrosine. The context of this reference to liver disease is to show the metabolic pathway for tyrosine. TR 1571-1574, American Ex. 5. It did not teach that only products with branched chain amino acids in the higher ranges of the Ghadimi patent would be helpful to patients with severe liver disease.

The Ghadimi patent discloses some formulations having a high ratio of branched chain amino acids to aromatic amino acids, and others that do not. Ghadimi did not teach the critical importance of this high branched chain amino acids ratio, for patients with severe liver disease. Ghadimi's formulations cover ranges that are also covered by the ranges in the Fischer patent, but Ghadimi does not teach the same invention.

There are significant differences between the prior art and the claims in issue, and these differences would not have been obvious to a hypothetical person with ordinary skill in the art in the early 1970's. The Fischer patent is not invalid as obvious under Section 103 in view of the Ghadimi patent.

Secondary Consideration Under Section 103

In Graham v. John Deere, (383 U.S. 1, at 17) the Supreme Court also indicated that secondary considerations might be important in determining nonobviousness under Section 103:

> Such secondary considerations as commerical success, long felt but unsolved needs, failure of others, etc., might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented. As indicia of obvious or nonobviousness, these inquiries may have relevancy.

The ideas set forth by Dr. Fischer were not widely accepted in the scientific community in the 1970's. (American Ex. 119; TR 134, 426-427, 764; American Ex. 80, p. 75). In the late 1970's and early 1980's, Travenol's own medical director, Dr. Robert Ausman, stated that he did not believe there was any reason for assuming that the normalization of plasma amino acid levels would have any effect on hepatic encephalopathy, and he questioned the safety of employing solutions designed to make that correction. (American Ex. 27, p. 2).

Yet as soon as the Fischer patent formulation become available on the market it was successful, and Travenol immediately began to consider developing a product to fill the same needs.

The Fischer patent formulation was a commercial success, and it filled a previously unsolved need, that of providing adequate nutrition to patients suffering from various degrees of hepatic encephalopathy. Sometimes it brought a patient out of hepatic coma. This does not necessarily mean that the patent

was nonobvious. It is unlikely that the formulation was obvious but that no one chose to develop it because of the expense involved, because as soon as McGaw began to sell the product, Travenol sought to produce a competitive product. The courts have held that commercial success is an indication of nonobviousness under Section 103 where the question is close.

3. Infringement of the Fischer Patent

American contends that "Travasorb Hepatic," the product made by Travenol, infringes claims 1, 5, 6, 7, 9, 14 of the Fischer patent by application of the doctrine of equivalents. American does not charge literal infringement of any claims. TR 906-07. Even though some of the amino acids in Travasorb Hepatic are outside the claimed ranges in the Fischer patent claims, American argues that they are outside the Fischer patent ranges only by "insignificant amounts."

The doctrine of equivalents is set forth in Graver Tank & Mfg. Co. v. Linde Air Products Co., 339 U.S. 605, 85 USPQ 328, 330-332 (1950). In that case the Supreme Court recognized that to permit imitation of a patented invention which does not copy every literal detail would be "to convert the protection of the patent grant into a hollow and useless thing." The "doctrine of equivalents" was created to provide greater protection for the patent. From the beginning it was recognized that this doctrine would be inconsistent with the patent law principle that the claim is the measure of the patent protection. When one applies the doctrine of equivalents, protection is given beyond literal infringement of the claim.

Two justices dissented to the Graver Tank decision, arguing that the doctrine of equivalents violated the principle that the claim is the measure of the patent grant. Nevertheless, under the majority opinion infringement can be found if the allegedly infringing patent performs substantially the same function in substantially the same way to obtain substantially the same results.

Under the doctrine of equivalents, consideration must be given to the purpose for which an ingredient is used, the qualities it has when combined with the other ingredients, and the function which it is intended to perform. "An important factor is whether persons reasonably skilled in the art would have known of the interchangeability of an ingredient not contained in the patent with one that was." 339 U.S. 605, 85 USPQ at 331.

The Supreme Court in Graver Tank stated that a finding of equivalence is a determination of fact. Like any other issue of fact, final determination requires a "balancing of credibility, persuasiveness and weight of evidence."

The degree to which the doctrine of equivalents will be used to expand the scope of the claim beyond the literal terms of the claims depends to a certain extent upon the degree of invention (a patent on a pioneer invention is entitled to a broader construction than a patent on a narrow improvement in a crowded field), and upon the scope of the invention as described in the specification rather than as described in a claim that is more narrowly drawn than the specification. Continental Paper Bag Co. v. Eastern Paper Bag Co., 210 U.S. 405 (1908).

In this case the idea of normalizing the plasma of patients with liver enzyme deficiencies was known in the prior art. Dr. Tucker testified that he raised the amount of amino acids in the food of patients with liver enzyme deficiencies when the level of those amino acids in the plasma was low, and vice versa. The Fischer 1974 article disclosed the same concept with respect to patients with severe liver disease. At the time of the patent application, however, the conventional teaching was that it could be harmful to a patient

with severe liver disease (other than enzyme deficiency) to give him protein. Dr. Fischer and Dr. Yoshimura were willing to try a theory which had been used in patients with liver enzyme deficiency but which was considered dangerous for patients with damaged livers or cirrhosis. The speculative theory that the high ratio of branched chain amino acids to aromatic amino acids might be beneficial to these patients was known but had not been tested. When tested, Dr. Fischer and Dr. Yoshimura found that the ratio was beneficial to patients with hepatic encephalopathy. It does not matter whether Dr. Fischer's theory of why this ratio worked is correct. The ratio did work, and it was a major breakthrough to use it in connection with patients with severe liver disease, rather than only an enzyme deficiency.

The Fischer patent was not a "pioneer" patent because the ideas were known in the prior art and had been used in the closely related field of liver enzyme deficiency. It was, however, more than a minor improvement in a crowded field, and it is entitled to a relatively broad range of equivalents. Although the argument was made that enzyme deficiency is also a liver disease, the effect of the lack of a single enzyme in the liver is to make the synthesis of certain amino acids impossible. The liver is otherwise healthy. Injury to or disease of the liver can be much more complicated, and the consequences of changing the amino acids pattern in the food or in the plasma of a patient are much less predictable if it is not known how much liver function is left or in what manner the injured or diseased liver will function.

Under the doctrine of equivalents, the question is whether Travasorb Hepatic uses substantially the same means to achieve substantially the same results in substantially the same way as the asserted claims in the Fischer patent.

The amino acid ingredients of the Travasorb Hepatic product are shown on the product packet. American Ex. 111, Travenol Ex. 18 and stipulation. Each packet of Travasorb Hepatic product is mixed with 270 ml. of water in a blender and the resulting solution has a volume of about 350 ml. Travenol Ex. 50; TR 1434. As reconstituted, the amino acids present in the powder have the concentrations shown in column 6 of Travenol's comparison chart, Travenol Ex. 50. TR 1433-34.

Using Travenol's "mole concentration" theory, Travasorb Hepatic is almost completely outside of the molar ranges in claim 1. Under this theory it would be impossible to find infringement under the doctrine of equivalents. As shown in Travenol Ex. 50, after Travasorb Hepatic is mixed in accordance with the directions, 12 of the 14 amino acids are present in Travasorb Hepatic in concentrations lower than those claimed in claim 1 of the Fischer patent, and one amino acid listed in claim 1 (serine) is not found in Travasorb Hepatic. Travenol Ex. 50, TR 1434-35. If Travenol's construction of "molar ranges" is used, there is no literal infringement nor infringement under the doctrine of equivalents.

Under American's "molar ratio" theory, using a common factor or multiplier of 6, five of the fourteen amino acids in Travasorb Hepatic are outside the defined molar ranges in claim 1. Serine is not present in Travasorb Hepatic, and the amounts of threonine, alanine, proline, and glycine in Travasorb Hepatic are outside the molar ranges in the patent claims. Travenol Ex. 18 or American Ex. 111; TR 264-65.

Threonine is classified by Dr. Rose as an essential amino acid. See p. 4 supra. Serine, alanine, proline and glycine are classified by Rose as non-essential amino acids. The classification of the amino acids as essential means that they are essential to human nutrition, and does not determine whether any of these amino acids plays a significant role in hepatic encephalopathy. Later research has shown that threonine may not be a necessary amino acid in a solution for patients with severe liver disease because the diseased liver may be able to metabolize threonine even though it is not processing other amino acids. TR 842-843. This was not known at the time of the Fischer patent invention.

Travenol contends that because American has already built in a plus or minus 20% factor (with a few variations) for all 19 of the claimed amino acids, it already has an equivalency range built into the claims, and that further extension of the asserted claims to cover amino acid levels outside the claimed ranges would result in a doubling of the range of the equivalency. Dr. Yoshimura, however, testified that the variances in the ranges reflected manufacturing variations, limitations on measuring accuracy, and his prior experience with FreAmine E. Travenol Ex. 61. This had nothing to do with the doctrine of equivalents. Dr. Fischer testified that the ranges also gave them some leeway because they were not sure that the precise F080 formula used on dogs would work equally well on people. TR 828. It was Dr. Yoshimura, however, who put in the ranges. Complainants would not be limited under the doctrine of equivalents to the ranges stated in claim 1 because the 20% range factor was intended to cover variations resulting from an attempt to reproduce F080 as closely as possible. The test for the doctrine of equivalents relates

to whether substantially the same ingredients achieve substantially the same results in substantially the same way, whether those with ordinary skill in the art would recognize certain ingredients as the equivalents of one another, and whether certain ingredients are not an essential part of the claimed invention.

Dr. Fischer testified that at the time of the invention he was not sure what role threonine played in connection with encephalopathy. TR 842-843. In view of this, those with ordinary skill in the art at the time of the Fischer patent invention would not have known what ingredient would be "equivalent" to threonine under the doctrine of equivalents, nor would one with ordinary skill in the art at that time have known whether threonine was an essential element of the formulation with respect to its effect upon hepatic encephalopathy or nutrition.

Dr. Fischer testified that the effect of amino acid solutions was not really known until they were tried. One amino acid might be increased to such a high level that no protein synthesis would occur. TR 835-836. One going outside the ranges given in the Fischer patent claims would be taking a risk as to how the formula would work. TR 828-846.

The record shows that Travenol developed Travasorb Hepatic with the express intention of competing with American's Hepatic Aid, and filling the same need. American Exs. 3 and 85 at 64, 65. Moreover, Travasorb Hepatic is advertised as having the same medical benefits or results as Hepatic-Aid (which is covered by claim 1), and the Travasorb Hepatic brochure cites Dr. Fischer's work as showing the benefits of Travasorb Hepatic.

Dr. Tucker testified that the application of the factor of 6 to Travasorb Hepatic would produce an unworkable, medically unsound product which could not be given to a patient because of multiple defects in fat separation, undissolved crystals, and high osmolarity. TR 1370-73. The multiplier of 6 is a factor which shows the maximum number of the 14 amino acids listed in claim 1 which are also found in Travasorb Hepatic and which are within the molar ranges of claim 1, using American's molar ratio theory. Under American's theory, however, the factor of 6 is used only to show that nine of the amino acids in Travasorb Hepatic are in ratios covered by claim 1. It is not a description of the actual product to be given to the patient. See American Ex. 1, column 5.

Dr. Tucker, with the assistance of Dr. David Madsen, designed Travasorb Hepatic. TR 1345-47. They used an extremely high ratio of branched chain amino acids to aromatic amino acids. They examined the literature to identify other possible contributing causes of complications due to liver disease, and as a result they reduced the level of methionine to a minimum. TR 1348. They reduced the levels of aromatic amino acids to their minimums, and reduced the amounts of ammoniagenic amino acids to their minimums. TR 1348-51. They eliminated the highly ammoniagenic amino acid serine and reduced the highly ammoniagenic amino acid glycine. TR 1350-51. They reduced histidine and tryptophan. TR 1351. Travasorb Hepatic had an ammonia generating factor of only 0.3. TR 1354-55. Travasorb Hepatic also has a low osmolarity, an easily tolerated fat source of medium chain tryglycerides, and vitamins, minerals, and electrolytes. TR 1356-67.

The Travenol product uses more branched chain amino acids and less ammoniagenic acids than the product defined in claim 1. Travenol argues that this higher ratio of branched chain amino acids (50% branched chain amino acid) produces an optimum rate of protein synthesis in the liver (thereby regenerating damaged liver tissue at optimal rates), avoids toxic loads on the liver and the bloodstream from free ammonia, and achieves different results by supplying sufficient amounts of branched chain amino acids to liver diseased patients to minimize or avoid the otherwise endogenous protein breakdown in their skeletal muscle and to minimize internal generation of ammonia, and of sulfur containing an ammoniagenic amino acid. Nevertheless, the literature inserted in the boxes of Travasorb Hepatic relies upon the publication of Dr. Fischer. TR 810; 813-814. Whether Travasorb Hepatic works better than the products made under the Fischer patent is not established by this record.

Travenol copied the high ratio of branched chain amino acids to aromatic amino acids from the Fischer patent, but it changed the rest of the product significantly.

Dr. Tucker estimated development costs for the Travasorb Hepatic product at half a million dollars (TR 1357-58), including costs for developing intravenous fluids for stress patients, but many patients with stress do not have liver disease (TR 1389-91), so that the costs were not all attributable to the development of the product in issue.

Travasorb Hepatic uses a formulation that differs from the ranges set forth in claim 1, and serine is not included at all. Claim 1 sets forth 19 amino acids and tells the reader to keep the amino acid ratios within the

claimed ranges. If the reader does so, the ratio of branched chain amino acids to aromatic amino acids will be high, but other relationships among the amino acids listed will also be fixed. The minimum ratio of certain branched chain amino acids to certain aromatic amino acids is spelled out by one of the requirements below the "molar range" chart, but this is not the only restriction in claim 1.

Travasorb Hepatic does not infringe the Fischer patent under the doctrine of equivalents because it does not use substantially the same means to achieve substantially the same results in substantially the same way as claimed in the Fischer patent. The same results claimed in the Fischer patent are achieved by Travasorb Hepatic, i.e., giving adequate nutrition to patients with severe liver disease who cannot tolerate the pattern of amino acids found in normal proteins without causing or aggravating hepatic encephalopathy.

Travasorb Hepatic may be an improvement over the Fischer patent invention, although this is not established by this record. In any event an improvement over a patented invention does not save a product from infringing the patent. Temco Electric Motor Co. v. Apco Mfg. Co., 275 U.S. 319 (1928).

The difficulty in finding infringement lies in the fact that claim 1 of the Fischer patent teaches not only that there should be a high ratio of branched chain amino acids to aromatic amino acids, but also that the ratios of all 19 of the amino acids to one another must be maintained within the ranges indicated in claim 1, or under the doctrine of equivalents, the product must use substantially the same means to achieve substantially the

same results in substantially the same way. It is not clear from the patent specification why these ratios (other than the branched chain to aromatic) should be maintained. The claim now appears to be more restrictive than it had to be, but this was not known at the time of the invention. TR 812-846. If the claims were more restrictive than they had to be, no explanation was made as to why a broader claim was not included in the patent application. At the time of the invention the inventors were entering an unknown area of research, they had a specific formula which worked, and they were not sure why it worked, although they theorized that it was the ratio of branched chain amino acids to aromatic amino acids that was the effective part of the formulation. All the restrictions in claim 1 other than the branched chain to aromatic amino acid ratio cannot be dropped merely by invoking the doctrine of equivalents, because at the time of the patent application it was known that the formula worked on dogs with hepatic encephalopathy, but not why. Claim 1 teaches that the relationships among the amino acids set forth in the chart is important, and that the ratio of branched chain amino acids to aromatic amino acids is important. The invention of the Fischer patent cannot be expanded as new information becomes available, and it is learned which ingredients and ratios in the formulation are important and which are not. Travasorb Hepatic would infringe claim 1 under the doctrine of equivalents only with respect to the ratio of branched chain amino acids to aromatic amino acids. It does not infringe claim 1 under the doctrine of equivalents with respect to the other amino acids listed in claim 1.

Travenol submitted extensive evidence indicating that the percentages of some amino acids intentionally were raised and others lowered in their product in order to change both the manner in which the Travasorb Hepatic worked and

the results obtained. Many of amino acids whose proportions were changed in Travasorb Hepatic are important amino acids in their effects upon ammonia. There is still a major theory that ammonia is a cause of encephalopathy. The changed proportions of these amino acids cannot be considered to be the equivalents of the proportions for these ingredients in claim 1, nor can the ingredients be disregarded as unimportant with respect to encephalopathy.

Travenol was entitled to try to make a product that would not infringe the Fischer patent. There is nothing reprehensible about trying to invent a better product which does not infringe another's patent, but achieves the same general results or perhaps improved results.

The sole question here is whether the Fischer patent can be read under the doctrine of equivalents as covering any amino acid product administered to patients with severe liver disease which has a high ratio of branched chain amino acids to aromatic amino acids.

Dr. Fischer testified that he thought that the ratio between the branched chain amino acids and the aromatic amino acids was the whole invention, TR 833, but a far more restricted claim was written, which required 19 amino acids to be within certain molar ranges. Dr. Fischer noted that no one was sure the F080 formula would work, TR 828, and he was not certain at that time which ingredients were important to its success. TR 833.

It is not clear whether the patent examiner would have found the broader claim suggested by Dr. Fischer as the invention to be patentable over the prior art. Such a claim relating to liver diseased patients with encephalopathy or incipient encephalopathy might have been patentable if it had

been included in any specific formula which had been reduced to practice. The concept alone, however, had been disclosed in the prior art, and could not be patented by itself because it would have been obvious under Section 103. Dr. Fischer himself had disclosed this concept in the 1974 Fischer prior art article. Without incorporation into a specific formula, it was only an untried and speculative theory which was known in the prior art.

The doctrine of equivalents cannot expand the scope of claim 1 to such an extent that it would make patentable a claim which would not have been patentable if presented in that form to the PTO in 1975. The Fischer invention needed a specific formula to be patentable.

The doctrine of equivalents cannot be used to expand a patent claim so far that it covers something that was already in the public domain in the prior art. The theory of Dr. Fischer's "heart of the invention" had been disclosed in the prior art.

The F080 formula could have been the basis for claim 1 and a broader claim, including any amino acid formula with the high ratio of branched chain amino acids to aromatic amino acids. Such a claim might have been patentable.

This broad construction cannot be given the existing claims because it would be inconsistent with the specification where it is stated that "in the special oral amino acid diets for use in liver disease therapy, the pattern of amino acids is of critical importance." This implies that the whole pattern is critical, not just the branched chain/aromatic amino acids pattern. American Ex. 1, column 9.

The doctrine of equivalents has not eliminated the patent law doctrine that one purpose of a patent claim is to notify the public as to what constitutes infringement, so that they can design around the patent. See D.S. Chisum, Patents, Section 8.03[3]. The Supreme Court stated in United Carbon Co. v. Binney Co., 317 U.S. 228 (1942):

> The statutory requirement of particularity and distinctness, in claims is met only when they clearly distinguish what is claimed from what went before the art and clearly circumscribe what is foreclosed from further enterprise. A zone of uncertainty which enterprise and experimentation may enter only at the risk of infringement... would discourage invention only a little less than unequivocal foreclosure in the field.

Complainants acquired a patent for a specific formulation with a number of amino acids in specific relationships to one another. It would be unfair now to allow them to claim through the doctrine of equivalents a broader invention than the one they sought and were granted without contest. Aro Mfg. Co. v. Convertible Top Replacement Co., 365 U.S. 336 (1969). It would have been simple to include the broader claim in the patent application and have the PTO rule upon its validity.

Travasorb Hepatic does not infringe claim 1 of the Fischer patent under the doctrine of equivalents.

The other claims asserted in the Fischer patent also are not infringed for the reasons stated above with respect to claim 1.

4. Enforceability

Equitable defenses are permitted in Section 337 cases under 19 U.S.C. 1337(c). The defense of unenforceability in a patent case is an equitable defense because of the public interest in permitting full and free competition in the use of ideas which are a part of the public domain. See Lear, Inc. v. Adkins, 395 U.S. 653, 670 (1969).

Assuming that the Fischer patent is valid and has been infringed, respondents contend that the Fischer patent is unenforceable due to inequitable conduct of the patentees before the Patent and Trademark Office (PTO). Inequitable conduct which falls short of fraud can be a defense to a charge of patent infringement. See E.I. DuPont de Nemours & Co. v. Berkley & Co., 620 F.2d 1247, 1256, 205 USPQ 1 (8th Cir. 1980).

The courts speak of a high standard of honesty, good faith and candor owed by a patent applicant to the PTO concerning patent applications because of the ex parte nature of the proceedings. A breach of this duty may constitute inequitable conduct. The duty of candor is met, however, if the patent applicant acts in good faith, and a mistake made in good faith does not constitute inequitable conduct unless gross negligence can be shown. The person charging inequitable conduct must prove it by clear, convincing and substantial evidence. Finally, a charge of inequitable conduct based on lack of candor or outright misrepresentation to the PTO by a patent applicant will not succeed unless the patent applicant has made a material misrepresentation or a material omission of information to the PTO. See Norton v.

Curtiss, 433 F.2d 779, 167 USPQ 532 (CCPA 1970), U.S. Industries, Inc. v. Norton Co., 210 USPQ 94, 107 (N.D.N.Y. 1980), Corona Cord Tire Co. v. Dovan Chemical Corp., 276 U.S. 358 (1928).

Therefore, to prove inequitable conduct by a patent applicant before the PTO that supports a charge that the patent is unenforceable, the following standards must be met:

1. there must be clear and convincing evidence that there was inequitable conduct,

2. the patent applicant must have made a material misrepresentation or a material omission of information to the PTO, and

3. the patent applicant must have acted in bad faith. Either an intent to deceive the PTO, or gross negligence representing such reckless disregard for the truth as to be tantamount to bad faith must be shown.

Even if an intent to mislead the PTO can be proved, in cases where the patent was issued before 1977 it is difficult to prove that the alleged misrepresentation or failure to disclose information to the PTO was material unless the patent would have been found to be invalid but for the misrepresentation to the PTO. In this case the patent was issued before 1977.

The PTO definition of materiality (37 CFR §1.56) changed in 1977. Before 1977, if the patentee misrepresented or failed to disclose prior art or information it had at the time of application, and if that art or information would not have precluded patentability at that time, the information or art would not be considered to be "material," at least by the CCPA. Norton v. Curtiss, supra, 167 USPQ at 544-545.

As a result of the change of §1.56 of the PTO Rules in 1977, the current rule requires the disclosure of prior art or information "where there is a substantial likelihood that a reasonable examiner would consider it important in deciding whether to allow the application to issue as a patent." As pointed out in U.S. Industries, Inc. v. Norton Co., 210 USPQ 94, 107 (D.C. N.Y. 1980), the question of the relevance of the prior art in close cases should be left to the examiner and not to the applicant. Since the patent in this case was issued before 1977, however, the old rule is applicable here.

Travenol argues that in the application for the '529 Fischer patent, the patent applicants mischaracterized the scope and content of the '465 Ghadimi patent, and failed to provide a copy of that patent to the patent examiner, they mischaracterized the scope and content of the 1974 Fischer article, and failed to provide a copy of that article to the patent examiner, and they concealed from the patent examiner their knowledge of Dr. Law's work as reported at a conference in Mexico in 1972. Travenol argues that American did not make it clear in the patent application that the Fischer patent taught the concept of normalization of plasma amino acids in the treatment of patients with liver disease, and that this theory was already disclosed in the 1974 Fischer article published by one of the inventors of the Fischer patent more than a year before the patent application was filed. Instead, the patent application discussed complicated theories relating to neurotransmitters, transfer paths and metabolic consequences, rather than the simple and previously known concept of "normalization."

As indicated previously, the parties stipulated that the most pertinent prior art to the Fischer patent was the Fischer 1974 article and the Ghadimi patent. Both were discussed in the specification of the Fischer patent. Neither was cited by the patent examiner, Mr Moyer, but he had to be aware of their existence if he read the specification. There is no evidence that copies of the Fischer 1974 article and the Ghadimi patent were sent to the patent examiner. Another patent which was summarized in the specification, the Bergstrom patent, was cited by the examiner, presumably because he found it and read it. The examiner testified that if he felt that the document as defined in the disclosure was pertinent to the claimed subject matter, in general he would seek it out. American Ex. 87, at 64. The patent examiners at that time were busy, and the pertinence of the 1974 Fischer article and the Ghadimi patent was not clearly explained in the patent application. It is unlikely under these circumstances that he tried to obtain the 1974 Fischer article and the Ghadimi patent and read them. If the examiner had read and considered the Fischer 1974 article and the Ghadimi patent, however, there is no explanation as to why he did not follow the same practice as with the Bergstrom patent, and cite them as well.

Much that was taught by the 1974 Fischer article and the Ghadimi patent was not disclosed in the Fischer patent application. The examiner, who had a limited amount of time, could have read the limited description of this prior art in the patent application and because more was not disclosed he might not have thought it necessary to read the article and the patent. The Ghadimi patent probably would have been readily available to the examiner, if not in use by another examiner, and the Fischer 1974 article could have been requested without difficulty.

The patent applicant did misrepresent at least one important fact to the PTO. Both the patent application and the patent state "nor has anyone previously proposed a relationship between plasma levels of branched chain amino acids and hepatic encephalopathy." Travenol Ex. 3, p. 6, and Travenol Ex. 10, col. 2. In fact, this concept was proposed in the Fischer 1974 prior art article. American Ex. 119. In addition, the patent application did not disclose everything in the two prior art references that the patent examiner might have wanted to consider in deciding whether the invention was obvious in the light of the prior art.

On p. 2 of the application it is represented that no specially formulated amino acid mixtures have been proposed for administration to liver diseased patients either for therapeutic effects or for nutritional purposes. Travenol Ex. 3. In fact, patients with liver enzyme deficiencies had been treated successfully by normalization of amino acids in their diet, and the 1974 Fischer article had disclosed the use of FreAmine and FreAmine E with encephalopathic patients. Although this was a misrepresentation, it was not a significant one. The 1974 Fischer article disclosed the work with FreAmine and FreAmine E, and neither that work nor the work with enzyme deficiencies was as relevant to the invention as Dr. Fischer's theory of a high branched chain to aromatic amino acids ratio for patients with encephalopathy.

There was at least one misrepresentation and there were a number of omissions relating to the relevant prior art known at the time of the invention to the patent applicant. Was this information material?

The failure to provide a full explanation of the prior art relating to the principle of normalization is not material as that word was construed by the CCPA in connection with patents issued before 1977.

Dr. Blackburn and Dr. Law were more interested in normalization than Dr. Fischer, and the emphasis in the patent application on Dr. Fischer's theory of false neurotransmitters does not constitute misrepresentation or concealment of the theory of normalization. The theory of false neurotransmitters and their relationship to hepatic encephalopathy was Dr. Fischer's theory, and it was the unexpected result of the patented formula on hepatic encephalopathy that was the principal result of the invention. Dr. Fischer's false neurotransmitter theory explained this unexpected result. The theory of normalization to improve nutrition had not addressed this problem specifically, and normalization principles had not been used before to alleviate hepatic encephalopathy. The Fischer patent invention improved the nutrition of patients with liver disease as well as benefitting patients with hepatic encephalopathy, but the theory of normalization had not made the Fischer patent obvious. At the time of the invention it was not conventional to give proteins to patients with hepatic encephalopathy for <u>any</u> reason, because it made them worse.

The next question is whether the misrepresentation that no one previously had proposed a relationship between plasma levels of branched chain amino acids and hepatic encephalopathy was material. The principal issue in determining patent validity in this case is whether the invention was obvious under Section 103 because the <u>concept</u> had been disclosed in the Fischer 1974 prior art article or whether the invention was not obvious because a specific formula using the

high branched chain amino acid ratio had not been tried and found to work. This is a close question. The patent examiner, however, was assured that the concept was not found in the prior art, so he may not have reached this question.

Under the law before 1977, this misrepresentation is not material because nothing in the record suggests that the patent examiner would have found the patent claims invalid over the Fischer 1974 article but for the misrepresentation.

Nothing in the record suggests that the patent examiner would have found the patent invalid over any of the prior art but for the omissions and misrepresentation. The failure to disclose the theory of normalization as it was known in the prior art relating to patients with enzyme deficiency and the failure to disclose the overlapping ranges of the Ghadimi patent were not material because if the examiner had known of this prior art there is no evidence that he would have found the patent invalid.

The record does not show whether the misrepresentation and omissions were deliberate, unintentional, or careless.

Failure to disclose the presentation of Dr. Law in Mexico in 1972 did not constitute a material omission. The parties have stipulated that the 1974 Fischer article and the Ghadimi patent are the most pertinent prior art. Dr. Law's presentation was not prior art under Section 102, but Dr. Law testified that he sent a copy of his report to McGaw Laboratories at their request. TR 492. Although the Law presentation was not circulated in written form except to McGaw, it was "available information" to the patent applicant. The failure to disclose the facts set forth in the Law

presentation does not constitute inequitable conduct on the part of the patent applicant because if the entire presentation of Dr. Law had been disclosed to the PTO it would not have disclosed anything more relevant to the Fischer patent than the information contained in the Fischer 1974 article and the Ghadimi patent. The approach of Dr. Law is closer to the "normalization" theory of Dr. Blackburn than it is to the "false neurotransmitter" theory of Dr. Fischer, but Dr. Fischer's article had discussed "normalization" as well. It is not inequitable conduct if the applicant fails to cite prior art which he believes in good faith to be less relevant than that expressly considered by the PTO. Becton, Dickinson & Co. v. Sherwood Medical Indus., Inc., 516 F.2d 514, 187 USPQ 200 (5th Cir. 1975).

In the present case, the failure to disclose certain information to the PTO is not found to be material because there is no evidence that the patent examiner would have found the patent to be invalid if he had had all the facts fully presented to him in the patent application.

Travenol cites CMI Corp. v. Barber-Greene Co., 683 F.2d 1061, 1064-67 (7th Cir. 1982), in which the most pertinent prior art was known to the applicants and was referred to in the specification, and as here, it was not cited of record by the patent examiner. The court found that the references to this prior art patent were made "in a manner which created an impression that only certain component parts of the [patented] method of apparatus were taught in the Snow patent" while at the same time "obscuring the more relevant fact that the Snow patent described machines remarkably similar to that described" in the application. No copy of the Snow patent was submitted to the Patent Office. The Court of Appeals held that CMI's failure to describe the Snow

patent accurately in its description of the state of the art, together with its failure to submit a copy of the patent to the Patent Office, "raises a strong inference of willful non-disclosure." The court found that the failure to cite this and certain other prior art items to be "more than clear and convincing evidence of fraud."

There is no clear and convincing evidence that the patent applicant here acted in bad faith. The facts here, unlike those in the Barber-Greene Co. case, did not show a selection of only faborable references from the prior art.

Respondents have not sustained their burden of proving that there was a material misrepresentation or a material omission. The patent is enforceable.

5. Domestic Industry

Travenol takes the position that since the Fischer patent is invalid, unenforceable, and not infringed, the issues involving domestic industry, economic and efficient operation, and injury must be automatically resolved against American. Travenol did not otherwise argue these issues substantively nor offer evidence on these issues.

The scope of the domestic industry in a patent-based Section 337 case is generally defined as that portion of the business of the patent owner or its licensees' devoted to the exploitation of the patent in issue. In this case, complainant makes one product under the patent for use in intravenous injections, and another to be taken as a food. Travenol, however, sells only a product to be taken as a food. The domestic industry in a patent case has been defined more narrowly by the Commission in a patent case where the allegedly infringing imports compete only with one part of the domestic business devoted to manufacturing and selling products covered by the patent.

In this case, the parties have stipulated that "the domestic industry is defined as that portion of the complainants' manufacturing, marketing, sales and distribution operations, if any, devoted to the exploitation of the Fischer patent in the enteral product market." American Proposed Finding of Fact No. 112. Although both oral and intravenous products are manufactured under the Fischer patent by American, the domestic industry is defined as covering only the oral products manufactured by American.

American's enteral and parenteral products are produced in separate facilities, using different production methods and equipment. TR 530-531, 577. Patients who are able to take food orally would not normally be given an intravenous solution, while patients who are comatose would be given the parenteral product intravenously. TR 471. The two types of products form distinguishable industries for the purposes of Section 337. Travenol's imported enteral product Travasorb Hepatic competes only with American's enteral product Hepatic-Aid. The record supports a finding of substantial injury to American resulting from Travenol's sales of Travasorb Hepatic whether the industry is defined as American's business devoted to the manufaturing and sale of Hepatic-Aid or as American's business devoted to the manufacturing and sale of any product covered by the Fischer patent.

The domestic industry as stipulated by the parties consists of McGaw's production facilities in Irvine, California, where manufacturing, packaging and quality control for the Hepatic-Aid products take place, and its national marketing, sales and distribution network for those products.

To prove injury to the domestic industry, American first must prove that it is making Hepatic-Aid products under the Fischer patent. The powdered food Hepatic-Aid manufactured by complainant contains the amino acids within the "molar ranges" of claim 1 of the Fischer patent, using American's interpretation of molar ranges. These ratios of amino acids to one another are not changed when liquids containing no amino acids are added to the powder to make it into a palatable drink. Hepatic-Aid is a product covered by all the claims in issue of the Fischer patent. See American Phys. Ex. A-3.

6. Efficient and Economical Operation of the Domestic Industry

American has introduced evidence establishing that both its entire operation and the operation of the domestic industry, as defined above, are economically and efficiently operated. Respondents have offered no evidence to the contrary.

The 1981 annual report (American Phys. Ex. Y) of the parent company, American Hospital Supply Corporation, shows an overall profit for the company.

The American McGaw plant in Irvine, California, which produces Hepatic-Aid, was built in 1979. It has 3,965 square feet devoted to production and 1,776 feet devoted to raw material storage. American Ex. 114, TR 566-567. Design, construction and start-up costs for the plant totalled approximately $ [C] . TR 556. The plant was equipped with the most modern machinery available. TR 559.

Seven production workers and one quality control technician are employed full-time in Hepatic-Aid production, and several others are involved indirectly on an allocation basis. American Ex. 114, TR 566-567. The videotape of the production process revealed some manual labor involved in the production process, but there is nothing in the record to indicate that a higher degree of mechanization would be feasible or more efficient than the methods now employed.

Research and development cost associated with the Hepatic-Aid product totalled approximately $ [C] . American Ex. 114, TR 566-567. Research continues to be emphasized. American Phys. Ex. J-2. Productivity at the

Hepatic-Aid plant has been improving. In 1979, [C] units were produced per [C]-hour shift, with a rejection rate of [C]%. Currently, [C] units are produced per [C]-hour shift with a rejection rate of [C]%. TR 563.

The intravenous HepatAmine product is produced at a larger plant where a variety of intravenous solutions are made. That plant was opened in 1979 at a cost of about $ [C] and was equipped with modern equipment. TR 558-559.

American uses computers to monitor customer orders, forecast sales, anticipate raw material requirements and perform other accounting functions. TR 530-531. The computer system permits customers to order directly from the plant (TR 564-566) and to place orders on an emergency basis. TR 600.

American employs a national sales force and operates 45 distribution centers throughout the country. American Ex. 114, TR 566-567.

Both the Hepatic-Aid and HepatAmine product lines have been profitable. American Ex. 114, TR 575, 727-728.

It is found that the domestic industry is efficiently and economically operated.

7. Injury

American has submitted evidence of substantial injury to the domestic industry including lost sales, declining market share, price suppression, and other indicia of injury. Respondents offered no evidence on the injury issue.

The following table, derived from American Phys. Exs. X and EE, shows rising levels of sales and market share for the imported product:

	Sales (units)			Market Share (%)	
Calendar Quarter	American	Travenol	Total	American	Travenol

[C O N F I D E N T I A L]

American Phys. Exs. X and EE support an inference of specific lost sales by American. From the fourth quarter of 1981 to the fourth quarter of 1982, American's sales to customers it has in common with Travenol have declined from [C] units to [C] units while Travenol's sales to the same customers have increased from [C] to [C] units. The record indicates that Hepatic-Aid and Travasorb-Hepatic are the only available products in the hepatic enteral formulation market. American Ex. 82 at p. 33, TR 655. In the absence of the accused imported product, total domestic demand for enteral nutrition products of this type would be filled by American alone, and could be filled by American without difficulty. TR 561, 562. Under the public

policy encouraging patents, American is entitled to all of the sales of products made under the patent during its life.

Since demand for these products is inelastic, the product is profitable, and no noninfringing domestic substitutes are available, it may also be inferred that lost sales have meant lost profits.

American's list price for Hepatic-Aid has not risen since January 1981, although prices for all other American enteral products have risen in that period. TR 650. American's failure to raise Hepatic-Aid prices was attributed to competition from Travenol. TR 649.

American operates its Hepatic-Aid plant [C] days a week, [C] hours a day. Its capacity at that rate is [C] packets a year, but it is currently operating at [C]% of capacity. TR 561. Output could be expanded substantially by going to more shifts, more days, and replacing the package filling machine (a relatively minor expense). TR 561-562.

The importation and sale of Travasorb Hepatic have injured substantially the domestic industry.

Evidence in the record also supports a finding that importation and sale of Travasorb Hepatic will tend to further substantially injure the domestic industry in the future. Pfrimmer presently possesses or could readily develop productive capacity to supply the U.S. enteral hepatic formulation market in at least the following amounts per year: 1983, [C] units; 1984, [C] ; 1985, [C] ; 1986 [C] ; 1987 [C] . Stipulation 53, Travenol Pretrial Memorandum. Travenol has taken an

aggressive posture in the hepatic enteral market and has the goal of obtaining 50% of that market by the end of 1983. American Ex. 84 at 22, 24, 58-59.

There is often a desire among customers to purchase an entire line of products from a single supplier. TR 653-654, 665. Since Travenol has a much larger share of the conventional parenteral solution market than does American ([C]% vs. [C]%), this desire would tend to shift market share in the hepatic enteral product market toward Travenol. TR 653-654, 665.

The fact that a patented product produces a good profit does not mean that a competitive product will not cause injury to a domestic industry. A patent owner is entitled to the profit on all domestic sales of the patented product, regardless of whether the profit is reasonable. The theory that new ideas would be made available to the public because of the protection offered though a patent would fail without this absolute protection for a limited period of time.

It is found that the importation of Travasorb Hepatic and its sales in the United States have the effect and the tendency to injury substantially the domestic industry involved in the production and sale of Hepatic-Aid. It also would have the effect and the tendency to injury substantially the domestic industry if that industry were defined as the total business related to the production and sale of Hepatic-Aid and Hepatamine, even though Travenol sells no product at this time that competes with Hepatamine.

CONCLUSIONS

It is found that:

1. The Fischer patent is valid and enforceable.

2. The Fischer patent is not infringed by respondents.

3. There is a domestic industry making products under the Fischer patent, the domestic industry is efficiently and economically operated, and the importation and sale of Travasorb Hepatic in the United States causes substantial injury to the domestic industry.

4. There is no unfair act or method of competition in connection with the importation of Travasorb Hepatic, and no violation of Section 337 has been proved.

The record in this case consists of all exhibits listed on American Exhibit 174, Travenol Exhibit 59, and Staff Ex. 1; Travenol Physical Ex. 64A; the transcript of the testimony at the hearing; and all papers and requests filed in this proceeding.1/

Janet D. Saxon

Janet D. Saxon
Administrative Law Judge

Issued: May 20, 1983

1/ Pursuant to Section 210.53(h) of the Commission's Rules the initial determination shall become the determination of the Commission unless a party files a petition for review of the initial determination pursuant to Section 210.54, or the Commission pursuant to Section 210.55 orders on its own motion a review of the initial determination or certain issues therein. For computation of time, see Section 201.14. For computation of additional time after service by mail, see Section 201.16(d).

APPENDIX A

Claims 1, 5, 6, 7, 9 and 14 of the Fischer patent are in issue. These claims read as follows:

1. An amino acid formulation for administration to human patients with liver disease, comprising a mixture of the following essential and nonessential amino acids combined in proportions defined by the following interrelated molar ranges:

Amino Acids	Molar Ranges
L-isoleucine	0.0549-0.0823
L-leucine	0.0670-0.101
L-valine	0.0574-0.0861
L-tryptophan	0.000816-0.00441
L-phenylalanine	0-M
L-tyrosine	0-0.00300
L-lysine	0.0333-0.0500
L-methionine	0.00491-0.0147
L-threonine	0.0228-0.0454
L-alanine	0.0686-0.103
L-arginine	0.0275-0.0413
L-histidine	0.0124-0.0186
L-proline	0.0556-0.0834
L-serine	0.0152-0.0571
glycine	0.0451-0.144
L-aspartic acid	0-0.0451
L-glutamic acid	0-0.0702
L-ornithine	0-0.0382
L-cysteine	0-0.00228

wherein M represents the upper limit of the range for phenylalanine and is equal to 0.009 minus the respective molar amount of tyrosine present in said mixture, the combined molar amounts of phenylalanine and tyrosine being at least equal to 0.002 on the same respective molar basis, the respective molar proportions of isoleucine, leucine, valine, tryptophan, phenylalanine, and tyrosine being selected from the above molar ranges thereof so that the ratio of the combined molar proportions of isoleucine, leucine, and valine to (a) the molar proportion of tryptophan is within the numerical range from 40 to 300, and to (b) the combined molar proportion of phenylalanine and tryosine is within the numerical range from 15 to 135.

5. The amino acid formulation of claim 1 prepared as an edible food for oral administration.

6. The method of supplying amino acids to a human patient having a diseased liver, comprising administering to said patient the amino acid formulation defined in claim 1.

7. The method of claim 6 in which said amino acid formulation is administered in an amount equivalent to at least 50 grams protein per patient per 24 hours.

9. The method of claim 7 in which said mixture of amino acids as defined in claim 1 is administered by oral feeding.

14. An amino acid preparation for oral administration to human patients with liver disease containing carbohydrate and/or fat nutrients together with a mixture of the following essential and nonessential amino acids combined in proportions defined by the following interrelated molar ranges:

Amino Acids	Molar Ranges
L-isoleucine	0.0549-0.0823
L-leucine	0.0670-0.101
L-valine	0.0574-0.0861
L-tryptophan	0.000816-0.00441
L-phenylalanine	0-M
L-tyrosine	0-0.00300
L-lysine	0.0333-0.0500
L-methionine	0.00491-0.0147
L-threonine	0.0228-0.0454
L-alanine	0.0686-0.103
L-arginine	0.0275-0.0413
L-histidine	0.0124-0.0186
L-proline	0.0556-0.0834
L-serine	0.0152-0.0571

CERTIFICATE OF SERVICE

I, Kenneth R. Mason, hereby certify that the attached Initial Determination was served upon Oreste Russ Pirfo, Esq., and upon the following parties via first class mail, and air mail where necessary, on May 24, 1983.

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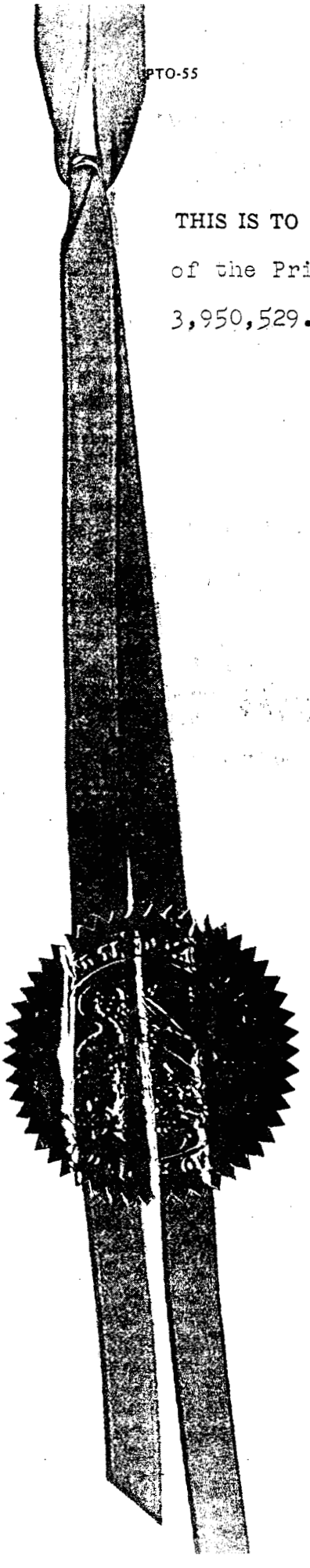
PTO-55

U. S DEPARTMENT OF COMMERCE
United States Patent and Trademark Office

EXHIBIT
2

June 22, 1982
(Date)

THIS IS TO CERTIFY that the annexed is a true copy from the records of this office of the Printed Specification and Drawings of U. S. Patent 3,950,529.



By authority of the
COMMISSIONER OF PATENTS AND TRADEMARKS

A. L. Jackson
Certifying Officer.

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 3,950,529

DATED : April 13, 1976

INVENTOR(S) : Josef E. Fischer et al.

It is certified that error appears in the above—identified patent and that said Letters Patent is hereby corrected as shown below:

In Claims 1 and 14, the Molar range for L-proline should read "0.0556 - 0.0834".

Signed and Sealed this

Fifteenth Day of June 1982

Attest:

Ruth M. Wrug

Attesting Officer

GERALD J. MOSSINGHOFF

Commissioner of Patents and Trademarks

United States Patent [19]
Fischer et al.

[11] 3,950,529
[45] Apr. 13, 1976

AMINO ACID FORMULATIONS FOR PATIENTS WITH LIVER DISEASE AND METHOD OF USING SAME

Inventors: Josef E. Fischer, Boston, Mass.; Norman N. Yoshimura, Woodland Hills, Calif.; Thomas L. Westman; Fred H. Deindoerfer, both of Northridge, Calif.

Assignees: Massachusetts General Hospital, Boston, Mass.; American Hospital Supply Corporation, Evanston, Ill.

Filed: Feb. 3, 1975

Appl. No.: 546,689

U.S. Cl. 424/273; 424/274; 424/319
Int. Cl.[2] ..... A61K 31/415; A61K 31/40; A61 K 31/195
Field of Search 424/273, 274, 319

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Primary Examiner—Donald B. Moyer

[57] ABSTRACT

Amino acid formulations for administration to human patients with liver disease comprise mixtures of essential amino acids combined in novel relative proportions, and preferably also include non-essential amino acids. In particular, the combined molar proportions of isoleucine, leucine, and valine are from 40 to 300 times the molar proportion of tryptophan and from 15 to 135 times the molar proportion of phenylalanine, or phenylalanine and tyrosine. The formulations may be adapted for either intravenous or oral administration, but the preferred method of administration is by hyperalimentation infusion. The formulations and method can be utilized to provide nutritional support for liver diseased patients while reducing the incidence and severity of hepatic encephalopathy, and/or as primary therapy for treatment of hepatic encephalopathy.

14 Claims, No Drawings

AMINO ACID FORMULATIONS FOR PATIENTS WITH LIVER DISEASE AND METHOD OF USING SAME

BACKGROUND AND PROBLEM

Intravenous amino acid solutions are known and are approved for clinical administration to patients requiring intravenous nutrition. They are usually administered along with glucose, fat, electrolytes, and vitamins. The present commercial intravenous amino acid solutions are formulated in accordance with the amino acid requirements of man as delineated by William C. Rose and associates. See, Rose, *Fed. Proc.* 8, 546 (1949); Rose et al., *J. Biol. Chem.*, 217, 987 (1955). U.S. Pat. No. 3,764,703 discloses the use of mixtures of essential amino acids combined in proportions according to the pattern of Rose for administration to patients suffering from reduced kidney function, uremia. According to this patent, the essential amino acids may be administered for the treatment of uremic conditions either intravenously or orally, with resultant lowering of blood urea nitrogen and increased nitrogen retention.

U.S. Pat. No. 3,832,465 discloses intravenous infusion solutions of amino acids containing both essential and nonessential amino acids, which are characterized by having at least 40%, and preferably from 42 to 68%, of the total amino acids comprising the branched chain amino acids, leucine, isoleucine, and valine. It is stated that the branched chain amino acids are metabolized by major pathways not involving the liver, and that therefore they can be intravenously administered in larger proportions than those amino acids dependent on the metabolic action of the liver.

Prior to the present invention, as far as is known, no specially formulated amino acid mixtures have been proposed for administration to liver diseased patients either for therapeutic effects or for nutritional purposes. Malnutrition is a serious problem with such patients. The patient with cirrhosis generally eats poorly, and such patients are usually placed on protein-restricted diets. Liver disease interferes with normal protein utilization. Moreover, encephaiopathy leading to coma and death is associated with advanced cirrhosis and other serious liver disease. By restricting protein intake, the tendency of the liver diseased patients to develop hepatic encephanlopathy may be reduced. However, such limitation of protein intake further contributes to the malnutrition of the patient.

Rose pattern intravenous solutions of amino acids have been administered to liver diseased patients both for nutritional support and experimentally for study of the effect on the patient's plasma amino acid levels. Such studies have shown that the content of amino acids in the plasma of liver diseased patients is seriously distorted, the branched chain amino acids (isoleucine, leucine, and valine) being lower than normal, while methionine and the aromatic amino acids phenylalanine and tryptophan are higher than normal. See Fischer et al., *Am. J. Surg.*, 127, 40 (Jan. 1974), and references cited therein. The amino acid formulations administered by Fischer et al. included solutions containing only essential amino acids, as well as solutions containing both essential and nonessential amino acids. The plasma levels of the branched chain essential amino acids and methionine were consistently decreased, while there was a consistent elevation above normal of phenylalanine and methionine. However, the tryptophan levels were near normal or only slightly elevated. With the mixture of essential and nonessential amino acids, tyrosine was considerably above the normal level, and was found to be elevated, although to a lesser extent, even with the mixture containing only the eight essential amino acids.

An attempt was made to increase the low plasma levels of branched chain amino acids by increasing the amount infused up to two and one half times the minimal daily requirements recommended by Rose for isoleucine, leucine, and valine. Such high level infusion of branched chain amino acids, however, failed to correct the low concentrations of these amino acids in the patients' plasma. The metabolic consequence of low plasma levels of branched chain amino acids is not known, nor has anyone previously proposed a relationship between plasma levels of branched chain amino acids and hepatic encephanlopathy.

It has been suggested that an excess of phenylalanine may inhibit the transport of tyrosine to the brain. Guroff et al., *J. Biol. Chem.* 237, 803 (1962). Further, it is known that tyrosine is important for the synthesis of some of the normal catecholamine neurotransmitters in the brain. It has also been suggested that the level of serotonin in the brain may be related to the association between plasma tryptophan, as opposed to plasma phenylalanine, tyrosine, and the branched chain amino acids. Fernstrom, et al., *Science*, 178, 414 (1972). However, earlier studies tended to establish that the principle factor modulating brain tryptophan was the ratio of plasma tryptophan to the sum of all of the plasma amino acids. See Perez-Cruet et al., *Nature*, 248, 693 (1974).

In accordance with the present invention, the amount administered of phenylalanine alone, or phenylalanine and tyrosine in combination, or tyrosine alone is controlled in relation to the total of the essential branched chain amino acids, specifically isoleucine, leucine, and valine to achieve metabolically acceptable levels of plasma phenylalanine and tyrosine. It appears that the formulations of the present invention permit adequate transfer of tyrosine to the brain, and that there is no serious inhibition of such transport due to excessive plasma phenylalanine. Further, the amount of phenylalanine administered may be reduced, or in some embodiments eliminated entirely, if the phenylalanine in the amino acid mixture is partially replaced by tyrosine. Such replacement is limited by the low water solubility of tyrosine. The tyrosine can be supplemented by more water soluble tyrosine derivatives, providing the derivative is convertible by the body to tyrosine.

The experimental work leading to the present invention has also indicated that the relative proportions of the essential branched chain amino acids should be controlled in relation to the proportion of tryptophane administered. By proper balancing of the proportions of isoleucine, leucine, and valine to tryptophan, it is believed that the transfer of excessive tryptophan to the brain can be avoided. This is desirable since tryptophan is converted by the brain to serotonin, which would be expected to complicate hepatic encephalopathy. It therefore appears that the quantity of amino acid administered for nutritional utilization by the patient can be significantly increased while therapeutically maintaining normal brain function. In general, all of the plasma amino acids may compete with the plasma tryptophan for transport to the brain. However, what seems to be of importance for the purpose of the present

invention is that phenylalanine and tryosine are relatively less competitive with tryptophane for entry into the brain compared to the branched chain essential amino acids.

It should be understood that the foregoing mechanisms are not known with complete certainty. Further, diseased livers do not respond predictably in all cases. Nevertheless, the available experimental evidence, strongly indicates that administration of the amino acid formulation of this invention can be expected to therapeutically reduce the incidence and severity of hepatic encephalopathy, while providing more nearly adequate nutritional support for the patients suffering from liver disease. The treatment of hepatic encephalopathy should also be clinically attainable. Moreover, by achieving more nearly adequate nutrition, while avoiding the complications of encephalopathy and coma, an opportunity is provided for improved liver function to develop. It is known that the liver has remarkable power to hypertrophy or regenerate. Consequently, if the patient can be maintained over a sufficient period of time with adequate nutrition, the liver may repair and fully recover.

The formulations of this invention may include both essential and nonessential amino acids, or only essential amino acids, but the inclusion of some nonessential amino acids is desirable. With respect to nutritional support, resultant plasma amino acid levels, brain function, and therapeutic benefits there is a complex interrelationship between the amino acid formulations of this invention. In addition to the considerations discussed above, therefore, the relative proportions of all of the amino acids incorporated, essential and nonessential, including amino acids which may be optionally included, are specified in terms of their respective molar ranges.

DETAILED DISCLOSURE

The amino acids used in practicing the present invention are preferably pure crystalline amino acids. In general, the amino acids should be in their L-form, rather than the D-form, or a mixture of D and L. Also, in general, the amino acids are employed as free amino acids rather than as amino acid salts or derivatives. L-lysine acetate may be used, and derivatives of L-tyrosine which are convertible to tyrosine by the body.

Mixtures of essential and nonessential amino acids prepared in accordance with the present invention for administration to human patients with liver disease should contain the amino acids in interrelated proportions. Desirable relative internal proportions are defined by the following molar ranges:

Amino Acids	Molar Ranges
L-isoleucine	0.0549–0.0823
L-leucine	0.067–0.101
L-valine	0.0574–0.0861
L-tryptophan	0.000816–0.00441
L-phenylalanine	0–M
L-tyrosine	0–0.003
L-lysine	0.0333–0.05
L-methionine	0.00491–0.0147
L-threonine	0.0228–0.0454
L-alanine	0.0686–0.103
L-arginine	0.0275–0.–413
L-histidine	0.0124–0.0186
L-proline	0.0556–0.0834
L-serine	0.0152–0.0571
glycine	0.0451–0.144
L-aspartic acid	0–0.0451
L-glutamic acid	0–0 0702
L-ornithine	0–0.0382

-continued

Amino Acids	Molar Ranges
L-cysteine	0–0.00228

Optionally, part of the L-methionine in the above formulation may be replaced by D-methionine, a mixture of DL-methionine being used on an equivalent basis to L-methionine. D-methionine has approximately 75% of the nutritional value of L-methionine, which percentage can be used to determine the desirable equivalent range for a mixture of DL-methionine. However, it is preferred to employ only L-methionine.

Certain other amino acids can be used in modified forms. For example, the lysine can be advantageously used in the form of its acetate salt (L-lysine acetate). Also, it is convenient to incorporate the cysteine in the form of its hydrochloride salt (L-cysteine·HCl·H_2O).

In the above formulation, the upper limit of the molar range for phenylalanine is indicated by the letter "M". Where the formulation includes no tyrosine, M will be equal to 0.009, that is, the molar range for phenylalanine will be 0-0.009. When tyrosine is incorporated, the amount of phenylalanine is correspondingly reduced. More specifically, M will be equal to 0.009 minus the respective molar amount of free tyrosine. For example, when the amount of tyrosine in the formulation is equal to 0.003, M will be 0.006. Both phenylalanine and tyrosine should not be omitted. The total of phenylalanine and tyrosine should be equal to at least 0.002 moles in relation to the molar proportions set out above.

As indicated by the lower limit of "0", several of the other amino acids listed in the above formulation are optional, that is, they can be omitted completely. These optional amino acids include aspartic acid, glutamic acid, ornithine, and cysteine. Phenylalanine may also be omitted in some embodiments if tyrosine is included. In most formulations, some phenylalanine also will be included, at least 0.00266 moles on the same basis, that is, a range of 0.00266–0.009 for phenylalanine if no tyrosine is included, or 0.00266-M if tyrosine is present.

It will be understood that in addition to the amino acids, the formulation may include preservatives or stabilizers, as required, such as sodium bisulfite, asocrbic acid (vitamin C), or other compatible preservative agents. Nitrogen gas may also be used to preserve the solution.

In accordance with the present invention, the respective molar proportions of isoleucine, leucine, valine, tryptophan, and phenylalanine (or phenylalanine and tyrosine) should be selected to provide certain ratios of these amino acids. More specifically, the ratio of the combined molar proportions of isoleucine, leucine, and valine to (a) the molar proportion of tryptophane should be within the numerical range from 40 to 300, and to (b) the molar proportion of phenylalanine, or the combined molar proportion of phenylalanine and tyrosine, should be within the numerical range from 15 to 135. Although, the complete optimization of the formulation within the specified ranges has not yet been fully defined, nutritionally and/or therapeutically applicable molar proportions for the total of the branched chain amino acids (isoleucine, leucine, and valine) to the molar proportion of tryptophan is from

50 to 90, and to the molar proportion phenylalanine, or phenylalanine and tyrosine, from 30 to 50.

The formulations are desirably free of ammonia. When prepared from crystalline amino acids, the resultant formulation will be low in free ammonia. In general, the formulations preferably contain less than 2 millimoles of ammonia per each 800 millimoles of amino acids, including all of the amino acids present (essential and nonessential).

The formulations may be advantageously prepared in the form of sterile aqueous solutions adapted for intravenous administration. In accordance with known practice for such solutions, the liver disease amino acid solutions will be sterile, pyrogen-free, and at a suitable pH for intravenous administration. The most desirable pH for the solution may vary depending on whether the amino acid solution is to be mixed with an intravenous dextrose solution before administration, but, in general, the pH of the amino acid solution can range from 5.0 to 7.8. Where the patient with liver disease is being fed a protein-restricted diet and the intravenous amino acid solution is to be used as a supplement to such diet, in some cases, peripheral intravenous infusion techniques may be used. However, the preferred technique involves administration into a central vein, which is a procedure known clinically as hyperalimentation. In this technique, the infusion is made into the central vein through a catheter. For example, either a subclavian or internal jugular indwelling catheter may be used.

Amino acid infusion solutions prepared for hyperalimentation use with liver diseased patients can contain from 2 to 9 weight percent of total amino acids based on the solution. In preferred embodiments, which can be used for total parenteral nutrition, it is believed that the optimum concentration of total amino acids will be from 3 to 5 weight percent based on the solution as prepared for infusion. Where the amino acid solution is prepared in more concentrated form, it can be mixed with other nutrient-containing solutions (viz. aqueous glucose) to prepare an infusate solution of the preferred amino acid concentration.

With intravenous solutions prepared as described above, it is expected that full protein nutrition can be provided by administration from about 1 to 3 liters of solution per patient during each 24 hours. The maximum amount which may be administered will depend on the amino acid tolerance of the particular patient. While the formulation of the present invention is capable of reducing the incidence and severity of hepatic encephalopathy, the desirable clinical procedure will be to begin the infusion at a daily level below full protein nutrition, and gradually increase the amount administered. For example, the administration can be started at levels equivalent to about 20 to 25 grams protein per day (24 hrs.), and then increased to at least 40 to 50 equivalent grams protein per day, providing the patient is tolerating the infusion. It is expected that the average patient will be able to tolerate at least the equivalent of 50 grams protein per 24 hrs., and in some cases, much higher administration levels up to as high as 100 to 140 grams protein equivalents may be feasible. For the purpose of the present invention, and as known to biochemists, the equivalency of amino acids to protein can be calculated by determining the total grams of amino acid nitrogen, and then multiplying this amount by 6.25 to obtain the grams of equivalent protein.

One formulation, including no tyrosine, which may be prepared as a concentrated infusion solution will now be described. The concentrations are given in moles per liter of solution. If the formulation is employed for oral administration, the relative concentrations indicated should be maintained, that is, the oral formulation will have the same amino acids in the same respective molar concentrations or ranges.

The formulation is as follows:

Amino Acids	Concentrations (moles/l. soln.)
L-isoleucine	0.059–0.0823
L-leucine	0.067–0.101
L-valine	0.0574–0.0861
L-tryptophan	0.000816–0.00441
L-phenylalanine	0.00444–0.0133
L-lysine	0.0333–0.0500
L-methionine	0.00491–0.0147
L-threonine	0.0228–0.0454
L-alanine	0.0686–0.103
L-arginine	0.0275–0.0413
L-histidine	0.0124–0.0186
L-proline	0.0556–0.0834
L-serine	0.0152–0.0571
glycine	0.0451–0.144
L-cysteine	0–0.00228

The amino acid formulation of this invention as designed for use with liver disease patients contains the amino acids, (both essential and nonessetial) in proportions widely different from the amino acid content of any naturally occuring proteins. Further, the relative proportions are markedly different than the amounts of essential amino acids heretofore believed to be necessary for proper nutrition. The comparison is indicated by the following table, where the essential amino acids are shown in the first column as they would be in accordance with the pattern of Rose. The next column illustrates a preferred formulation of the present invention.

Comparison with Rose's Pattern for Essential Amino Acids

Amino Acid	Rose*	Illustrative Liver Disease Formulation
Isoleucine	110	216
Leucine	173	263
Valine	126	201
Tryptophan	39	18
Phenylalanine	173	24
Lysine	126	146
Methionine	173	24
Threonine	79	108

*In mg./g. total amino acids.

Specific formulations for practicing the present invention are set out in the following examples.

EXAMPLE I

A sterile, non-pyrogenic, stable solution suitable for intravenously infusing into liver diseased patients is prepared from pure crystalline amino acids, which are dissolved in distilled water in the following concentrations:

Amino Acid	g./l.		mole/l.
L-isoleucine	9.0		0.0686
L-leucine	11.0		0.0838
L-valine	8.4		0.0717
L-tryptophan	0.75		0.00367
L-phenylalanine	1.0		0.00605
L-lysine acetate	8.6	(base, 6.09)	0.0417

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Amino Acid	g./l.		mole/l.
L-methionine	1.0		0.0067
L-threonine	4.5		0.0378
L-alanine	7.65		0.0858
L-arginine	6.0		0.0344
L-histidine	2.4		0.0155
L-proline	8.0		0.0695
L-serine	5.0		0.0476
glycine	9.0		0.120
L-cysteine.HCl.H_2O	0.2	(base 0.14)	0.00114

In the foregoing formula, the ratio of the essential branched chain amino acids to phenylalanine is about 37 and to tryptophan is about 61.

To this solution is added 1.152 g./l. of 85% phosphoric acid to adjust the pH to a more physiological pH (approx. 6.8), and to serve as a source of phorphorous, an important element for good nutrition. The volume is then brought to the desired volume with distilled water. Sodium bisulfite U.S.P. grade, 1.0 g./l., is added and stirred until dissolution is complete. Two grams of activated charcoal is then added and stirred for an additional 10 minutes. The solution is then filtered and filled into appropriate containers for intravenous fluids and steam sterilized at 250°F. for 10 minutes.

EXAMPLE II

If a formulation of amino acids for liver diseased patients is desired which contains only essential amino acids, the nonessential amino acids in the intravenous solution of Example I can be omitted. The same relative proportions of the essential amino acids (isoleucine, leucine, valine, tryptophan, phenylalanine, lysine, methionine, and threonine) will be present; and the solution will be prepared in the same manner. Preferably, however, arginine, histidine, and cysteine are also included in the indicated relative proportions with the eight essential amino acids.

EXAMPLE iII

Following the procedure of Example I, an alternate amino acid formulation for liver disease therapy is provided in which the molar ratio of the sum of valine, leucine, and isoleucine to (a) phenylalanine plus tyrosine and (b) tryptophan is 50 to 275, respectively.

Amino Acid	g./l.		mole/l.
L-isoleucine	9.0		0.0686
L-leucine	11.0		0.0838
L-valine	8.4		0.0717
L-tryptophan	0.2		0.000816
L-phenylalanine	0.73		0.00444
L-lysine acetate	8.6	(base, 6.09)	0.0417
L-methionine	1.0		0.0067
L-threonine	3.4		0.0285
L-alanine	9.18		0.103
L-arginine	7.1		0.0408
L-histidine	2.5		0.0161
L-proline	8.0		0.0695
L-serine	1.6		0.0152
glycine	3.4		0.0451
L-cysteine.HCl.H_2O	0.4		0.00228

EXAMPLE IV

Following the procedure of Example I, an alternate amino acid formulation for liver disease therapy is prepared from the following pure crystalline amino acids and in the following concentrations:

Amino Acid	g./l.		mole/l.
L-isoleucine	9.0		0.0686
L-leucine	11.0		0.0838
L-valine	8.4		0.0717
L-tryptophan	0.75		0.00367
L-phenylalanine	0.55		0.00333
L-tyrosine	0.45		0.00248
L-lysine acetate	8.6	(base, 6.09)	0.0417
L-methionine	1.0		0.0067

Amino Acid	g./l.	mole/l.
L-threonine	4.5	0.0378
L-alanine	7.65	0.0858
L-arginine	6.0	0.0344
L-histidine	2.4	0.0155
L-proline	8.0	0.0695
L-serine	5.0	0.0476
glycine	9.0	0.120
L-aspartic acid	5.0	0.0376
L-glutamic acid	8.6	0.0585
L-ornithine	4.2	0.0318
L-cysteine.HCl.H_2O	0.2	0.00114

With respect to the formulations of Examples I to III, as a supplement to oral feeding, wherein this amino acid solution is preferentially infused into peripheral veins, i.e. arm or leg veins, an isotonic or near isotonic concentration of an amino acid solution having a composition within the specified ranges can be utilized. Thus a 3.0 to 5.0% w/v amino acid solution having the above composition can be used.

Another alternate route of administration for the solution is to administer all nutrients via a nasogastric tube or a jejunostomy tube. As in the I.V. administration, the amino acid solution is added to sufficient calories provides as carbohydrates and/or far, vitamins and minerals. The complete diet is then administered slowly over a 24 hour period.

EXAMPLE V

For oral consumption, the amino acid mixture, having the same molar ratios and the same ranges as described previously, 80 – 120% of the recommended daily allowance of essential minerals, sufficient calories in the form of monosaccharide, sugar and malto dextrins and/or fat are mixed with natural and/or synthetic food flavors such that reconstitution with water or gelatinous base yields an edible food preparation in the form of a palatable liquid drink or a semisolid food. A typical formulation of the principal ingredients of a food preparation is given below:

Ingredient	%w/w	
Amino Acids	9.23	
L-isoleucine		1.01
L-leucine		1.23
L-valine		0.95
L-tryptophan		0.08
L-phenylalanine		0.11
L-lysine acetate		0.96
L-methionine		0.11
L-threonine		0.50
L-alanine		0.86
L-arginine		0.67
L-histidine		0.27
L-proline		0.90
L-serine		0.56
glycine		1.00
L-cysteine.HCl.H_2O		0.02
Carbohydrates (Sugar Malto-dextrin)	77.8	
Fat	6.69	
Citric Acid	0.846	

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Ingredient	%w/w
Potassium Citrate	0.419
Calcium Glycerophosphate	0.89
Sodium Chloride	0.470
Potassium Sulfate	0.194
Potassium Phosphate, Dibasic	0.182
Magnesium Oxide	0.0875
Zinc Sulfate.H_2O	0.0055
Ferrous Sulfate	0.00524
Copper Gluconate	0.002
Manganous Sulfate.H_2O	0.00[illegible]1
Potassium Iodide	0.000[illegible]0252
Flavor or Color	1.00

It will be understood that in the special oral amino acid diets for use in liver disease therapy, the pattern of amino acids is of critical importance. Calories as carbohydrates and/or fats, vitamins and minerals are also needed, but can be supplied in various forms. In the oral administration of amino acids to liver diseased patients, it may be desirable to sterilize the intestines by also orally administering an antibiotic such as Kanamycin. See Fischer et al., *Surgical Forum*, Vol. XXV, 369 (1974).

EXAMPLE VI

Following the procedure of Example V, the amino acids combined with the other components include:

Amino Acid	%w/w
L-isoleucine	9.20
L-leucine	11.25
L-valine	8.60
L-tryptophan	0.77
L-phenylalanine	0.56
L-tyrosine	0.46
L-lysine acetate	6.23
L-methionine	1.02
L-threonine	4.60
L-alanine	7.82
L-arginine	6.14
L-histidine	2.45
L-proline	8.18
L-serine	5.11
glycine	9.20
L-aspartic acid	5.11
L-glutamic acid	8.79
L-ornithine	4.29
L-cysteine.HCl.H_2O	0.22

The foregoing formulation will be combined with the other components set out in Example IV in from 5 to 10 parts by weight per the specified parts by weight of the other ingredients as set in Example IV. As will be noted therefore the total weight percent of amino acids in the complete formulation is a little greater than that of Example IV. However, the amino acids present in both formulations are included in substantially the same proportions with respect to each other.

EXAMPLE VII

Following the procedure of Example I, an alternate amino acid solution for liver disease therapy is prepared from the following pure crystalline essential amino acids and in the following concentrations:

Amino Acid	g./l.	mole/l.
L-isoleucine	9.0	0.0686
L-leucine	11.0	0.838
L-valine	8.4	0.0717
L-tryptophan	0.75	0.00367
L-phenylalanine	0.55	0.00333
L-tyrosine	0.45	0.00248
L-lysine acetate	8.6 (base, 6.09)	0.0417

-continued

Amino Acid	g./l.	mole/l.
L-methionine	1.0	0.00670
L-threonine	4.5	0.0378
L-alanine	7.65	0.0858
L-arginine	6.0	0.0344
L-histidine	2.4	0.0155
L-proline	8.0	0.0695
L-serine	5.0	0.0476
glycine	9.0	0.120
L-aspartic acid	5.0	0.0376
L-glutamic acid	8.6	0.0585
L-ornithine	4.2	0.0318
L-cysteine.HCl.H_2O	0.2	0.00114

We claim:

1. An amino acid formulation for administration to human patients with liver disease, comprising a mixture of the following essential and nonessential amino acids combined in proportions defined by the following interrelated molar ranges:

Amino Acids	Molar Ranges
L-isoleucine	0.0549–0.0823
L-leucine	0.0670–0.101
L-valine	0.0574–0.0861
L-tryptophan	0.000816–0.00441
L-phenylalanine	0–M
L-tyrosine	0–0.00300
L-lysine	0.0333–0.0500
L-methionine	0.00491–0.0147
L-threonine	0.0228–0.0454
L-alanine	0.0686–0.103
L-arginine	0.0275–0.0413
L-histidine	0.0124–0.0186
L-proline	0.0556–0.00834
L-serine	0.0152–0.0571
glycine	0.0451–0.144
L-aspartic acid	0–0.0451
L-glutamic acid	0–0.0702
L-ornithine	0–0.0382
L-cysteine	0–0.00228

wherein M represents the upper limit of the range for phenylalanine and is equal to 0.009 minus the respective molar amount of tyrosine present in said mixture, the combined molar amounts of phenylalanine and tyrosine being at least equal to 0.002 on the same respective molar basis, the respective molar proportions of isoleucine, leucine, valine, tryptophan, phenylalanine, and tyrosine being selected from the above molar ranges thereof so that the ratio of the combined molar proportions of isoleucine, leucine, and valine to (a) the molar proportion of tryptophan is within the numerical range from 40 to 300, and to (b) the combined molar proportion of phenylalanine and tyrosine is within the numerical range from 15 to 135.

2. The amino acid formulation of claim 1 in which said ratio with respect to (a) is from 50 to 90, and said ratio with respect to (b) is from 30 to 50.

3. The amino acid formulation of claim 1 in which said mixture of amino acids is dissolved in a sterile aqueous solution havng a total amino acid concentration of from 2 to 9 weight percent based on the solution.

4. The amino acid formulation of claim 3 in which said ratio with respect to (a) is from 50 to 90, and said ratio with respect to (b) is from 30 to 50.

5. The amino acid formulation of claim 1 prepared as an edible food for oral administration.

6. The method of supplying amino acids to a human patient having a diseased liver, comprising administer-

ing to said patient the amino acid formulation defined in claim 1.

7. The method of claim 6 in which said amino acid formulation is administered in an amount equivalent to at least 50 grams protein per patient per 24 hours.

8. The method of claim 7 in which said mixture of amino acids as defined in claim 1 is in the form of an aqueous solution of said amino acids and in which said solution is administered by intravenous infusion.

9. The method of claim 7 in which said mixture of amino acids as defined in claim 1 is administered by oral feeding.

10. An intravenous infusion solution of amino acids for administration to human patients with liver disease, consisting essentially of a sterile aqueous solution of the following essential and nonessential amino acids in the following moles per liter of solution concentrations:

Amino Acids	Concentrations
L-isoleucine	0.0549–0.0823
L-leucine	0.0670–0.0101
L-valine	0.0574–0.0861
L-tryptophan	0.000816–0.00441
L-phenylalanine	0.00444–0.0133
L-lysine	0.0333–0.0500
L-methionine	0.00491–0.0147
L-threonine	0.0228–0.0454
L-alanine	0.0686–0.103
L-arginine	0.0275–0.0413
L-histidine	0.0124–0.0186
L-proline	0.0556–0.0834
L-serine	0.0152–0.0571
glycine	0.0451–0.144
L-cys.eine	0–0.00228

the respective concentrations of isoleucine, leucine, valine, tryptophan, and phenylalanine being selected from the above concentration ranges therefor so that the ratio of the total moles per liter of isoleucine, leucine, and valine to (a) the respective concentration of tryptophan is within the numerical range for said ratio of 50 to 90, and to (b) the respective concentration of phenylalanine is within the numberical range for said ratio of 30 to 50.

11. The method of supplying amino acids to a human patient having a diseased liver, comprising intravenously infusing said patient with the amino acid solution defined by claim 10.

12. The method of claim 11 in which said solution is infused in an amount equivalent to at least 50 grams protein per patient per 24 hours.

13. The intravenous infusion solution of claim 8 in which said ratio with respect to (a) is from 50 to 90, and said ratio with respect to (b) is from 30 to 50.

14. An amino acid preparation for oral administration to human patients with liver disease containing carbohydrate and/or fat nutrients together with a mixture of the following essential and nonessential amino acids combined in proportions defined by the following interrelated molar ranges:

Amino Acids	Molar Ranges
L-isoleucine	0.0549–0.0823
L-leucine	0.0670–0.101
L-valine	0.0574–0.0861
L-tryptophan	0.000816–0.00441
L-phenylalanine	0–M
L-tyrosine	0–0.00300
L-lysine	0.0333–0.0500
L-methionine	0.00491–0.0147
L-threonine	0.0228–0.0454
L-alanine	0.0686–0.103
L-arginine	0.0275–0.0413
L-histidine	0.0124–0.0186
L-proline	0.0556–0.00834
L-serine	0.0152–0.0571

Amino Acids	Molar Ranges
glycine	0.0451–0.144
L-aspartic acid	0–0.0451
L-glutamic acid	0–0.0702
L-ornithine	0–0.0382
L-cysteine	0–0.00228

wherein M represents the upper limit of the range for phenylalanine and is equal to 0.009 minus the respective molar amount of tyrosine present in said mixture, the combined molar amounts of phenylalanine and tyrosine being at least equal to 0.002 on the same respective molar basis, the respective molar proportions of isoleucine, leucine, valine, tryptophan, phenylalanine, and tyrosine being selected from the above molar ranges thereof so that the ratio of the combined molar proportions of isoleucine, leucine, and valine to (a) the molar proportion of tryptophan is within the numerical range from 40 to 300, and to (b) the combined molar proportion of phenylalanine and tyrosine is within the numerical range from 15 to 135.

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