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PROCESS FOR PREPARING A MODIFIED LACTALBUMIN HYDROLYSATE

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1 Claim. (Cl. 167-58)

This invention relates to a new and improved therapeutic agent for local topical application in the treatment of pruritus, and is more particularly concerned with the production of a therapeutic agent highly useful in the local topical treatment of pruritus ani.

Pruritus ani has always been difficult to treat and a problem of real importance to the patient and physician. The disease occurs in apparently healthy individuals and is characterized by a history of marked itching of the perianal skin which becomes reddened, fissured, and sometimes moist and macerated.

Numerous shallow fissures are usually present, often extending back to the coccyx and often anteriorly to the scrotum or vagina. The presence of whitish edges of skin along these fissures and even beyond is often observed. External hemorrhoids or tags are usually thickened and when excised the wounds heal sluggishly with the same white, fibrotic edges.

Many causes have been advanced for pruritus ani. By reason of the symptomatic relief produced the nervous system has been the target of attack both by means of local anesthetic agents and by means of antispasmodics and sedative agents. There is a long list of so-called causative agents such as: fistulae, infected crypts, fissures, food allergy, hepatic insufficiency, caustic soap, pin worms, and others. These, together with the nervous syndrome, comprise the group which may be medicated collaterally with good results.

The remainder comprises a great bulk of cases which must be treated directly and the long list of treatments suggests that no single good result has been obtained. This large group may be called "essential" pruritus and no satisfactory treatment has yet been discovered.

Up until the advent of the present invention many different types of treatment have been recommended and employed. These treatments fall into the following main classes: (1) Avoidance of irritating external factors; (2) dietary changes; (3) bromides and phenobarbital; (4) laxatives; (5) potassium iodide to relieve fungus infections; and (6) various empirical formulas such as phenol and calomine lotion, acetanilid and petrolatum, dithymol di-iodide and bismuth subcarbonate, lime water and milk or mercuric chloride, phenol, salicylic acid, camphor, and glycerine, balsa Peru and castor oil.

Attempts at imitating the action of pruritus on healthy skin led to the use of an agent known as ammonium oleate. This causes actual pruritus in some cases. In addition, experimental evidence has shown that the irritant forming the whitish edges of skin along the fissures may be reproduced at the same time by an astringent agent such as tannic acid. Another series of compounds inducing irritation similar to pruritus ani are the ammonia series. Dilute solution of ammonia water reproduces many of the itch symptoms. Finally, the general condition of poor nutrition in the area of pruritus ani may be reproduced by an ointment containing large amounts of microscopic crystalline methionine (an amino acid).

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To sum up the experimental clinical findings in reference to causative agents we have the following list: (1) ammonium oleate; (2) tannic acid; (3) ammonia water; and (4) microscopic crystals of methionine.

5 Astringent, direct irritant, or protein precipitant properties reproduce pruritus ani in healthy skin. Together with the specific finding in reference to methionine, this knowledge was found to aid considerably in elaborating the mechanism causing this treacherous disease. It is 10 entirely possible that a combination of the excretion leaking from the anus and the excessive amount of sweat found in the perineal area combine to cause pruritus ani, whenever the nutrition of the skin is so changed to allow the result.

15 In accordance with the present invention, it has now been discovered that, because of certain deficiencies characteristic in this disease, a particular mixture of amino acids and polypeptides may be provided which, when brought into contact with the perineal surface in the 20 form of a poultice, causes the itch to subside and the skin to regenerate to form normal skin without itch. The discovery of this principle has made it possible to elaborate a new therapeutic agent for the treatment of pruritus.

25 It has been determined, further in accordance with the invention, that the usual combination of so-called essential amino acids found in conventional protein hydrolysates is not satisfactory for this purpose. This usual amino acid mixture, which is the result of enzymatic digestion or acid digestion of milk protein or milk casein 30 or yeast proteins, contains argenine, histadine, lysine, tyrosine, tryptophane, phenylalanine, cystine, methionine, threonine, leucine, isoleucine, and valine.

A study of these amino acids separately has shown 35 that some are partly beneficial, some are indifferent in their effect, and some irritate; but none alone are completely satisfactory in pruritus therapy. A study made of the effect of a poultice of each of these separate amino acids has revealed the following.

40 Amino acid:	Effect
Argenine -----	Indifferent.
Histidine -----	Slight irritation.
Lysine -----	Indifferent.
Tyrosine -----	Indifferent.
45 Tryptophane -----	Slightly beneficial.
Phenylalanine -----	Slightly beneficial.
Cystine -----	Slightly irritating.
Methionine -----	Strongly irritating.
Threonine -----	Indifferent.
50 Leucine -----	Slightly beneficial.
Isoleucine -----	Indifferent.
Valine -----	Slightly beneficial.

The discovery that certain of the amino acids in the combination caused irritation, led to the formation of a novel complex from which significant amounts of methionine, cystine and histidine, together with certain water-insoluble components, have been removed. This novel complex, containing a particular amino acid mixture, 60 along with polypeptides and unreacted proteins, is the basis of the present invention and the essential ingredient of final therapeutic agent. Of equal importance is the novel procedure by which this complex is formed.

The new therapeutic agent for local application in the treatment of pruritus ani is composed of a specially prepared protein digest containing a particular mixture of amino acids and polypeptides, and is prepared by subjecting a protein such as lactalbumin to conventional hydrolysis, treating the hydrolysate in a special way to remove undesirable amino acids and some of the more water-insoluble fractions of the digested protein, and 70 then further digesting and dehydrating by heat.