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COLLAGEN STRANDS AND METHOD
OF TREATING

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This invention relates to collagen strands and more particularly to collagen sutures.

According to one commercial method, sutures are usually obtained from the intestine of the sheep, hog or cow, preferably from the small intestine of the sheep and from a particular layer thereof called the submucosa. The intestines are received from the abattoir in barrels or other containers, packed in salt or not, are re-hydrated in water and then split lengthwise into two ribbons one of which is referred to as the "rough" side, the other as the "smooth" side. These ribbons, after being washed in sodium bicarbonate water and scraped free of debris, slime and so on, are combined in multiples of 1, 2, 3 or more to form a strand consisting of the required number of plies or submucosal ribbons, the plied strand is tanned, as with chromium or formaldehyde, a plurality of the strands are spun to form a wet suture, and the suture is dried under tension and polished to the required diameter.

Collagen strands suitable for use in sutures may also be obtained by extruding a mass of collagen fibers in suspension, or a solution of collagenous material, through a suitable filament-forming device into a coagulating and dehydrating bath. The filaments thus formed may be withdrawn from the bath and, after suitable processing, finally dried under tension. A plurality of the filaments may be twisted together to form a multi-filament thread useful as a suture or in the preparation of twisted, plied or braided strands for other purposes.

When these plied or twisted structures are dried under tension there is a tendency for the individual plies, or for short fibers if the elemental filaments comprise a plurality of short fibers, to separate under the stretching tension with the result that the final dried product may not have uniform characteristics, including strength, at all portions along its length. Uniformity is an important characteristic for sutures. The problem is complicated by the fact that the use of many available bonding agents for binding the strand components together during the tension-drying is not practical because such agents may not be allowed to remain on the suture when it is used to sew an incision and removal of such agents from the suture prior to use would require rewetting.

The object of the present invention is to provide collagen sutures comprising strands made up of a plurality of components, as submucosal ribbons or a plurality of short fibers or of filaments, bonded together by a bonding agent which is absorbable by humans and animals and physiologically harmless. Other objects of the invention will appear hereinafter.

The objects of the invention are accomplished by impregnating the collagen strands with dextran which adhesively bonds the components of the strand into a compact structure of indefinite length and which is capable of accepting a uniform stretch along its length.

The dextrans are high molecular weight polysaccharides made up of anhydroglucopyranosidic units, joined by molecular structural repeating linkages some of which are alpha-1,6 and some of which are non-alpha-1,6 link-

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ages and at least 50% of which are of the alpha-1,6 type. They vary widely in their physical properties including their molecular weight, molecular structural repeating alpha-1,6 to non-alpha-1,6 linkages ratios and water sensitivity. The preferred dextrans for the present purpose are those which are water-soluble or water-dispersible, having a molecular weight in the range 5000 to 150×10^6 , as determined by light scattering measurements, and a molecular structural repeating alpha-1,6 to non-alpha-1,6 linkages ratio of 1.9:1 to 30:1.

Dextrans having the aforementioned properties may be obtained in various ways. For example, they may be obtained by enzyme synthesis from sucrose in the presence or substantial absence of bacteria and cellular debris.

Thus, a suitable microorganism, such as those of the *Leuconostoc mesenteroides* or *L. dextranicum* types may be cultured on a sucrose-containing medium, the culture may be inoculated into a sucrose-bearing nutrient medium containing appropriate inorganic salts and nitrogenous material, and the mass may be incubated until the dextran is synthesized in maximum yield. This is so-called "whole culture" synthesis or synthesis in the presence of the bacteria and cellular debris. Or the enzyme dextranucrase may be produced in a separate step, filtered from the culture, and the filtrate, the enzyme isolated therefrom, or an aqueous solution of the isolated enzyme of suitable enzyme potency may be introduced into the sucrose-bearing nutrient and the mass held until the dextran is synthesized. This is the "filtered enzyme" method in which the synthesis is effected in the substantial absence of bacteria or cellular debris.

In either process, the native dextran obtained initially, which may be precipitated from the fermentate by the addition thereto of a water-miscible aliphatic alcohol or ketone, has a very high molecular weight calculated to be in the millions, and may be readily water-soluble, difficultly water-soluble or for all practical purposes substantially insoluble in water. Thus, the native dextrans obtained by the use of whole cultures of the microorganisms or their enzymes bearing the Northern Regional Research Laboratory classifications *Leuconostoc mesenteroides* B-512, B-1146, B-119, and B-1190 are readily soluble in water.

These readily water-soluble native dextrans, or native water-dispersible dextrans, may be used as such, after suitable purification, as bonding agent for the collagenous fibers or the native dextrans may be partially hydrolyzed to dextrans of lower molecular weight. So-called "clinical dextran," i. e., dextran which complies with the specifications established by U. S. military authorities, obtained in any suitable way, as by hydrolyzing the native (usually *L. m.* B-512) material to a molecular weight acceptable for intravenous injection (25,000 to 200,000, preferably 60,000 to 90,000) may be used and may be preferred. As is known, in the conventional production of clinical dextran, the native dextran is hydrolyzed under appropriately controlled conditions and the dextran of desired molecular weight is isolated from the hydrolyzate. This is usually accomplished by fractionation and, in addition to the medium fraction desired for clinical purposes, there are obtained a low fraction of molecular weight about 5000 to 50,000 and a fraction of very high average molecular weight. Any one of these water-soluble dextran products may be dissolved in water and applied to the collagen strand for adhesively bonding the components together and maintaining the integrity of the strand during tension-drying thereof. The extruded collagenous strand or twisted or plied extruded collagenous filaments may be treated with an aqueous 1% to 10% by weight solution or dispersion of the dextran after withdrawal from the coagulating and dehydrating bath and following the usual after-treatments, includ-

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ing final washing. In the case of sub mucosal ribbons or plied structures comprising them, these may be treated with the dextran solution or dispersion after withdrawal from the chrome or formaldehyde tanning bath. The dextran solution may be applied to the collagenous strand, or to the clean, tanned submucosal ribbons, in any way, as by spraying, immersion, or passage through a bath of the dextran solution. The collagenous strand or submucosal ribbons may be wound on a spool and treated thereon with the dextran solution. The collagenous strands carrying the dextran may be passed through a drying zone between godets or between a spool and a godet rotating to apply tension to the strand as it dries. If tanned or untanned submucosal collagenous combined ribbons or plies are treated with the dextran these plies can then be spun and dried under tension in the usual way, and prior to polishing thereof to the desired final diameter.

The final product is a compact integral structure which is uniform throughout its length, after polishing if necessary, and which may be used as a surgical suture without removing the dextran from it. The dextran, which adheres adhesively to the strand, bonds the collagenous fibrils or filaments, or the submucosal ribbons, firmly together, serves as a protective for the suture and being bland, non-toxic, non-irritating, and assimilable by humans and animals, it can be absorbed without harmful physiological effect.

The following examples are illustrative of specific embodiments of the invention.

Example I

A collagen solution is prepared as follows: kip skin is fleshed and unhaird down to the clean corium, that lamination of the animal hide containing the greatest proportion of collagen. The corium is cut into strips or small pieces and these are covered with a dilute solution of 0.05 to 0.10 N formic acid having a pH of 2-4. The corium is allowed to swell for 16 to 24 hours in the acid solution at 10-30° C., so that the swelling is effected without significant gelatine formation. The excess liquid is drained off and the swollen corium is mechanically shredded in a meat grinder to break down the collagen fibers to the point where dissolution will subsequently be facilitated. The dissolved collagen is separated under heating (40° C. maximum temperature) with agitation to insure complete solution of any traces of undissolved collagen, and then centrifuged to remove elastin, hair fragments and other insoluble matter. The solution is then filtered, as through cotton batting pads, to obtain a filtrate comprising a clear, heavily concentrated solution of collagen.

A 15% solution of the pure collagen in dilute acetic acid is extruded through a spinneret having orifices 0.004 mil. in diameter into a coagulating and dehydrating bath at 20-30° C. and comprising a 35% saturated solution of ammonium sulfate with sufficient free ammonia to maintain the bath at a pH of about 7.3. The thread thus formed is withdrawn from the bath by winding it up on a spool rotating to impart twist to the filaments and at a speed to impart a stretch thereof below their breaking point. The spooled thread is washed, run off the spool and through a bath consisting of a 3% by weight solution of B-512 "clinical" dextran, and thence passed through a drying zone in which it is heated at a temperature of 50° C., to a second spool rotating at a speed such that the impregnated thread is given a stretch of about 20%. A coherent uniform suture is thus obtained. It is sterilized and packaged in a sterile, germ-proof envelope for use.

Example II

Collagen fibers cut to a length of about 0.1 to 0.2 millimeters are suspended in dilute acetic acid at room temperature to obtain a 10% fiber suspension. The suspension is extruded under pressure through an elongated

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spinning tube having a bore of small diameter into a coagulating bath at 25° C. and comprising 25% by weight magnesium sulfate buffered with triethanolamine to pH 7.8. The strand or seemingly continuous filament comprising the multiplicity of longitudinally arrayed short fibers is withdrawn from the bath over a rotating godet, washed, passed through a 5% aqueous B-512 clinical dextran solution, and then through a drying zone in which it is heated to 50° C., to a second godet rotating at a peripheral speed such that the strand is stretched 50% as it dries. The compact, uniform strand thus obtained, in which the fibers are adhesively bonded by the dextran, is then sterilized and packaged in a sterile, germ-free glass tube for storage until it is to be used.

Example III

The small intestine of sheep are hydrated in water, and split lengthwise into two ribbons which are washed in sodium bicarbonate water in the usual way and scraped clean. Two of the cleaned submucosal ribbons are plied together and the plied structure is tanned in a formaldehyde bath in accordance with conventional practice. These tanned two-ply structures are then immersed for one minute in a 5% aqueous solution of purified native B-512 dextran. After withdrawal from the dextran bath, the structures are spun to form a wet suture, and the wet suture obtained is dried under tension and polished in the usual way.

The strands and twisted or plied structures may be used as surgical sutures or they may be used as tennis string or for any other purpose for which such products are useful.

Various changes and modifications may be made in details in carrying out the invention without departing from the spirit and scope thereof and, therefore, it is to be understood that the invention is not to be limited except as defined in the appended claims.

I claim:

1. A multi-component collagen strand the components of which are bonded together by dextran.
2. A multi-component collagenous surgical suture impregnated with dextran which bonds the components of the suture together.
3. A collagen strand comprising a multiplicity of discontinuous collagen fibers bonded together by dextran.
4. A collagen strand comprising a plurality of continuous collagenous filaments twisted together and bonded in the twisted relation by dextran.
5. A collagen strand comprising a plurality of submucosal ribbons plied together and bonded in the plied relation by dextran.
6. In the production of multi-component collagen strands, the improvement which comprises treating the strands, prior to tension-drying thereof, with a 1% to 10% by weight aqueous dispersion of dextran, whereby the strand is impregnated with dextran and the components thereof are bonded together by the dextran.
7. In the production of a collagen suture comprising a multiplicity of short collagen fibers, the improvement which comprises treating the strand, in the course of its production and prior to tension-drying thereof, with a 1% to 10% by weight aqueous dispersion of dextran, whereby the strand is impregnated with dextran and the short fibers thereof are bonded together by the dextran.
8. In the production of a collagen suture comprising a plurality of extruded continuous collagen filaments twisted together, the improvement which comprises treating the strand comprising the twisted filaments, and prior to tension-drying thereof, with a 1% to 10% by weight aqueous dispersion of dextran, whereby the strand is impregnated with the dextran and the filaments are bonded together in the twisted relation by the dextran.
9. In the production of a collagen strand comprising cleaned, tanned submucosal ribbons in plied relation, the improvement which comprises treating the ribbons prior to plying and tanning thereof, with a 1% to 10% by

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weight aqueous dispersion of dextran, and then plying a plurality of the ribbons together, and then spinning, tension-drying, and polishing the plied structure, the plies of the structure being held in bonded relation by the dextran.

10. In the production of a collagen strand comprising cleaned, tanned submucosal ribbons in plied relation, the improvement which comprises treating the ribbons, after plying and tanning thereof, and prior to the spinning, tension-drying and polishing steps, with a 1% to 10% by weight aqueous dispersion of dextran, and thereafter spinning, tension-drying and polishing the structure.

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