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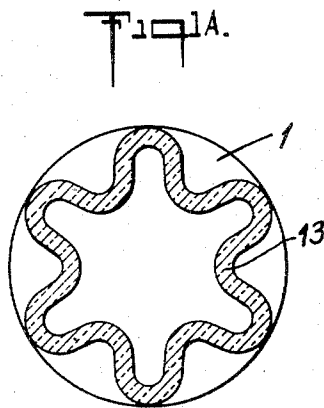
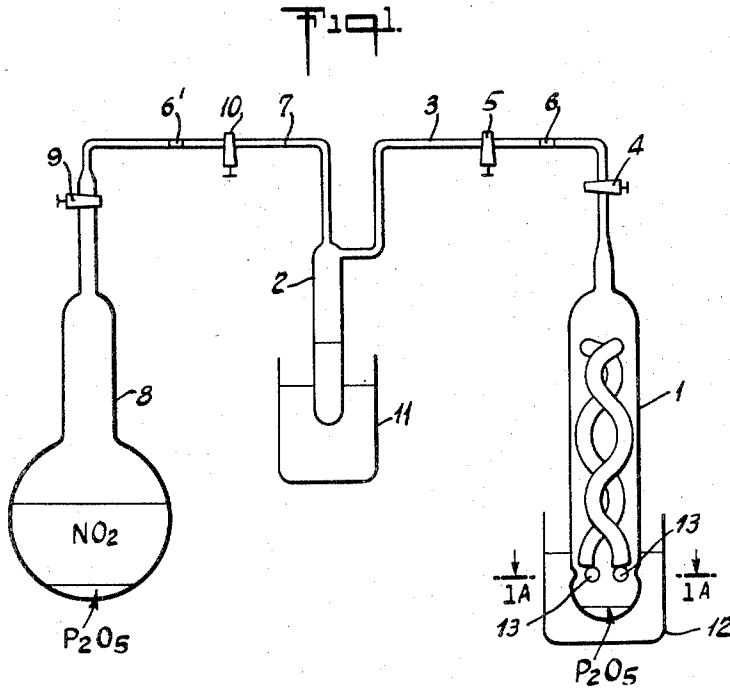
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OXIDIZED CELLULOSE SUTURE

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4 Sheets-Sheet 1



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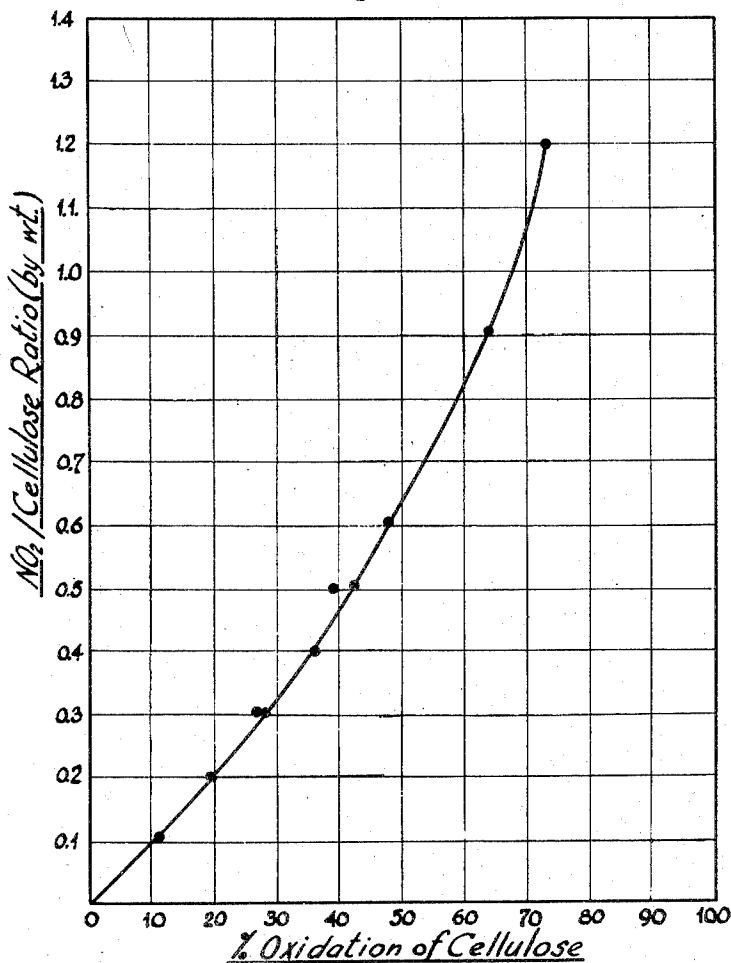
OXIDIZED CELLULOSE SUTURE

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Fig. 2.

*Degree of Oxidation of Cellulose obtained
with various NO_2 -Cellulose Ratios.*



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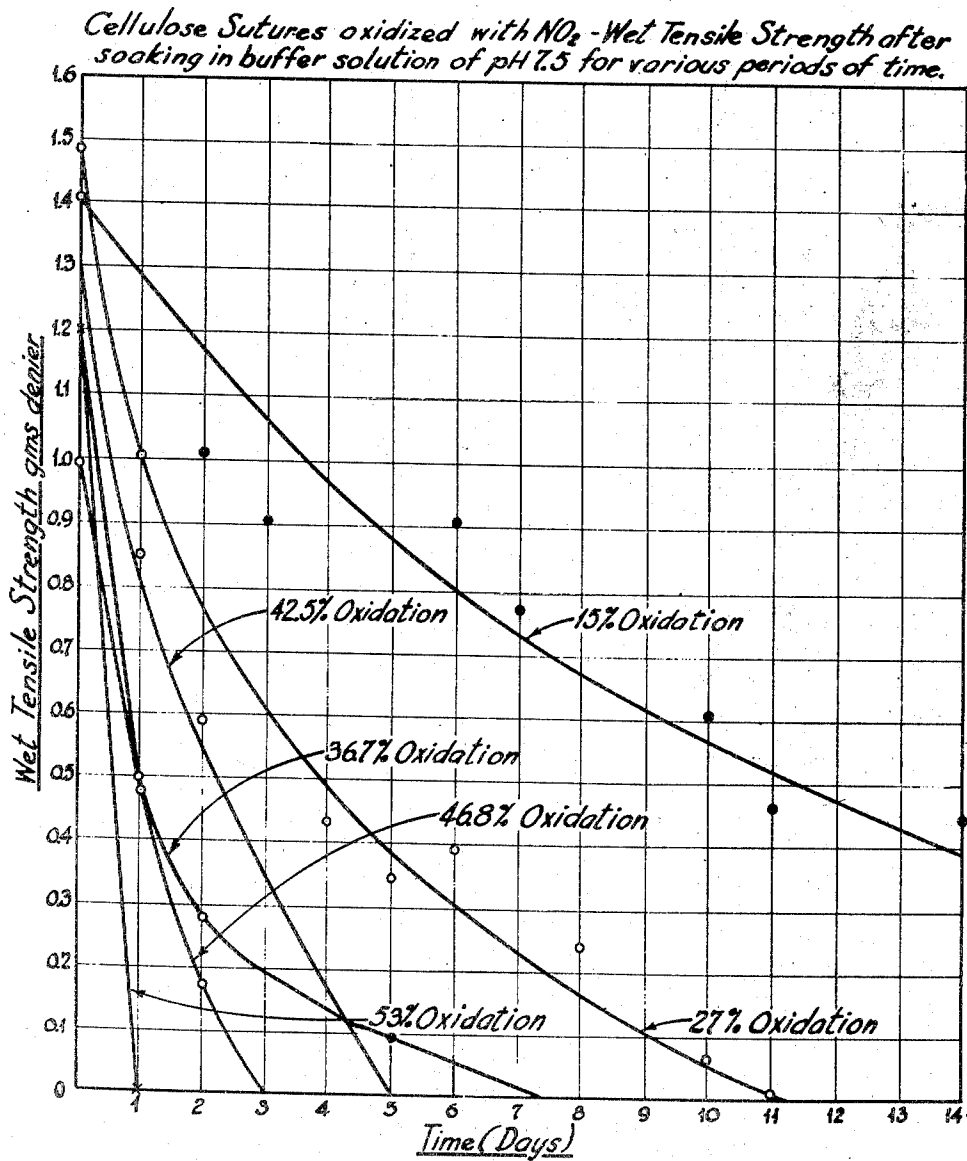
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Fig. 3.



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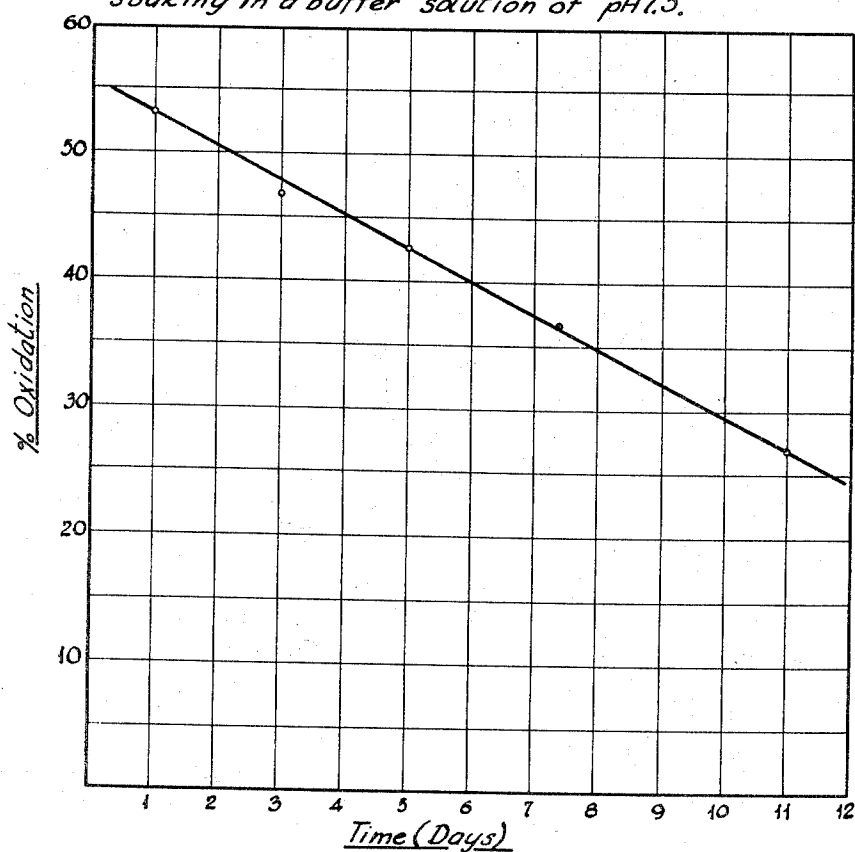
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Fig. 4

Time in days for Sutures oxidized to different percentages with NO_2 to go to Zero strength after soaking in a buffer solution of pH 7.5.



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UNITED STATES PATENT OFFICE

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OXIDIZED CELLULOSE SUTURE

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Application November 25, 1949, Serial No. 129,473

2 Claims. (Cl. 128—335.5)

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This invention relates to absorbable sutures made from oxidized cellulose threads.

Most absorbable sutures heretofore used have been of the catgut variety, although actually made from sheep intestines. These are non-homogeneous both as to strength and digestibility, due to differences in the structure of the sheep's intestines from end to end, differences in individual sheep, and seasonal variations. The best known manufacturing processes are uneconomical because of the low yields that are obtained and the high labor costs that are entailed.

These disadvantages are absent with oxidized cellulose sutures made in accordance with the instant invention. The improved sutures also possess many advantages in their own right. For example, the digestion time of an oxidized cellulose suture, i. e., the time required for the suture to disintegrate in human tissue may be fairly accurately controlled by adjusting the degree of oxidation. A surgeon's knot made with an oxidized cellulose suture has less tendency to slip than is the case with catgut. Such sutures are potentially less irritating to the tissue since they do not behave like dead tissue in the human system. They are non-proteinous in nature and hence do not provide a culture medium for saprophytic organisms. Their use thus reduces the chance of infection. Many other advantages inherent in the improved suture will be evident as the description of the invention proceeds.

It has been discovered in accordance with the invention that sutures meeting U. S. Pharmacopoeia standards as regards tensile strength, and strength over a surgeon's knot may be prepared by oxidizing strands of substantially pure cellulose to different degrees depending upon the ultimate rate of absorption the suture is to possess when in use, provided the initial strength and character of the cellulose thread or strand is such that after the oxidation processes, sufficient strength remains in the various categories to satisfy suture requirements.

According to U. S. Pharmacopoeia standards, catgut sutures of good quality possess a dry tensile strength in the neighborhood of 2 grams per denier. Knot strength requirements range from 1.0 to 1.4 grams per denier, the lower value relating to the smaller sizes of catgut (Nos. 00000 and 0000) and the higher value to the larger sizes.

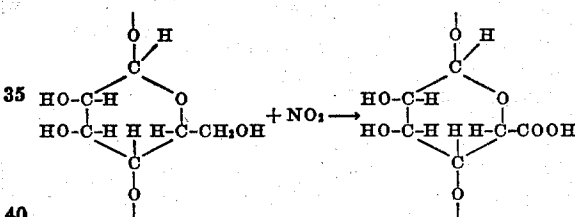
Absorption time for catgut, i. e., the period required for digestion in the human system, does not carry a U. S. P. designation. Catgut is merely classified as Type A Plain, Type C Medium Chromic and Type D Extra Chromic. Type C,

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under ordinary conditions in the striate muscle, retains its integrity from 10 to 20 days and Type A and Type D a shorter and a longer period of time, respectively. However, the absorption rate of catgut depends to some extent upon the condition of the patient, absorption being most rapid in a healthy man and slowest in young, aged, tubercular and anemic patients. In mucous membranes, the digestion rate is about four times as fast as in muscular tissue.

Oxidized cellulose sutures may be made in accordance with the invention having rates of digestion fully equivalent to catgut. Actually the digestion rate of the improved sutures may be forecast with greater accuracy than is possible for catgut since that of the former, at least to the point of zero strength, depends upon the pH of the body tissue whereas that of the latter depends solely on enzymatic attack. The pH is substantially constant from person to person and is also more constant throughout the body than is enzyme distribution.

The improved sutures are oxidized with nitrogen dioxide. The oxidizing action is selective to produce oxidized cellulose threads of definite and predictable characteristics and which will disintegrate by hydrolysis at the pH of body tissue. When cellulose is oxidized by nitrogen dioxide or its dimer, the primary alcohol is converted to a carboxyl group according to the following formula:



According to an article by E. C. Yackel and W. L. Kenyon, vol. 64 (1942) of the Journal of the American Chemical Society at page 121, in which the NO₂ oxidation is fully described, complete theoretical oxidation with nitrogen dioxide results in a carboxyl content of approximately 25%. The instant invention contemplates a partial oxidation with nitrogen dioxide which throughout the specification is defined in percentage on the basis of complete oxidation as 100% oxidation. In other words, 50% oxidation corresponds to a carboxyl content of approximately 12.5%.

In the accompanying drawings:

Fig. 1 is a diagrammatic illustration of appa-

ratus in which cellulose thread may be oxidized by nitrogen dioxide.

Fig. 1-A is a transverse section on line 1-A-1-A through the oxidizing chamber of the apparatus shown in Fig. 1.

Fig. 2 is a curve showing the per cent oxidation of cellulose for different nitrogen dioxide cellulose ratios.

Fig. 3 are curves showing the wet tensile strength of cellulose sutures, oxidized to different degrees with nitrogen dioxide, after soaking in a buffer solution of pH 7.5 for various periods of time.

Fig. 4 is a curve showing the time in days required for sutures oxidized to different percentages to go to zero strength after soaking in a buffer solution of pH 7.5.

This application is a continuation-in-part of application Serial No. 577,309, which became abandoned after the filing of the present application.

In preparing oxycellulose sutures in accordance with the invention it is necessary to start with cellulose threads of high initial tensile strength. Exact figures cannot be given because the required strength will vary depending upon the kind of cellulose thread used and its construction. However, since the oxidation of cellulose thread lowers its strength, it is necessary that the initial strength be high enough to enable the thread to undergo the oxidation process and still produce a usable suture.

The process of oxidizing cellulose threads by nitrogen dioxide may be substantially similar to that used by E. C. Yackel and W. L. Kenyon and described in their article previously referred to. Suitable apparatus is disclosed in Fig. 1 and includes, in part, a reaction chamber 1 which is closed at the bottom and a measuring chamber 2. These chambers are connected together at the top by a tube 3 which includes a pair of stop cocks 4 and 5 with an intermediate connecting seal 6. The measuring chamber is similarly connected by a tube 7 with a chamber 8 constituting a reservoir for a supply of liquid nitrogen dioxide. The tube 7 also contains a pair of stop cocks 9 and 10 and an intermediate connection 6'. The apparatus shown may be glass, although commercial runs may be made in apparatus otherwise designed.

The thread to be oxidized is located in the reaction chamber 1 where it is supported by any suitable means as by protrusions 13 upset inwardly from the walls thereof (Fig. 1-A) above the level assumed by the liquid NO_2 which is later introduced. To prevent the formation of nitric acid which, in a gaseous oxidation, has a deleterious effect on the strength of the oxidized threads, all moisture is exhausted from the reaction chamber with the aid of a vacuum pump. This may be done before the seal 6 is made. It may also be desirable to place a suitable amount of phosphorous pentoxide in both the chambers 1 and 8 to absorb any water that finds its way into the nitrogen dioxide.

An amount of pure liquid nitrogen dioxide (boiling point 21°C.) necessary to oxidize a cellulose thread the desired amount is then introduced into the reaction chamber 1. This is accomplished by closing the stop cock 5, opening the stop cocks 9 and 10 and distilling a measured amount of nitrogen dioxide from the chamber 8 into the measuring tube 2, the lower end of which may be located in a container 11 of ice and rock salts. The stop cocks 9 and 10 are then closed, 75

and the stop cocks 4 and 5 opened and the measured amount of nitrogen dioxide distilled into the reaction chamber 1 which likewise may be immersed at its lower end in a container 12 of ice and rock salts. After the measured quantity of nitrogen dioxide has been completely transferred to the reaction chamber, the stop cock 4 is closed and the container 12 removed to allow the nitrogen dioxide to assume its gaseous form. The reaction is allowed to proceed for a period (say 64 hours) which is sufficient to insure the maximum oxidizing effect for the amount of nitrogen dioxide used.

The amount or weight of nitrogen dioxide used will depend upon the weight of the cellulose thread undergoing oxidation and the percentage of oxidation desired. The relationship between per cent oxidation of cellulose and the nitrogen dioxide-cellulose ratio is shown in Fig. 2. The data for this curve may be found in the Yackel and Kenyon article.

At the end of the reaction time, the seal 6 is broken and the chamber 1 placed on a vacuum line for about two hours. The oxycellulose threads are then removed, thoroughly washed with distilled water to remove such nitric and nitrous acid as may have formed, and then dried.

Example I

7.55 grams of cotton thread, comprising a single strand were placed in reaction chamber 1. All moisture was exhausted from the reaction chamber by means of a vacuum pump, stop cock 10 being closed. A chamber 8 containing liquid NO_2 over P_2O_5 was sealed by a glass-to-glass seal to the section of the apparatus containing the reaction chamber. 3.4 grams of pure liquid NO_2 was introduced into reaction chamber 1. This was accomplished by closing stop cock 5, opening stop cocks 9 and 10, and distilling the NO_2 from chamber 8 into measuring tube 2, the lower end of which measuring tube was located in a container 11 holding an ice bath. Stop cocks 9 and 10 were then closed and stop cocks 4 and 5 were opened. The NO_2 in tube 2 was then distilled into reaction chamber 1 which was immersed at its lower end in container 12 containing an ice bath. Stop cock 4 was then closed and container 12 was removed from proximity with chamber 1, whereupon the NO_2 in chamber 1 changed from the liquid to the gaseous phase. The oxidation reaction was allowed to proceed for a period of about 64 hours. At the end of the reaction time seal 6 was broken and a vacuum line was attached to the top adjacent to stop cock 10 at the point where the seal was broken, and a vacuum was applied for a period of 2 hours. The thread was then removed, thorough washed with distilled water, and dried. An analysis of the thread showed that it was oxidized to the extent of 46.8%. The threads were placed in a solution buffered at a pH of 7.5. A weight of 398 grams (1.2 grams/denier) was required to break the wet strand after 5 minutes' immersion in the solution buffered at a pH of 7.5. A weight of 141 grams (0.48 grams/denier) was required to break the wet strand after 24 hours' immersion in the buffer solution. A weight of 59 grams (0.17 gram/denier) was required to break the strand after immersion in the buffer solution for 48 hours. The strand had gone to zero strength after 72 hours' immersion in the buffer solution and it required no measurable weight to break the wet strand after immersion in the buffer solution after 72 hours.

Example II

This experiment was conducted in the same manner as Example I except that the thread used weighed 7.45 grams, and the weight of NO₂ introduced into reaction chamber I was 3.3 grams. The washed and dried strand after removal from the reaction chamber showed on analysis that it had been oxidized to the extent of 36.7%. The thread was placed in a solution buffered at a pH of 7.5. A weight of 314 grams (0.99 grams/denier) was required to break the wet strand after 5 minutes' immersion in the solution buffered at a pH of 7.5. The wet strand required a 159 gram weight (0.50 grams/denier) to break it after having been immersed for 24 hours in the buffer solution. Eighty-nine grams (0.28 grams/denier) were required to break a wet strand after immersion for 48 hours in buffer solution; 27 grams (0.84 grams/denier) were required to break the wet strand after immersion for 120 hours in the buffer solution.

In the following table there is given, by way of example, the characteristic features of oxidized cellulose sutures prepared by oxidizing Egyptian cotton thread with nitrogen dioxide:

TABLE

	Diameter	Denier	Strength before treatment	Oxidation	Dry strength characteristics after oxidation	Wet strength characteristics after oxidation
	Inches		G./denier	Per cent	G./denier	G./denier
1	.0058	310	3.8	15	1.5	1.1
2	.0058	306	3.8	15	1.8	1.4
3	.0060	314	3.8	27	1.8	1.5
4	.0057	320	3.8	27	1.7	1.5
5	.0060	356	3.8	38	1.8	1.3
6	.0070	391	3.8	48	1.7	1.1
7	.0070	405	3.8	53	1.8	1.2
8	.0078	441	3.8	61	1.4	0.8

It will be observed from the foregoing table that cellulose thread oxidized with nitrogen dioxide up to about 55% will produce good suture material as far as strength is concerned. Wet strength which actually is the most important factor is greater than it is for catgut. The dry strength is somewhat less than the U. S. Pharmacopoeia requirements for catgut, although still adequate for suture material. Knot strength is adequate in all instances where the thread otherwise satisfies suture requirements. It might be mentioned that all figures given in the table represent an average of 10 readings.

The absorbability of oxidized cellulose sutures, i. e., the length of time they retain their integrity in use depends upon their degree of oxidation. Within the range of oxidation that produces acceptable sutures as regards strength, a range of oxidation may be selected that will result in a suture having a rate of digestion equivalent to catgut. The rate of digestibility of oxidized cellulose sutures may be obtained by soaking the sutures in a solution which simulates body conditions as, for instance, a phosphate solution buffered to pH 7.5 (pH of tissue) and maintained at a temperature of 37° C. Such a solution may be prepared as follows:

1000 cc. Na₂HPO₄ 12H₂O containing 23.88 g./liter
178.3 cc. KH₂PO₄ containing 9.078 g./liter

The oxidized cellulose threads of tests 2, 4, and 7 of the table and of Examples I and II were soaked in the above solution and the results plotted in Figure 3. The results indicate that a

thread with 27% oxidation goes to zero strength after about 11 days and a thread with 53% oxidation goes to zero strength in about 1 day. Threads of greater and lesser percentage oxidation lose strength in shorter and longer periods of time respectively. Within the range of from 27% to 53% oxidation there is a decrease in the time required for an oxidized thread to go to zero strength which is substantially linearly proportional to oxidation increase; for each 2.6% increase in oxidation, the time required to go to zero strength is one day less. This linear relationship is graphically shown in Figure 4.

By interpolation, one skilled in the art will be able to select the proper degree of oxidation necessary to produce a suture which will digest to zero strength at body conditions in any desired period of time. The curve in the drawing of Figure 3 which represents 42.6% oxidation is obtained by interpolation and no actual oxidation was made. Clinical tests confirm the results obtained under laboratory conditions. It might be added here that only rarely would it be desirable to prepare a suture having a digestion rate of less than five days. This invention is directed to

the provision of oxidized cellulose suture strands which will go to zero strength at the pH of body tissue (7.3-7.5) in a period of at least 5 days.

The standards for tensile strength of catgut sutures as given in the U. S. Pharmacopoeia are arbitrary and not necessarily applicable to sutures of the type comprehended herein. The dry tensile strengths of the improved sutures are, in many instances, superior to catgut. But, even when dry strength is inferior, wet strength—which actually is the most important factor—is oftentimes superior to catgut. Because of the many factors involved, it is quite impossible to arbitrarily place a numerical value on the lower limit of tensile strength the treated suture should possess. Any cellulose thread, treated in the manner described and which is strong enough to perform the function of a suture is within the scope of the invention. In the claims, therefore, this strength factor has been termed "suture tenacity."

It is also relatively difficult to fix quantitatively the maximum degree of oxidation for the cellulose thread. Therefore, in the claims, this has been defined as that which will cause the thread to proceed to zero strength at the pH of body tissue in not less than the period of time required for normal healing of a sutured wound, i. e., five days.

The invention has been described in its preferred embodiments but many modifications thereof are included within its spirit. It is to be limited, therefore, only by the scope of the appended claims.

What is claimed is:

1. A thread of suture tenacity comprising cellulose oxidized selectively with nitrogen dioxide by converting primary alcohol groups to carboxyl groups to an extent not greater than 42.6% of the theoretical oxidation with nitrogen dioxide, oxidation to this extent being sufficient to cause reduction of the thread to zero strength at the pH of body tissue (7.3-7.5) in a period of at least five days.

2. A thread of suture tenacity comprising cellulose oxidized selectively with nitrogen dioxide by converting primary alcohol groups to carboxyl groups to an extent within the range of from 42.6% to 27% of the theoretical oxidation with nitrogen dioxide, oxidation to this extent being sufficient to cause reduction of the thread to zero strength at the pH of body tissue (7.3-7.5) in a period of at least five days but in a period substantially not greater than eleven days.

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