ABSORBABLE COTTON, PAPER AND GAUZE*

(OXIDIZED CELLULOSE)

VIRGINIA KNEELAND FRANTZ, M.D.
NEW YORK, N. Y.

FROM THE DEPARTMENT OF SURGERY AND THE SURGICAL PATHOLOGY LABORATORY, COLLEGE OF PHYSICIANS AND SURGEONS, COLUMBIA UNIVERSITY, NEW YORK, N. Y.

FOR AT LEAST THIRTY YEARS, in the Department of Surgery of Columbia University, there has been a continuing interest in the possibility of finding a relatively nonirritating, absorbable material. Many chemical products were tested, but few offered enough promise to justify further investigation. Recently (1935) Dr. Hans Clarke, of the Department of Biochemistry, suggested polyvinyl acetate, which proved nonabsorbable in its fully esterified condition and too irritating after partial or complete hydrolysis. In 1941, he proposed a trial of oxidized cellulose which had just been prepared by Kenyon, and his collaborators[2, 3] (U. S. Pat. No. 2,232,990), Eastman Kodak Research Laboratories.†

The experiments here described, though less extensive than could be desired, are now reported, in view of the interesting and important results secured with the same material by Dr. Tracy J. Putnam,[4] of the Department of Neurology.

To the surgeon it is of some interest whether such a product is in the form of cotton, gauze or paper. The material first investigated was in the form of cotton; later, some oxidized paper, prepared by the same method, was secured, also through the kindness of Dr. Kenyon. This was in response to our desire for a nonirritating absorbable membrane which might be used to fill defects in such mesodermal structures as tendon sheaths and blood vessels. The cotton naturally suggested the possibility of hemostasis with a packing which would not have to be removed. This idea has been further extended to embrace oxidized gauze.

The introduction of these materials into the tissues of animals was, therefore, undertaken. The product used had been prepared by oxidizing long-fibered cotton with nitrogen dioxide for seven hours. It had the appearance of ordinary surgical cotton, slightly off white, and somewhat more friable. It was, as reported by Yackel and Kenyon,[2] soluble in dilute aqueous alkalis because of extensive carboxyl group formation during oxidation. It was, therefore, thought that the product should also be capable of gradual dissolution in the tissue fluids in contact with relatively undamaged tissue. It did not withstand sterilizaton in the autoclave, but it kept its tensile strength when boiled in water for three minutes. The sterilization so obtained

* Submitted for publication April 30, 1943.

† The writer wishes to express her appreciation of the information regarding this substance communicated by Dr. Kenyon, in advance of publication (1942).

is obviously not enough for use in human surgery, since spores would not be destroyed by this method, but if the material should prove useful this difficulty might be overcome, possibly by preparation and packing under sterile conditions.

Ten samples of oxidized paper were available a year later. These had been oxidized: (A) 1 hour; (B) 2 hours; (C) 3 hours; (D) 4 hours; (E) and (F) 5 hours; (G) 21 hours; (H) 29 hours; (I) 45 hours; and (K) 69 hours. The longer the oxidation the greater was the shrinkage of the paper from its original size, the greater the brittleness and surface glazing and the less the tensile strength, although the fiber structure was grossly maintained. Microscopically, however, possibly through further degradation in the process of paraffin embedding and staining, the fibers of the cotton and gauze do not have the usual glassy appearance with central canal seen in unoxidized material, but appear as homogeneous eosinophilic bands, difficult to distinguish from coagulated protein.

Preliminary experiments suggested that the more highly oxidized samples, which were more acid, were more irritating to the tissues, and as, after boiling, these samples tore very readily when wet, sample H, I and K were soon discarded. Sample G, 21-hour oxidation was used in the first series, since it was thought that the less oxidized samples might not be absorbed. Later, however, through a chance selection, it was found that sample D was absorbed, and this, after only four-hours oxidation, had considerably more tensile strength than sample G. The papers, kept for a year at room temperature in the laboratory, continued to change slowly, and samples G through K at the end of that time were so brittle and parchment-like that they could no longer be used.

In the first group of experiments the cotton, seven-hour oxidation, was introduced into the abdominal muscles of cats and dogs. This, as was the case in all of the procedures, was done with the animal under nembutal anesthesia, and with strict asepsis maintained. The abdomen was opened through a right rectus incision, and the parietal peritoneum over the transversalis exposed by gentle retraction. It was then incised, and a pocket made in the muscle by blunt dissection. The sample, a fragment about 4 x 3 x 2 mm., was introduced. The pocket was closed by a black silk suture in the peritoneum and fascia, placed at some distance away from the implanted cotton. The implantation was also as far as possible from the incision in the abdominal wall, to avoid risk of skin contamination. Some of the animals employed were those used in the introductory course in Second Year Surgery, and had, in addition to the deliberate introduction of the experimental foreign bodies, other procedures in the abdominal cavity. These, however, were clean operations. Nevertheless, the danger of contamination in this group was considered greater than in those done without the presence of numerous observers and with unskilled assistance. The results are shown in Table I. It will be seen that in eight cases, at and after four weeks, the cotton was absorbed, with varying degrees

TABLE I

OXIDIZED COTTON IN MUSCLE—SEVEN-HOUR OXIDATION

S.P.No.	Days	Absorption		Reaction	Comment
		Gross	Microscopic		
20121	4	0	0	0	Animal dying.
20129	9	0	0	Polys. Mild	
20050	14	±	±	F.B. Mild	
19093	28	+	+	Scar tissue	Class.*
19094	28	+	±	F.B. Very mild	Class. Tiny fragments microscopically.
19095	28	+	+	Polys. Abscess	Class. Abscess around suture.
19096	28	+	+	Polys. Intense	Class. Abscess around suture.
19110	28	+	+	Polys. Intense	Class.
19112	28	+	+	F.B. Mild	Class. Polys. around suture.
20613	35	+	+	Scar tissue	Suture in scar.
20614	35	+	+	F.B. Moderate	

of foreign body reaction and phagocytosis. Solution, in the true sense, is likely to be retarded in the presence of damaged tissue, where the buffering power of the fluids is reduced. The lack of reaction in the four-day test (Fig. 1) was thought probably due to the fact that the animal was failing steadily and perhaps was unable to produce any tissue response to the irritant.

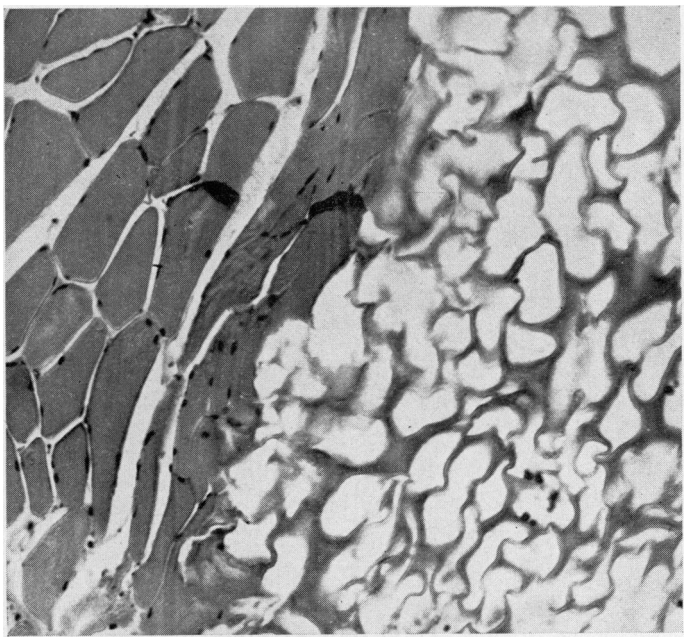

FIG. 1.—S. P. No. 20121: Photomicrograph. Oxidized cotton in muscle, four days. No reaction. This shows the appearance of the material when it has not been altered by the tissues, but after paraffin embedding, sectioning and staining.

In one case, S. P. No. 19094, a few microscopic fragments were found surrounded by giant cells. In the 14-day case there was partial absorption grossly and microscopically. There was in every case difficulty of distinguishing between a tissue reaction which might have been due to the cotton and that obviously expected from the presence of the black silk suture. The

* Where "Class" appears in Tables I and II, it refers to an animal used in class instruction.

suture was, of course, necessary for two reasons: First, to insure the sealing of the material in the pocket in the muscle; and, second, to mark the site.

The paper which was introduced into the muscle was sample G, oxidized 21 hours. Four of these animals were those in which the cotton had been introduced on the opposite side. It will be seen from Table II that in all but two of the seven implantations the paper was absorbed. The first case was that of the animal who lived only four days. The other was one of three animals, used also for class study, and sacrificed at the end of 26 days. The bulk of the material had been absorbed in this case, and what remained was microscopically fragmented. The nine-day absorption was a surprise, and it is possible that the wrong plane of section may have been taken, since the paper was very thin. None was seen grossly, however, on transillumination.

TABLE II
OXIDIZED PAPER IN MUSCLE—21-HOUR OXIDATION

S.P. No.	Days	Absorption		Reaction	Comment
		Gross	Miscoscopic		
20121	4	0	·0	0	Animal dying.
20129	9	+	+	F.B. Mild	
20150	14	+	+	F.B. Very mild	
20342	26	+	+	F.B. Mild	Class. Polys. around suture.
20343	26	±	0	F.B. Mild	Class. F.B. reaction around suture.
20344	26	+	+	F.B. Mild	Class.
20613	35	+	+	F.B. Very mild	

Further detailed work is obviously desirable to determine as nearly as possible the usual absorption time, but it is clear that the material is absorbed and that it excites a foreign body reaction which is not necessarily excessive. Again, it should be emphasized that the more the tissue damage, by operative trauma or bacterial action, the greater the inflammatory reaction and possibly the retardation of true solution of the material in the less alkaline medium.

The next tissue investigated was brain, with the idea of the possible value of the cotton in hemostasis. We are indebted to Dr. James G. Galbraith for the meticulous care with which he introduced this material into the parietal lobes of cats. Through a midline incision in the shaved scalp the right temporal muscle was retracted and a trephine opening was made in the right parietal bone. This was enlarged by rongeur to 1.5 cm. in diameter. A linear incision was then made in the dura over the posterior part of the cerebral hemisphere and, with a bayonet forceps by blunt dissection, the cortex was split. A No. 19-gauge cannula was introduced into the brain, anteriorly and medially, to a 15-mm. depth, and a small bit of oxidized cotton, 4 x 3 x 2 mm., was expressed into the subcortical white matter. The dura was closed by interrupted, fine silk sutures, and the wound in layers with interrupted silk. One case was controlled by also introducing, somewhat posteriorly, a piece of temporal muscle of about the same size as the cotton.

The results of these experiments may be seen in Table III. In S. P. Nos. 21218 and 21219 the cotton had been soaked in soluble thrombin[4] provided

TABLE III

OXIDIZED COTTON IN BRAIN—RIGHT PARIETAL LOBE—SEVEN-HOUR OXIDATION

S.P. No.	Days	Absorption		Reaction	Comment
		Gross	Microscopic		
20576	10	±	0	F.B. Mild	
21326	18	+	±	F.B. Intense	
21327	18	±	±	F.B. Intense	
21320	21	±	0	Polys. Necrosis	
21321	21	+	±	F.B. Mild	
20698	42	+	+	F.B. Mild	
21218	43	+	+	Inflam. Trace	Soaked in thrombin. Muscle control.*
21219	43	+	+	F.B. Trace	Soaked in thrombin.

by Dr. Tracy J. Putnam of the Department of Neurology. In these two cases there was less reaction to the damage than in any of the others. Both were 43 days after operation. It will be seen that in all instances there was some tissue reaction (Fig. 2), but this was mild in five out of eight, and was also elicited by the muscle implant. Absorption was incomplete at ten days. All three six-week cases showed complete absorption. In the 18- to 21-day period there was some variation. Unfortunately no four-week cases were done in this group, but it can be said that the material is absorbed in the brain some time between three and six weeks, is not unduly irritating, and provokes a minimum of glial reaction. All these animals recovered well from the procedure after a few days of lethargy, and showed no focal nor general signs immediately before autopsy.

In five instances oxidized paper was tested in relation to the dura. Four

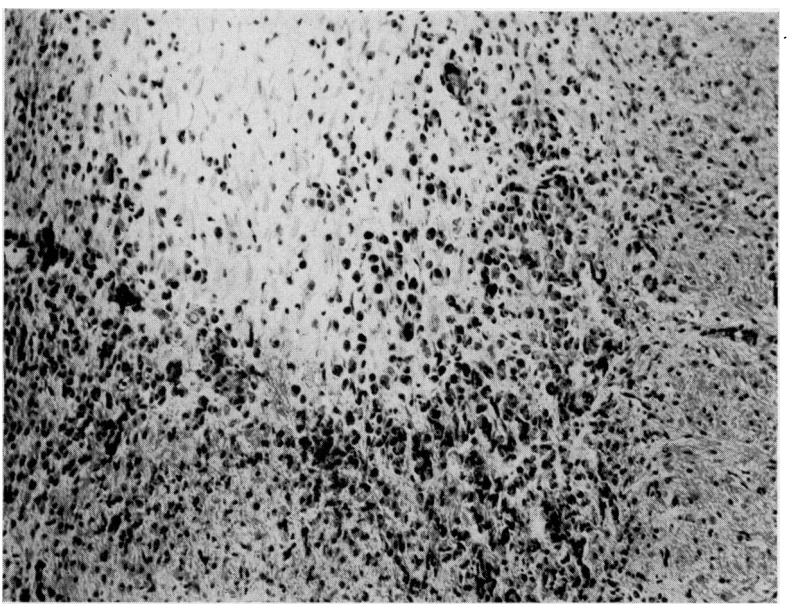

FIG. 2.—S. P. No. 20698: Photomicrograph. Oxidized cotton in brain, 42 days. None of the material remains. No polymorphonuclear leukocytes present. A few hemosiderin-laden phagocytes and slight glial proliferation.

* Muscle Implant Control: Muscle had been absorbed. Reaction the same as to the paper, *i.e.*, hemosiderin in phagocytes, slight glial proliferation, no multinucleated giant cells.

TABLE IV

S.P. No.	Days	Size in Mm.	Hours Oxidation	Absorption: Gross	Absorption: Microscopic	Reaction	Comment
			OXIDIZED PAPER—SUBDURAL				
20697	42	10 x 10	21	+	+	F.B. Mild	
21218	43	5 x 5	4	+	+	F.B. Mild	3 mm. gap in closure, dura.
21219	43	5 x 5	4	+	+	F.B. Mild	
			OXIDIZED PAPER—EPIDURAL				
21327	18	2 x 5	4	+	+	Abscess	Bone wax.
21321	21	2 x 5	4	+	±	F.B. Mild	

of these animals were those in which the cotton pledget had also been put in the brain. In three cases the paper was placed on the surface of the brain, twice over the puncture wound at the site of the cotton introduction, and once on the uninjured surface. The dura was then closed over the material with fine interrupted sutures. In two cases the paper was placed on the surface of the dura, over the opening which had not been sutured, thus making the closure in the wound. In both of these cases the animal also had the brain wound.

As will be seen in Table IV no paper was found in the three cases where

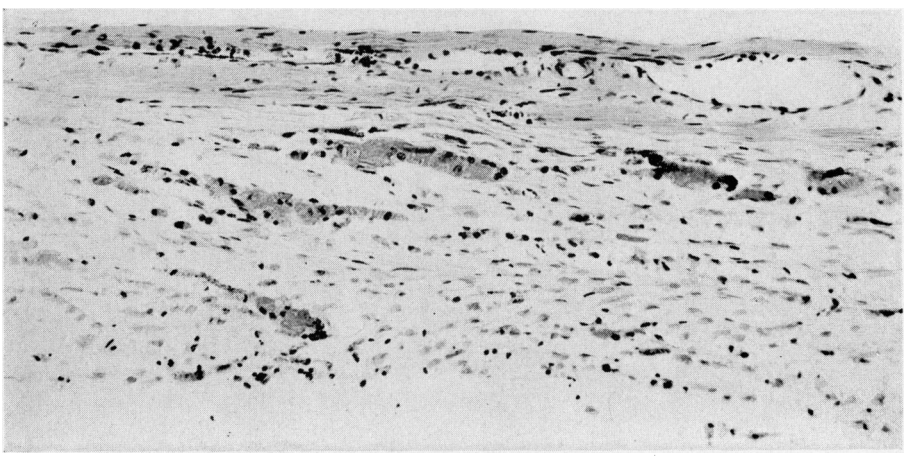

FIG. 3.—S. P. No. 21218: Photomicrograph. Oxidized paper, subdural, 43 days. No material remains. Few phagocytes present.

it had been placed between the brain and the dura. The incision in the dura was cleanly healed, there was no adhesion between the brain and the dura, and both surfaces were smooth and glistening. The disappearance was grossly complete. Microscopically, there were no polymorphonuclear leukocytes present and no multinucleated giant cells, but there were phagocytic mononuclear cells in the dura, often laden with hemosiderin (Fig. 3).

In the two cases where the dura had not been closed, and the paper placed over the defect, there was clean wound healing in one, but in the other there was an epidural collection of thick reddish-brown exudate in which gross particles of bone wax were seen. Microscopically, no paper was recognized in either of these instances, but there was a foreign body

TABLE V
OXIDIZED PAPER IN KNEE JOINT—FOUR-HOUR OXIDATION

S.P. No.	Days	Size in Mm.	Absorption		Reaction	Comment
			Gross	Miscoscopic		
21326	18	5 x 3	+	+	F.B. Mild	Trichinae
21327	18	5 x 3	+	0	F.B. Mild	
21320	21	5 x 3	+	+	F.B. Very mild	
21321	21	5 x 3	+	+	F.B. Very mild	

reaction which might have been due to the material, but also might have been associated with the bone wax. The repaired deep surface of the dura was smooth, however, and there were no adhesions between this and the brain. Since, microscopically, some foreign body reaction was found in all these wounds of the dura, it is not possible to say that the paper disappeared by true solution. However, in no instance was it so irritating that adhesions formed between the dura and the brain.

Because of our original hope of finding something to use as a non-irritating membrane for repair of tendon sheaths, and because of the dif-

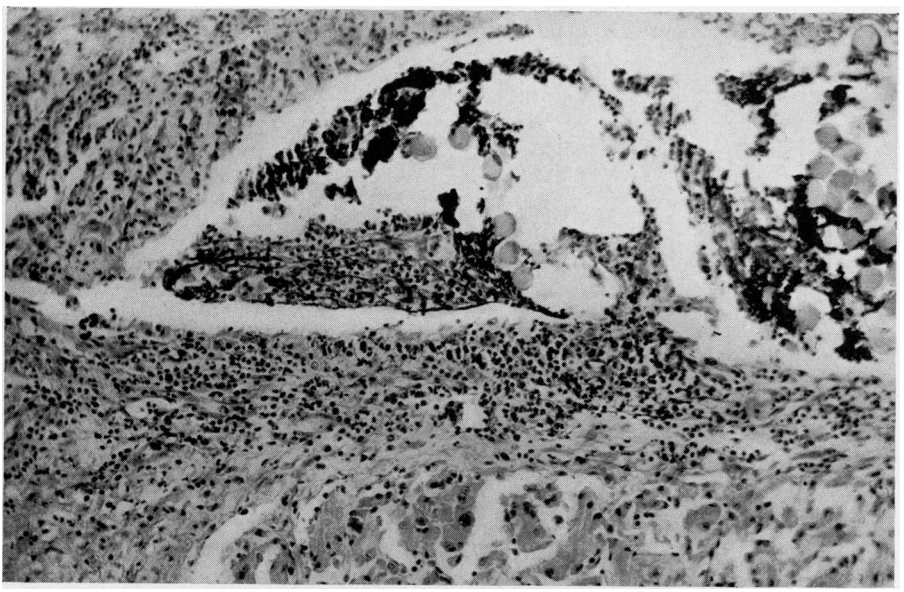

FIG. 4.—S. P. No. 21327: Photomicrograph. Oxidized paper in knee joint, 18 days. A fairly intense inflammatory reaction to the suture is seen in the upper portion of the photomicrograph, and a mild foreign body reaction to the paper in the lower portion.

ficulty of testing this out in animal tendon sheaths, the knee joint was used to determine the effect of the material on synovial tissues. The animals used were those who had also had, at the same operation, the craniotomy. This made them unusually suitable for joint surgery, since, for the first few days after operation, their lethargy caused them to avoid undue use of the extremity. The knee joint was opened through a lateral incision, and a strip of paper, sample D, four-hour oxidation, 4 x 2 mm., was introduced into the suprapatellar bursa. An effort was made in closing the defect with three interrupted eye silk sutures, not to place these in the synovial

membrane, but just outside. The skin was closed with four interrupted black silk sutures. As will be seen in Table V, at autopsy, in the first 18-day case no trace of the foreign body was found free in the joint where it had been placed, nor in the tissues outside. The joint lining was smooth, glistening and not injected, and the sutures lay well outside the cavity. There was, microscopically, a mild foreign body reaction but no evident paper fragments. An incidental finding was the presence of minute encysted trichinae larvae. In the second 18-day case there was, just to the lateral

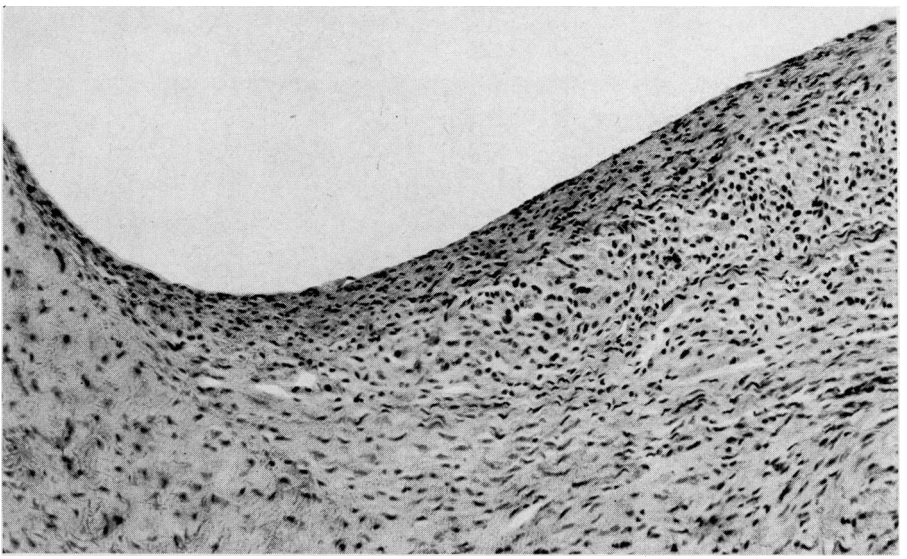

FIG. 5.—S. P. No. 21321: Photomicrograph. Oxidized paper in knee joint 21 days. There is slight thickening of the synovia, with a few lymphocytes and phagocytic cells.

side of the upper portion of the patella, an oval, slightly elevated pink zone, 6 x 3 mm. Otherwise the joint lining was smooth and glistening, without injection. There was no exudate. Microscopic examination of the red zone showed a localized mass of the material with a mild foreign body reaction, less intense than that around silk sutures in the same preparation (Fig. 4). In the two 21-day cases the knee joint showed no gross signs of inflammation and only a trace of foreign body reaction microscopically (Fig. 5). No material was found. In these four instances, at least, therefore, we have no evidence that the material causes undue inflammatory response in the joint such as might be followed by adhesions.

Oxidized cellulose in the form of gauze was then investigated. The shrinkage of this material is shown in Figure 6, and it is interesting that the texture of the oxidized samples is smoother and more silky than the original gauze, and, naturally, with the shrinkage, finer meshed. The 16-hour sample, however, was quite friable, and was only used once. The procedure was to deliver the omentum through a right rectus incision, onto warm moist pads. A square of gauze, 1.2 cm., was then laid on the surface, the omentum

TABLE VI

OXIDIZED GAUZE ON PERITONEAL SURFACE

S.P. No.	Days	Hours Oxidized	Absorption		Reaction	Comment
			Gross	Microscopic		
21364B	6	7	±	0	Polys. Intense	Second trauma.
21364A	7	7	+	±	Polys. Intense	More reaction to suture.
21329	11	7	+	+	F.B. Moderate	
21347	14	16	+	+	F.B. Mild	
21402	20	7	+	+	F.B. Trace	

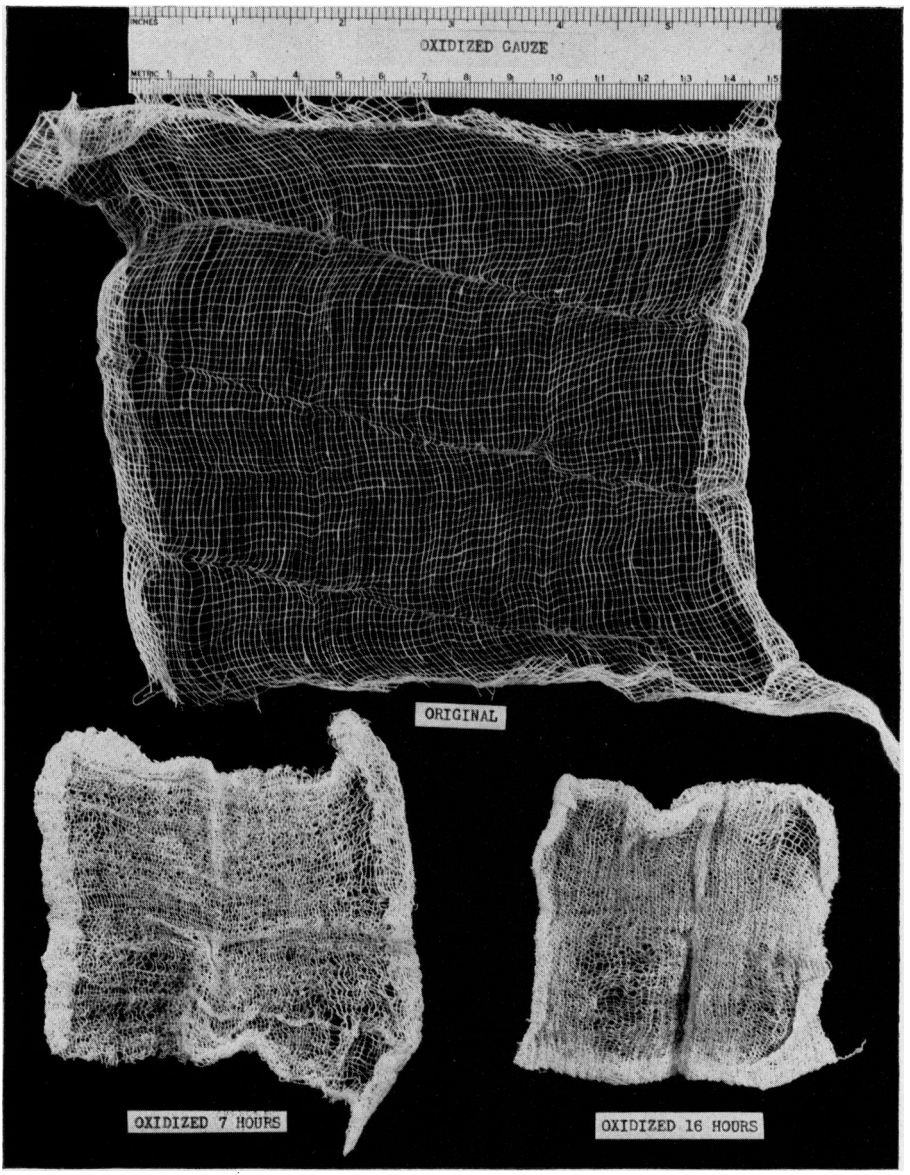

FIG. 6.—Photograph of three samples of gauze, all originally approximately the same size. Shrinkage following oxidation is illustrated.

folded over it, and tacked down with silk sutures which did not pass through the material. In the 11-day case the sutures used were a thread ravelled from the edge of the gauze itself. The results are shown in Table VI. The first case listed, six-days, is the same animal as the seven-day experiment. An exploratory operation was performed, seven days after the first procedure. The omentum was found to be thickened in the neighborhood of the marking sutures. This portion was amputated, after suitable hemostasis had been secured by ligature, and a second piece of gauze, rolled this time instead of flat, was placed in the folded, already traumatized. omentum. On reexploration at six days much greater thickening was found than previously, but there were no other signs of inflammation about the gauze. Around the ligatures, however, there was redness as well as swelling. The gauze appeared as a sticky, light brown fluid and semi-

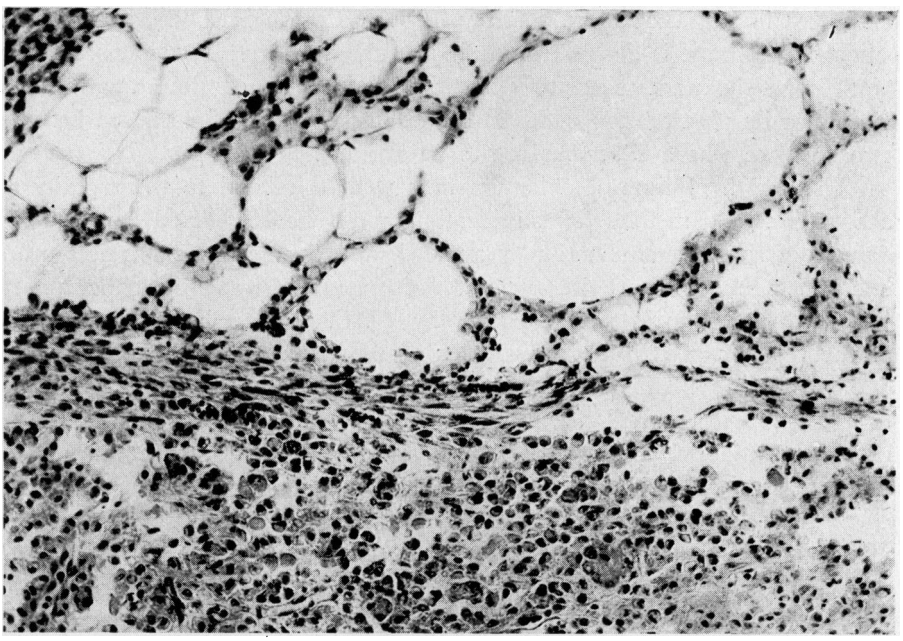

FIG. 7.—S. P. No. 21329: Photomicrograph. Oxidized gauze in omentum, 11 days. No material remains. Mononuclear and multinuclear phagocytic cells are seen and some foamy fat cells.

solid material lying in a smooth cavity. Microscopic examination showed an intense inflammatory reaction both to the foreign body and the ligatures, with polymorphonuclear leukocytes present in each case. More dilated blood vessels were seen about the sutures than about the gauze. At 11, 14 and 20 days no gauze remained. There was thickening in the omentum in each case, but no more inflammatory reaction than might have been expected from the operative trauma and the sutures (Fig. 7).

SUMMARY

Oxidized cellulose in the form of cotton, paper and gauze was found to disappear in muscle, brain, dura, joint and peritoneum of dogs and cats.

Control experiments of unoxidized material were not made because of the universal experience that gauze and cotton are not absorbed, and our familiarity with the reaction of the tissues to these materials.

In all but one instance there was some tissue reaction, and in this case the cotton was not absorbed. How much the disappearance of the material is due to true solution and how much to solution after digestion by phagocytes it is not possible to say. Not much proliferation of connective tissue, nor of glia was found. No adhesions were formed between the dura and the brain or within joints.

CONCLUSIONS

A relatively nonirritating foreign material, oxidized cellulose, has been tested. It is hoped that, after further observations to determine the oxidation time associated with the most favorable properties, this may be employed in hemostasis and possibly in protecting injured surfaces where a smooth membrane is desired in the final healing. For this latter use further work must be undertaken to determine the length of time the material maintains its physical properties in the tissues when it is interposed between two surfaces where adhesions are to be avoided.

The length of time of oxidation may well be related to the rapidity of absorption. A method of sterilization must be developed so that all danger of spore contamination is avoided, and the desirable physical properties of the material are not altered. It is suggested by earlier experimental work with celloidin in this laboratory by W. C. Clarke,[1] in 1916, that some of the reaction observed with samples of the new material may have been due to contact with the skin of the investigators. The material was handled to a considerable extent before it was boiled for use, and epithelial débris may have adhered to it. New samples, not fingered except with gloves, will be tried. The degree of irritation to the tissues from any cause, however, does not seem to be extreme, and is usually less than that from the nonabsorbable sutures so freely used in plastic work.

REFERENCES

[1] Clarke, William Cogswell: Experimental Mesothelium. Anat. Rec., 10, 301–316, 1916.

[2] Yackel, E. C., and Kenyon, W. O.: Oxidation of Cellulose by Nitrogen Dioxide. Jour. Am. Chem. Soc., **64**, 121, 1942.

[3] Unruh, C. C., and Kenyon, W. O.: Investigation of the Properties of Cellulose Oxidized by Nitrogen Dioxide. Jour. Am. Chem. Soc., **64**, 127, 1942.

[4] Putnam, Tracy J.: The Use of Thrombin on Soluble Cellulose in Neurosurgery: Preliminary Note. ANNALS OF SURGERY, **118**, 127, July, 1943.