Bouginage and Steroids Used Singly or in Combination in Experimental Corrosive Esophagitis

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Corrosive esophagitis with the associated acute complication of esophageal perforation and the disabling sequelae of stricture formation continues to be a serious problem.

Historically, bouginage, popularized by Salzer [16] in 1920, and more recently therapy with corticosteroids [8, 5, 12] have appreciatively reduced the incidence of stricture. It must be emphasized that careful study of many such recent series reported in the literature shows that a significant percentage of patients had sustained only superficial esophageal burns. In the deep caustic burn where necrosis has extended to, and often has included the esophageal muscularis, the incidence of subsequent stenosis, however, it still significant.[4] In such burns esophageal stricture formation can be as high as 27% despite early and intensive antibiotic-steroid therapy.[3]

The present study was undertaken to evaluate the effectiveness of steroids and bouginage separately, and in combination, in preventing stricture formation in a standardized segmental caustic burn in the canine esophagus. The technic eventually employed resulted in a reproducible sodium hydroxide burn of a segment of the distal esophagus which was comparable to the severe corrosive esophagitis sustained by patients. Surviving animals, maintained on antibiotic therapy for a minimum of 3 weeks postoperatively, were evaluated for periods up to 6 months following the burn. The follow-up period is significantly longer than has previously been reported for an experimental study of this type.

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Experimental Technic

A total of 114 mongrel dogs were used in the course of the study which subtended a 2-year period. In each animal a segmental alkali burn of the distal esophagus was performed in the following manner:

Under intravenous Nembutal endotracheal anesthesia a nasogastric tube was inserted into the esophagus. A left thoracotomy was performed, and a 4-cm. segment of the distal one third of the esophagus was isolated between umbilical tapes. The nasogastric tube was advanced until its tip was contained within the isolated segment. The umbilical tapes were then tied. Care was taken not to injure the esophageal wall or the esophageal blood supply. Ten per cent sodium hydroxide (2.5N) was introduced into the isolated esophageal segment via the nasogastric tube to fill, but not overdistend the esophageal segment. The corrosive chemical was in contact with the entire mucosal surface of this segment for 60 seconds. The caustic solution was then aspirated from the segment via the nasogas-

tric tube, and the isolated segment gently lavaged three times through the same tube with distilled water. The duration of each lavage was 15 seconds. The occluding tapes were then removed and the thoracotomy incision closed. Each animal on the day of operation received 1.2 million units of Bicillin intramuscularly, and a similar amount was administered at weekly intervals thereafter. The antibiotic was continued for a minimum of three weeks postoperatively in all animals. All dogs were weighed at weekly intervals and observed for evidence of excessive salivation, food regurgitation, infection, and pneumonia.

Gross and microscopic examinations were performed of each esophageal burn on the death or sacrifice of the animal. Initially routine esophagoscopies were carried out in selected dogs, but this was found an unreliable method of documenting the progression of the esophageal stenosis. Barium x-ray studies were quite suitable to authenticate objectively changes in the injured esophageal segment. Such barium studies were undertaken at intervals of 1 week, 1 month and thereafter at 2-month intervals postoperatively in all animals. These esophagograms were done under endotracheal anesthesia with the contrast material introduced via a nasogastric tube.

A final series of 68 dogs was derived from the total of 114 dogs. This series had the esophageal lesion well shown by periodic barium esophagograms. The necessity for the total of 114 animals emphasizes the trial and error efforts needed to obtain a reproducible deep caustic burn with low operative mortality rate. A significant numzer of dogs were eliminated early in the study because of difficulties in establishing a safe control method. Variables encountered in establishing the burn control included the concentration of sodium hydroxide, the duration of exposure of the mucosa to the caustic substance, and the degree of distention of the esophageal segment with the caustic solution. Over-distention of the esophageal segment produced a high incidence of esophageal perforation, usually occurring within one week of the burn.

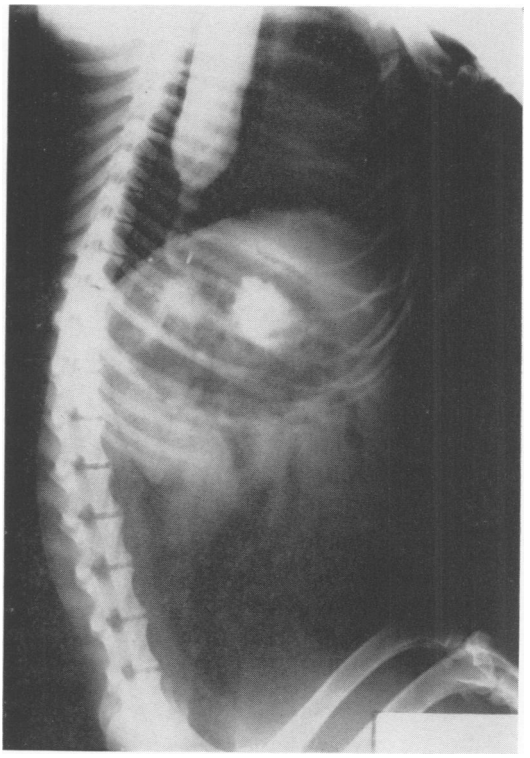

FIG. 1A. Barium esophagram in control dog showing moderate stenosis at 13 days postburn.

The 68 animals comprising the study were divided into five categories as follows (Table 1): 1) 20 dogs served as controls; 2) 12 dogs were treated by bouginage alone. Dilatation was done with a mercury-weighted #40 French bougie. Bouginage, performed under endotracheal anesthesia, was started on the seventh post-burn day and was repeated every 3 or 4 days for 2 months following the burn or as long as the animal survived. Bouginage performed before 7 days postburn resulted in a prohibitive mortality, as has been reported by Hardin[9] and Fatti[7]; 3) Nine animals received Prednisolone intramuscularly starting on the day of operation in dosage of 0.5 mg./Kg./day for a total of 60 days postburn or for as long as the dog survived;

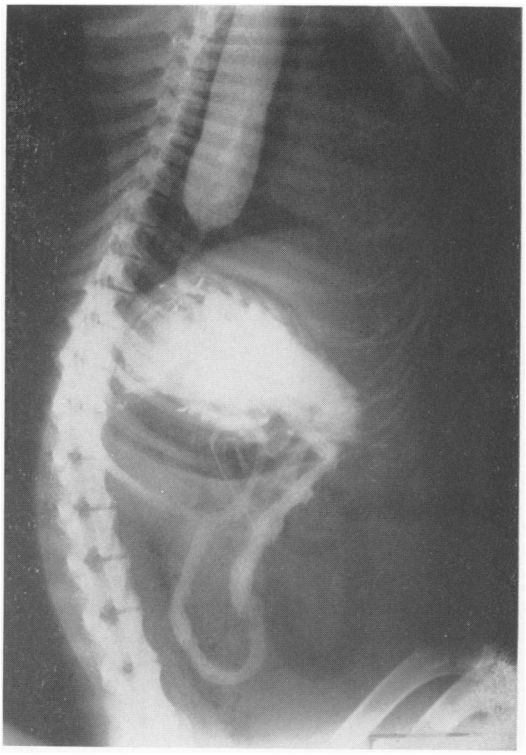

FIG. 1B. Same animal as in Figure 1A, 22 days postburn, showing progression of stenosis.

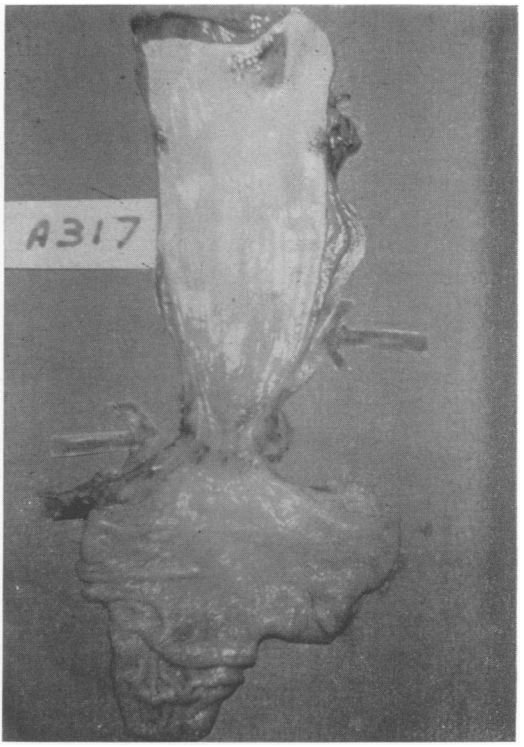

FIG. 1C. Esophageal segment of dog shown in Figure 1A, B, demonstrating a severe cicatrix (22 days).

4) Twelve dogs received Prednisolone intramuscularly 0.1 mg./Kg./day beginning on the day of operation and maintained for the survival time of the dog (one animal, surviving 225 days, received this daily dosage for a total of 160 days postburn); 5) Fifteen animals were treated with a combination of Prednisolone (0.1 mg./Kg./day) and bouginage. The latter was started on the seventh postburn day and continued as described in the Group II animals. Bouginage was performed at four day intervals for all surviving dogs for 30–40 days postoperative. The Prednisolone was maintained for survival time, which often was as long as 150–160 days postburn in the long-term survivors.

Results

Group I. Controls (Table 2). In the 20 control dogs the degree of stenosis, as determined by serial barium studies, was defined as follows: A) *minimal stenosis*—No stricture, or minimal radiographic deformity; no proximal esophageal dilatation; B) *moderate stenosis*—Narrowing up to 25% of the diameter of the normal esophageal lumen with some luminal dilatation proximal to the stenotic segment. C) *severe stenosis*—Narrowing of the luminal diameter to more than 25% of the normal esophagus. All animals with complete stenosis were included in this group.

Pathology. Despite standardization of the operative technic, there was some variation in the burn created. This was due probably to the degree of secondary infection at the burn site, and differences in host resistance and fibroblastic response among the control dogs. All animals, however, by clinical standards [4] sustained a severe, corrosive esophagitis. The depth of injury was classified as follows: 1) *Partial-*

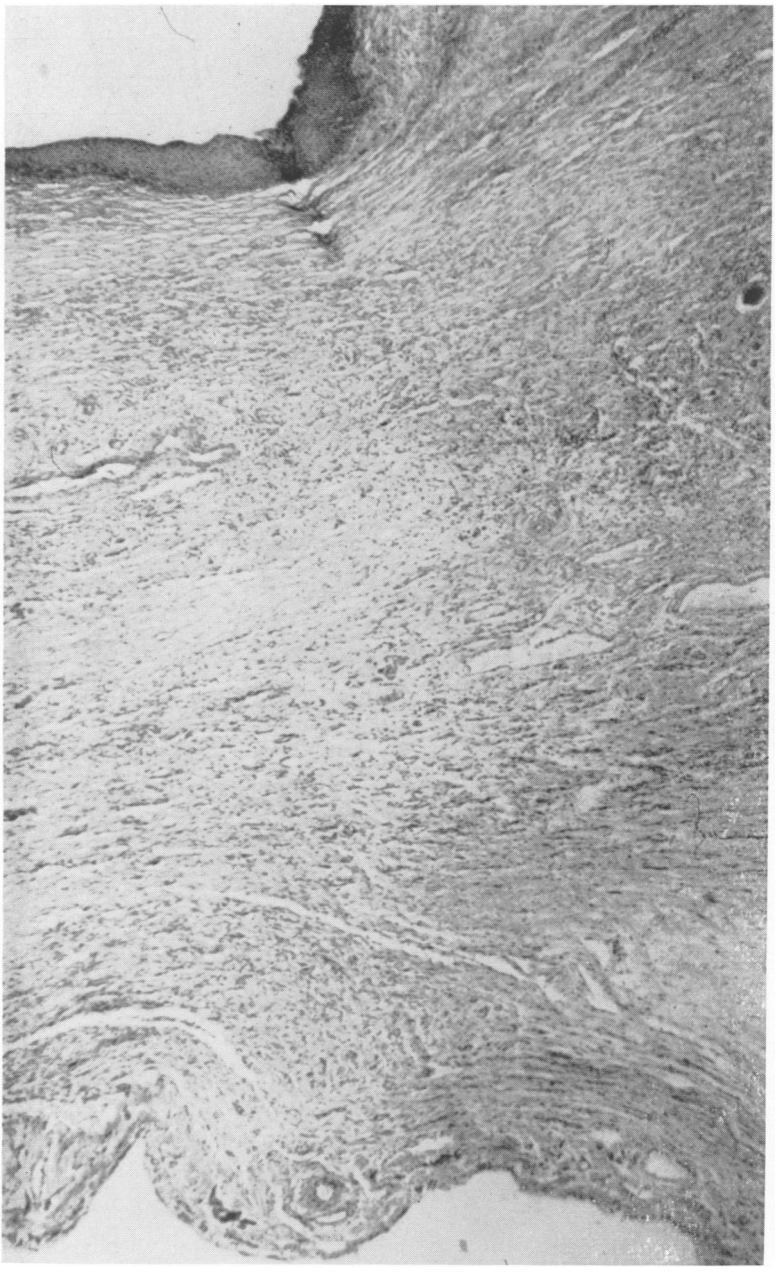

FIG. 1D. Photomicrograph of esophagus seen in Figure 1C demonstrating a full-thickness burn with replacement of all layers by mature connective tissue. (H and E, ×50.)

thickness burn—There were areas of denudation of the mucosa, and the submucosa was replaced by chronically inflamed granulation tissue with superimposed acute inflammatory cells. Other parts of the submucosa were replaced by varying degrees of maturing connective tissue; 2) *Partial-thickness burn with extension into the muscularis*—Similar mucosal and submucosal changes were seen, and part of the circular muscularis was replaced by granulation tissue or mature connective tissue or both; 3) *Full-thickness burn*—Similar changes in the mucosa and submucosa as in the partial thickness burn with complete replacement of both layers of the muscularis with

FIG. 2A. Esophagus of dog 26 days following burn. Bouginage started on 9th post-burn day and repeated at 4 day intervals until sacrifice.

granulation tissue in varying stages of maturity or mature connective tissue. Often periesophagitis was seen.

Minimal stenosis developed in two of the dogs; unfortunately, both of these animals died of pneumonia within the first week. Nine animals developed moderate stenosis. The length of survival averaged 129 days. Despite the partial stricture, the dogs had little difficulty in swallowing after the early postoperative period. Their weight remained stable, and they remained in a healthy condition until they were sacrificed. Nine animals which developed marked stenosis (Fig. 1A, B, C) were observed for an average survival time of 25 days and were sacrificed because of regurgitation of food, increasing weakness, weight loss, eventual inanition or pneumonia. It is of interest that no perforations occurred within the first week in any control animals, and subsequently only one out of the 18 surviving animals later developed a perforation. This complication occurred on the 11th postoperative day in an animal with moderate stenosis, probably the result of undiagnosed infection beneath the area of burn.

TABLE 1. *Composition of the Study*

Group	Title	Number of Dogs
I	Control	20
II	Bouginage	12
III	Prednisolone, 0.5 mg./Kg./day	9
IV	Prednisolone, 0.1 mg./Kg./day	12
V	Bouginage + Prednisolone, 0.1 mg./Kg./day	15
Total		68

TABLE 2. *Group I, Control*

Degree of Stenosis	Number (%)	Perforation (%)	Aver. Survival
Minimal	2	0	6 days*
Moderate	9	1	129 days
Severe	9	0	25 days
Total	20	1	

* Deaths due to pneumonia (5, 7 days).

It is to be emphasized that each of the three histological burn categories represented a severe, corrosive esophagitis. The three depths of burn were evenly distributed among control animals. A definite correlation between the degree of stenosis and the depth of the burn could not always be made. A full-thickness burn was usually associated with severe esophageal stenosis (Fig. 1D). Significantly, in no animal with a full-thickness injury was there a perforation. Those animals with moderate stenosis usually had a partial-thickness burn, often, however, with some necrosis of the muscularis.

Group II. Bouginage (Table 3). Twelve dogs were treated by bouginage alone. There were no deaths from bouginage, which was performed under general anesthesia. No dogs developed minimal steno-

FIG. 2B. Full-thickness esophageal burn in different animal in bouginage-treatment group, also with severe stenosis, sacrificed on postburn day 15. (H and E, ×50.)

sis. Four dogs developed moderate stenosis, with an average survival of 188 days. The remainder of this group, 8 of 12 dogs, or 67%, had severe stenosis in the burned area (Fig. 2A, B). This latter group survived for an average of 32 days. The high incidence of severe stenosis may have been due to the repeated trauma of dilatation, with recurrent mucosal fissures, and tearing of newly formed fibrous tissue, which resulted in excessive, infected, granulation tissue with subsequent increased cicatrization. Significantly, however, no perforation occurred in the bouginage group.

It was shown that animals may develop moderate or marked stenosis, possibly due

TABLE 3. *Group II, Bouginage*

Degree of Stenosis	No.	Perforation (%)	Aver. Survival
Minimal	0	0	0
Moderate	4	0	188 days
Severe	8	0	32 days*
Total	12	0	

* 2 deaths due to pneumonia (15, 42 days).

TABLE 4. *Group III, Prednisolone, 0.5 mg./Kg./day*

Degree of Stenosis	No.	Perforation (%)	Aver. Survival
Minimal	4	0	140 days
Moderate	3	3	24 days
Severe	2	0	64 days
Total	9	3	

TABLE 5. *Group IV, Prednisolone, 0.1 mg./Kg./day*

Degree of Stenosis	No.	Perforation	Aver. Survival
Minimal	2	2	5 days
Moderate	2	1	135 days*
Severe	8	0	47 days**
Total	12	3	

* 1 survivor, 255 days; 1 perforation, 15 days.
** 1 death due to pneumonia (12 days).

TABLE 6. *Group V, Bouginage and Prednisolone, 0.1 mg/Kg./day*

Degree of Stenosis	No.	Perforation	Aver. Survival
Minimal	9	0	184 days
Moderate	3	0	177 days
Severe	3	0	17 days*
Total	15		

* 2 deaths due to pneumonia (13, 16 days).

to edema, within 7 to 9 days following the burn. At that time, however, a #40 French bougie could still be passed without difficulty. During a critical period from the 7th to 14th postoperative days bouginage was essential to maintain the esophageal lumen. If dilatation was not performed at least once during this critical period, severe stricture was noted by the fourteenth day postburn. Further, bouginage performed at intervals of every 3 to 4 days after the initial week did not always prevent complete esophageal stenosis from developing. However, complete occlusion in these cases was usually delayed until 21 to 28 days postburn. Eventual failure of bouginage occurred in five animals in this group.

When bouginage was performed every three or four days with #40 French bougie, the stenosis was usually slightly less at the critical period of one month postoperatively as compared with one week postoperatively. In three of the four dogs moderate stenosis did not progress after the first month postoperatively if bouginage were continued on the same schedule for a second month. Bouginage was unnecessary after two months. Such animals, observed up to six months, showed no further progression of stenosis.

Pathology. Full-thickness injury of the esophageal wall was usually present. In contrast to the control series this was associated with only a moderate, rather than a severe degree of stenosis. With the exception of more cicatrix formation, the histological changes (Fig. 2B) were similar to those found in the controls during either the first few weeks or at several months following the initial injury.

Group III. Prednisolone 0.5 mg./Kg./day (Table 4). Nine animals received Prednisolone in dosage of 0.5 mg./Kg./day starting on the day of operation. Four developed minimal stenosis and survived an average of 140 days. Two with severe stenosis had to be sacrificed at 57 and 71 days because of inanition and progression of the stenosis to complete esophageal occlusion. Three perforations occurred, all in animals with moderate stenosis, on the 17th, 24th and 30th postoperative days (Fig. 3A).

This represented the highest incidence of esophageal perforation in the study.

Pathology. Histopathological changes of importance were thinning of the esophageal wall and diminished fibroplasia (Fig. 3B). Scanty strands of eosinophilic, collagenous material extended through fibroblast-capillary network. There were no sheets of dense, relatively acellular mature connective tissue. These changes could be correlated with the subsequent complication of esophageal perforation. In two of the three animals with perforation there was either a full-thickness burn, or a partial-thickness burn involving the muscularis. This was in contrast to the control group where a full-thickness burn was not associated with perforation, illustrating the reduction of fibroblastic response by the steroid therapy.

Group IV. Prednisolone 0.1 mg./Kg./day (Table 5). In Group IV, 12 dogs each received 0.1 mg. Prednisolone/Kg./day. Two of these animals developed minimal stenosis, and both died of esophageal perforation with five days of the sodium hydroxide burn. Two animals developed moderate stenosis, and one perforated on the 15th postoperative day. The remaining animal with moderate stenosis survived 255 days before being sacrificed. This was the only long-term survivor in this group. It is of interest that the remaining eight animals developed severe stenosis, an incidence similar to the bouginage group. It should be stressed that the rate of progression of stenosis in these animals was noticeably slower than in the control group, particularly during the first two weeks; the average eventual survival, 47 days, was of course shortened in the above eight animals because of the severe esophageal cicatrization.

Pathology. The pathological examination revealed changes which were similar to those previously described in the control group. The degree of fibroplasia, although occurring later, was similar to the controls.

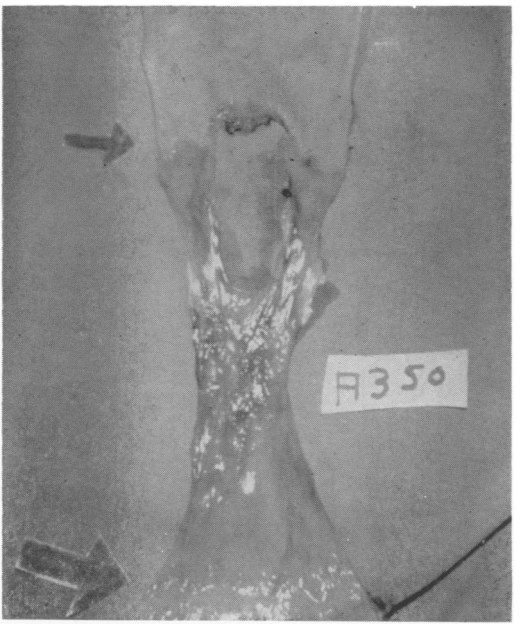

FIG. 3A. Esophageal perforation in dog receiving 0.5 mg. Prednisolone/Kg./day, occurring on 24th postburn day.

Group V. Bouginage and Steroids, 0.1 mg./Kg./day (Table 6). Fifteen animals were studied in the combination-treatment group. Nine animals developed minimal stenosis, and three developed moderate stenosis. Three developed severe stenosis, the lowest incidence in the study despite the presence of the severe esophageal injury. These represent the best results found within the five groups. Significantly, no esophageal perforations occurred in either the acute phase or during the period of cicatrization.

There was less resistance encountered during bouginage of the area of cicatrization. In this group of animals bouginage was performed every three to four days for the first month, and at the end of this month the luminal diameter was greater than in those animals treated by bouginage alone (Fig. 4A).

Pathology. Histological examination indicated that a full-thickness or deep partial-thickness injury had been sustained. This was associated with minimal or moderate

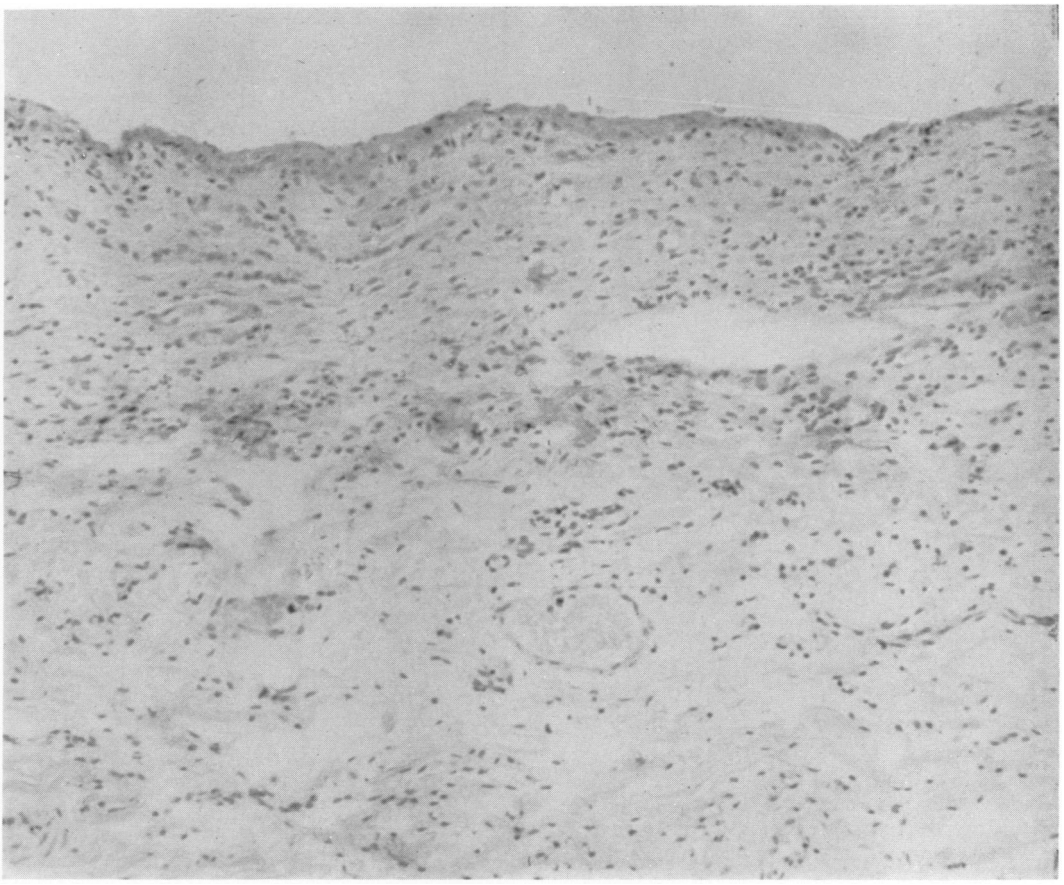

FIG. 3B. Photomicrograph, in another animal in Group III, showing inhibited fibroplasia with scanty collagen formation. This dog received 0.5 mg. Prednisolone/Kg./day, was sacrificed on day 87 post-burn with minimal stenosis. (H and E, ×160.)

stenosis, a contrast which should be noted with the control group (Fig. 4B). There was some thinning of the esophageal wall, though there was no evidence of inhibition of fibroplasia. The remainder of the histological changes were similar to the control group.

Discussion

In the preceding experimental study a standardized reproducible severe corrosive esophageal burn was produced in dogs, all of which were maintained on adequate antibiotic therapy. It is pertinent to stress that the target of this investigation relates to an analysis of the effect of various therapeutic modalities in preventing stricture in a severe caustic esophagitis.

The majority of clinical reports on corrosive esophagitis secondary to lye ingestion relate to all forms of burn injury, with the largest percentage of patients reported on usually having only minimal to moderate esophagitis.[4, 6, 12, 18] The effect of present day therapy, when applied solely to deep burns of the esophagus where involvement of the muscularis is included, still is associated with a significant percentage of stricture, perforation, or death as sequelae.[4]

All but two control animals in this study developed moderate or marked stenosis. Not all animals, however, developed complete esophageal occlusion. In some con-

trol dogs the stricture, almost complete at one month, seemed somewhat less after three months. This may be related to the dogs "bolting" their food, with the ingested bolus serving as a dilator.[2, 19] Those animals (Group II) treated with bouginage all developed stricture of a severe degree. Eventual complete stenosis could occasionally be avoided if bouginage were instituted by the 7th to 9th postburn day and then repeated at 3–4 intervals for up to two months. No animal treated solely by dilatation escaped permanent esophageal segmental injury, since some degree of stricture was always present. These results should underscore the conclusions that bouginage in the full-thickness esophageal lye burn is ineffective in preventing stricture formation, and, in fact, such instrumentation usually augments cicatrical deformity. It is of interest that no perforation occurred in the group treated solely by bouginage. This latter may be related to the fact that bouginage was not begun until one week after the burn.

When one considers corticosteroid therapy and the many optimistic reports in the literature,[13, 20–22] it must be understood that strictures do occur in patients on adequate steroid therapy. It is well documented[10, 19] that, to be effective, steroids must be given immediately following the esophageal injury. Delaying even 48 hours before instituting therapy has often completely negated the expected suppressive effect on the inflammatory reaction and granulation tissue formation.[13]

The effect of a corticosteroid on the inhibition of cicatrix formation, as originally described by Baker[1] and Spain,[17] was well illustrated by the 9 animals in Group III who received 0.5 mg. Prednisolone/Kg./day. Although it was shown that in these severe esophageal burns stricture formation occurred in each of the animals, severe stenosis was noted in only two of the nine. However, as has been emphasized frequently in the literature,[11, 14, 15] high steroid

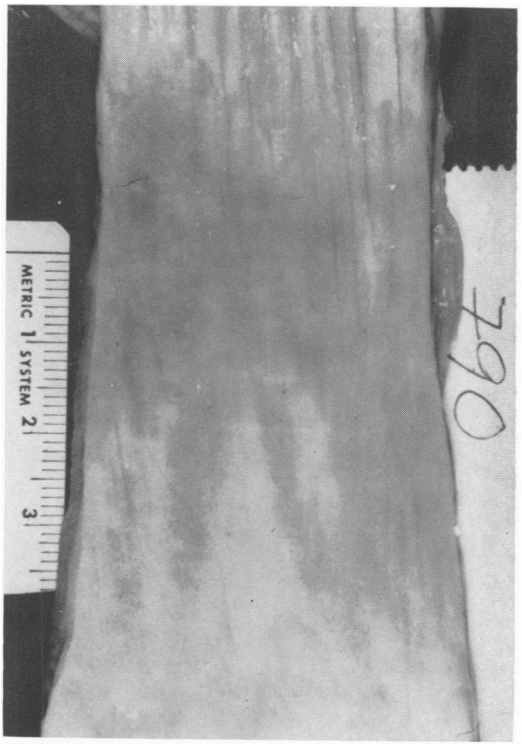

FIG. 4A. Note minimal esophageal stenosis in dog sacrificed at 97 days. Treated by combination bouginage and steroid therapy.

dosage was accompanied by a high incidence of esophageal perforation.

Reducing the daily steroid dosage to 0.1 mg./Kg./day produced no real improvement over the control group in regard to eventual stricture formation. Eight of 12 animals developed severe stenosis, and three of four animals developing minimal, or moderate stenosis died of esophageal perforation. The one significant difference in these animals, in comparison with the control group, was that the progression of the stenosis in the burned segment was much delayed, often requiring 4–6 weeks to reach a stage of stricture comparable to that shown by the controls at 14 days postburn.

In animals treated by a combination of low dosage steroids (Prednisolone 0.1 mg./Kg./day) and bouginage begun on the 7–10th postburn day, only three animals developed severe stenosis. Nine of 15 dogs

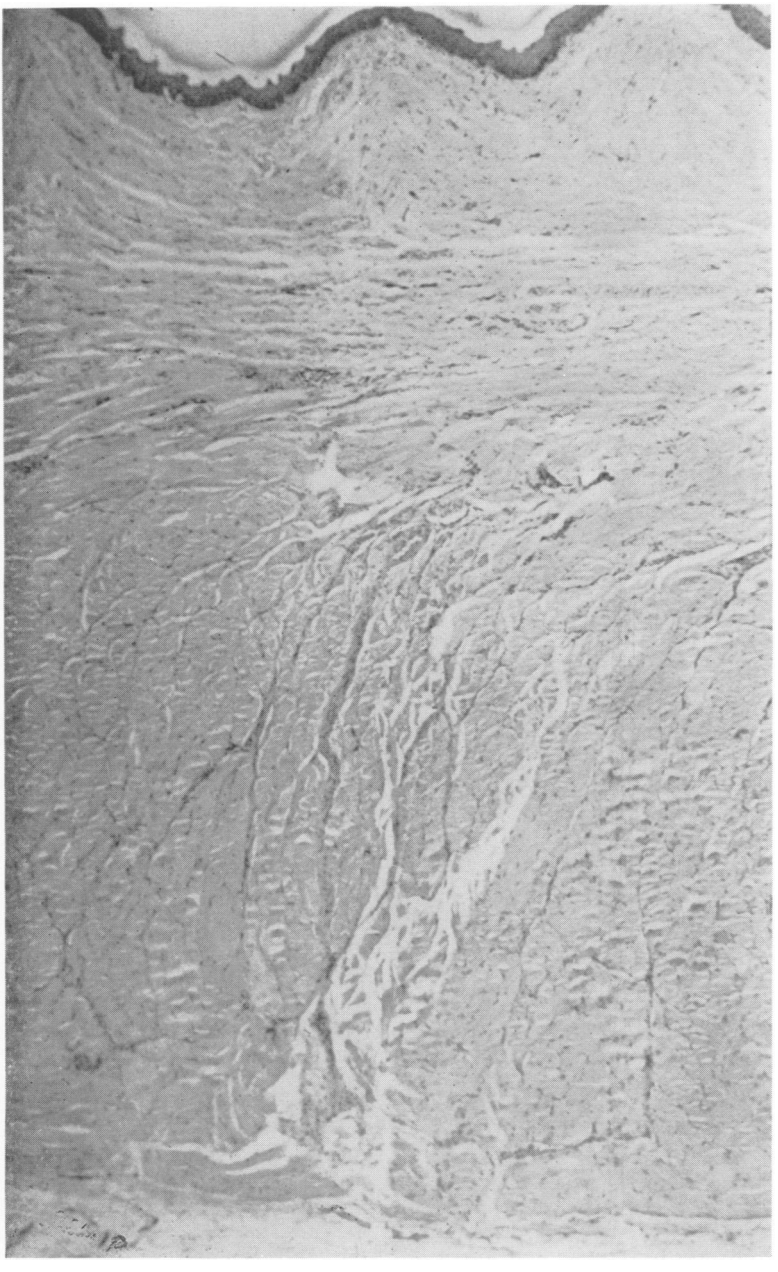

FIG. 4B. Photomicrograph demonstrating severe burn extending into muscularis with no diminution of fibroplasia. (H and E, ×50.)

showed only minimal stenosis, and three developed moderate stenosis. Again, the progression of the cicatrix in these severely burned esophagi was slowed, and bouginage was accomplished with little local resistance when contrasted to the dilatations performed on the Group II animals. Of importance is the fact that bouginage was required less frequently and not required at all after one month following the burn. This finding contrasts to a single previous experimental study by Haller and Bachman [8] using cats, in which they concluded that the addition of bouginage to steroids did not decrease the incidence of stricture.

The combination therapy when applied

to the severe esophageal lye burn appears to have the following advantages: 1) There is avoidance of any significant esophageal perforation, which is inherent when steroids are administered in larger doses; 2) The use of bouginage in combination with low steroid dosage is effective even when begun as late as 10–14 days postburn. Dilatations can be performed less frequently and are not required after 30 days postburn. This obviates much of the risk for this modality; 3) In the severely burned esophagus the combination therapy yielded the lowest incidence of stricture formation and perforation and the highest percentage of surviving animals.

Summary

A standardized method of producing a segmental, deep, esophageal caustic burn was produced in a series of 68 dogs, all receiving antibiotic therapy.

A comparison is presented between a control group and animals treated by bouginage, low dosage steroids, high dosage steroids, and a combination of bouginage and low dosage steroids.

The lowest incidence of stricture following a segmental, deep, esophageal caustic burn occurred in those animals treated with low dosage (0.1 mg./Kg./day) Prednisolone combined with bouginage.

Acknowledgment

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