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A NEW ULCER MODEL, "UNHEALED GASTRIC ULCERS", INDUCED BY CHRONIC TREATMENT WITH INDOMETHACIN IN RATS WITH ACETIC ACID ULCERS

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The healing of experimental gastric ulcers induced in rats is consistently delayed upon chronic treatment with indomethacin. This study was designed to examine both the fate of such delayed ulcers and the effects of various antiulcer drugs on the delayed ulcers. Four-week treatment with indomethacin significantly delayed the healing of acetic acid ulcers. Such ulcers remained unhealed for up to 12 weeks after cessation of indomethacin treatment, and were thus designated as "unhealed ulcers". Two-week administration of sucralfate, cimetidine or omeprazole significantly reduced the ulcerated area, yet aluminum hydroxide had little or no effect. Four-week administration of sucralfate also extensively reduced the size of the "unhealed ulcers", yet aluminum hydroxide, cimetidine and omeprazole had an insignificant effect on "unhealed ulcers". In the 2 and 4 week sucralfate-treated group, the pH of the gastric contents was 4.0 vs. 1.7 and 4.5 vs. 2.1 in the control groups, respectively. Gastric acid secretion was extensively inhibited by cimetidine and omeprazole. It is concluded that prolonged indomethacin treatment results in the development of "unhealed ulcers" and that only sucralfate has a beneficial effect on such ulcers, irrespective of the length of the treatment.

Key words: *acetic acid ulcer, "unhealed gastric ulcer", indomethacin, acid pump inhibitor, sucralfate*

INTRODUCTION

Since two types of acetic acid ulcer models were devised in rats (1, 2), these models have been used for both the study of the mechanism underlying the ulcer healing and the screening of antiulcer drugs. In general, test drugs are usually administered either directly following ulceration or several days after ulceration to determine whether or not the drugs can accelerate the spontaneous healing of newly-formed, fresh ulcers (3—6). Repeated treatment with indomethacin for 2 or 4 weeks is generally known to significantly prevent the healing of acetic acid gastric ulcers (7—9). One of the authors (10) reported that

NC-1300, an acid pump inhibitor, given together with indomethacin for 4 weeks, significantly prevented the delay in ulcer healing. In such experiments, it was found that the ulcers in the control animals remained unhealed for up to 8 weeks after cessation of the indomethacin treatment. This study confirms, first, the healing of ulcers in rats for up to 12 weeks after 4-week treatment with indomethacin. Secondly, the study also examines the effects of various antisecretory and antiulcer drugs on the healing of "unhealed ulcers"produced by 4-week treatment with indomethacin. The effects of these drugs on "unhealed ulcers" were compared with those observed on freshly-produced ulcers.

MATERIALS AND METHODS

Animals

Male Donryu rats (260—280 g; Nihon SLC, Shizuoka) were used for this study. The animals were kept in a room under regulated temperature (20—22° C) and humidity (55%) conditions, with a 12/12-hr light/dark cycle. To induce ulcers the animals were first deprived of food for 5 hrs prior to the operation to allow for easy injection of the acetic acid solution into the gastric wall. The animals were kept in mesh-bottom cages to prevent coprophagy. To determine gastric acid secretion, the animals with ulcers were deprived of food for 18 hrs and water for 2 hrs prior to the experiments.

Ulcer induction

Gastric ulcers were induced according to a previously described method (1, 8). In brief, under ether anesthesia gastric ulcers were induced by submucosal injection of 0.03 ml of 20% acetic acid (v/v) into the border between the antrum and the fundus in the anterior wall of the stomach. The acid was injected using a 0.25 ml microsyringe (Terumo, Tokyo). After closure of the abdomen, the animals were normally maintained on food and water. After killing animals under ether anesthesia at specified intervals, the stomachs were removed, opened along the greater curvature and flattened with pins on a cork board. The ulcerated area (mm^2) was determined under a dissecting microscope (× 10; Olympus, Tokyo) with a square grid. The author (S.O.) who determined the size of the ulcers was unaware of which treatment any given animal received. Since deep, well-defined ulcers were consistently observed 5 days following the acid injection, the 5th day was defined as the initial day of ulceration (day 0).

Indomethacin treatment

In our previous studies, 1 mg/kg/day of indomethacin was subcutaneously (s.c.) administered to delay ulcer healing (8, 9). With such a dose, a significant reduction of gastric mucosal PGe_2 persists for 12 to 24 hrs. As one potential mechanism for the delay in ulcer healing, it was postulated that a marked reduction in the PGE_2 level in the ulcerated area caused by indomethacin was an important factor. Consequently, to ensure the persistent reduction of the mucosal PGE_2 level for over 24 hrs, 1 mg/kg of indomethacin (Sigma, St. Louis, MO) was administered s.c. twice

daily in the present study. 4-week treatment with indomethacin (s.c., 1 mg/kg) is empirically shown to markedly delay spontaneous ulcer healing (8—10). Accordingly, the status of the healing of 4-week-old ulcers (treated with 2×1 mg/kg/day of indomethacin or the vehicle alone) was observed for the following 12 weeks without further administration of indomethacin. Animals were killed at 2-week intervals and the ulcer areas (mm^2) were subsequently determined.

Determination of gastric acid secretion

The effects of the test drugs on basal gastric acid secretion in rats with ulcers, either with or without indomethacin treatment, were determined on the day after the final treatment with the drugs. Under ether anesthesia, the abdomen was incised and the pylorus was ligated. The animals were killed 4 hrs after the ligation, after which the gastric contents were collected and analyzed with regards to volume and acidity. The total acidity was determined by automatic titration of the gastric contents against 100 mM NaOH to pH 7.0 (Hiranuma; Comtite 5), the acid output being expressed as μEq/hr. An additional dose of each test drug was orally administered 18 hrs following the final treatment, after which the pylorus was ligated 1 hr later. In the cases of aluminium hydroxide and sucralfate, only the gastric pH was determined. The presence of aluminium ions in the samples intereferes with the accurate titration of gastric acid with NaOH by the formation of $[Al(OH)_4]^-$.

Drug treatment

Aluminium hydroxide (Wako Junyaku, Osaka), sucralfate (Chugai Co., Tokyo), cimetidine (Smith-Kline-Beacham, Tokyo) and omeprazole (provided by Nihon Chemiphar Co., Tokyo) were used for the study. The effects of the test drugs on either indomethacin-delayed healing or spontaneous healing were examined by oral administration, once or three times daily, for either 2 or 4 weeks. In the control groups, the animals were administered the vehicle alone.

Histological study

At the time of autopsy, small pieces of tissue that contained ulcers were embedded in paraffin and sectioned at 4 μm. Haematoxylin and eosin staining was subsequently performed.

Statistical analysis

All data are presented as means $\pm$ SEM. Statistical analysis was performed using the Student's t-test, $P < 0.05$ being regarded as significant.

RESULTS

Effects of cessation of indomethacin treatment on ulcer healing

Five days after acid injection, deep, well demarcated ulcers were observed in the stomachs of all the animals, with an average ulcerated area of 29.3 ± 2.1 mm^2. Four weeks later, the ulcers in the control animals had

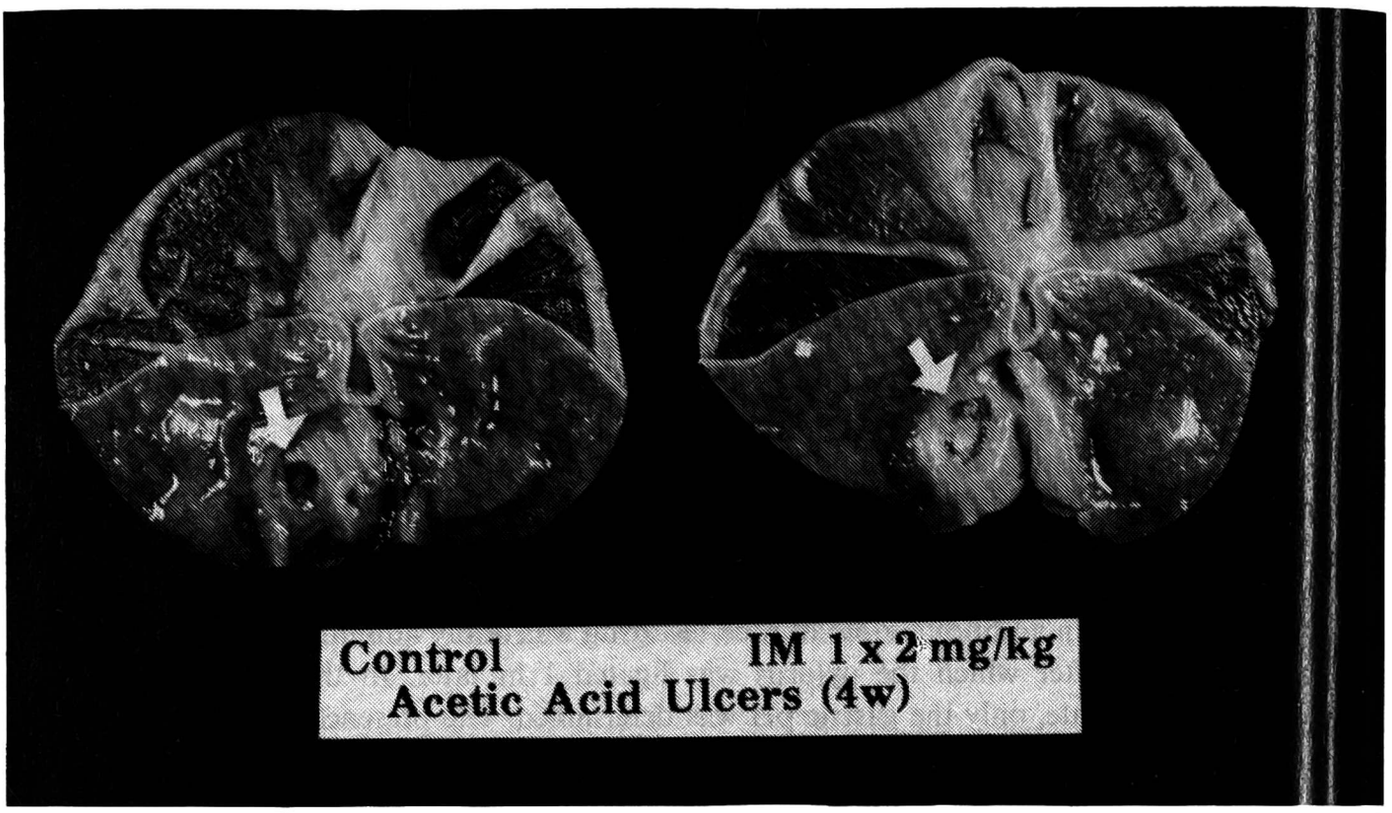

Fig. 1. Macroscopical appearances of acetic acid ulcers in rats. An "unhealed gastric ulcer" observed the day after the cessation of 4-week treatment with indomethacin (s.c.) (right), and a normal ulcer treated with the vehicle alone (left).

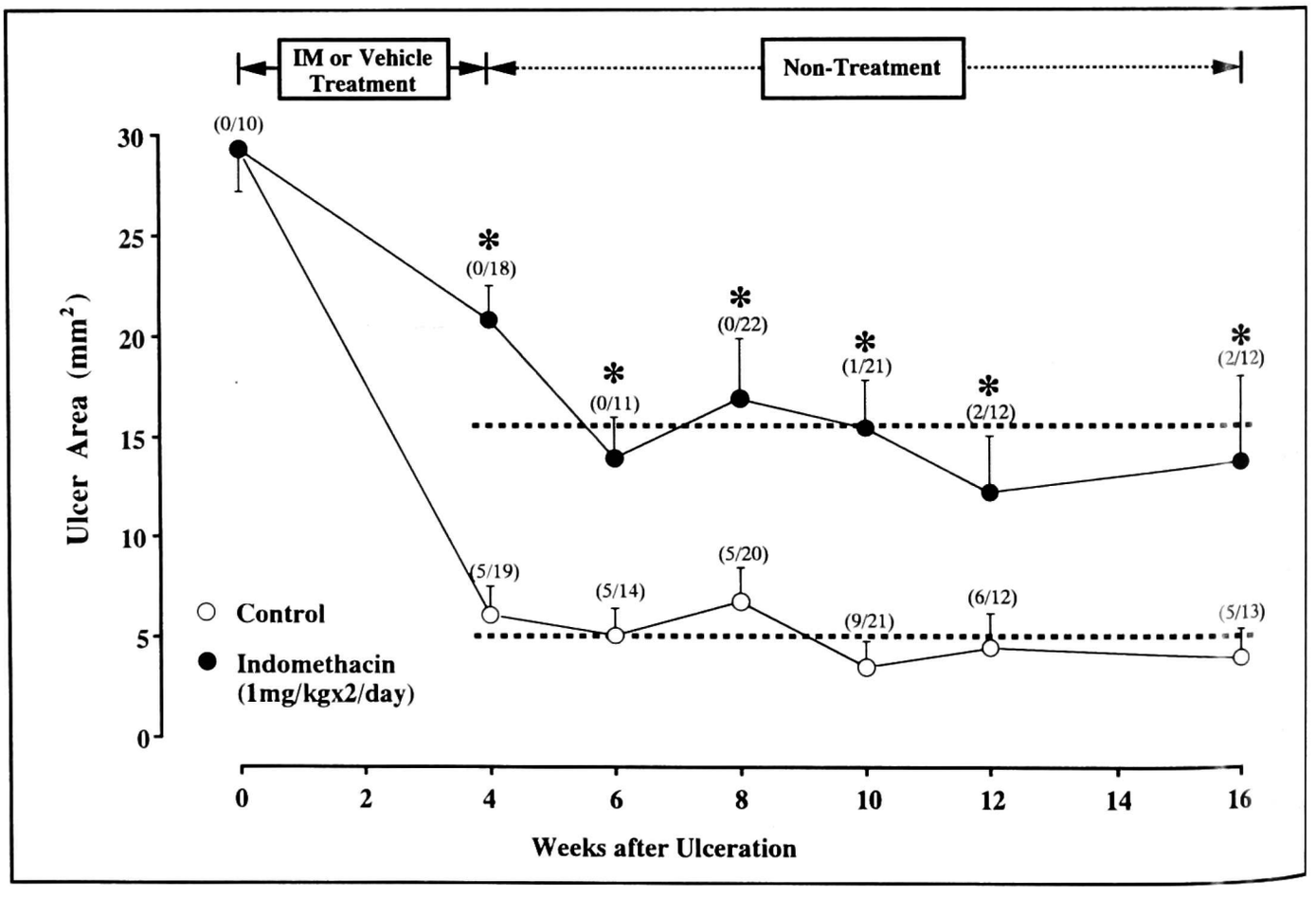

Fig. 2. Healing of acetic acid ulcers in rats treated with the vehicle alone or with indomethacin for 4 weeks after the onset of ulceration. Note that the size of ulcers observed after 4-week treatment with indomethacin remained at the same for up to 12 weeks (dotted line).

diminished in size to 6.1 ± 1.5 mm^2 (*Figs. 1, 2*). The size of these ulcers remained nearly unchanged for the following 12 weeks, with an average area of approximately 5.0 mm^2 throughout the period. In contrast to in the control animals, the ulcerated area in the animals previously treated with indomethacin for 4 weeks (*Fig. 2*) also remained unchanged for the following 12 weeks without further treatment with indomethacin, but the size was much greater (approximately 15.5 mm^2). After 12 weeks the average ulcerated area was 13.8 ± 4.2 mm^2 vs. 4.0 ± 1.4 mm^2 in the non-treated group.

Effects of 2-wk treatment with various drugs on "unhealed ulcers"

Two weeks after cessation of the indomethacin treatment, the ulcer size in the control groups was approximately 12—15 mm^2, with an ulcer incidence of 100%. Accordingly, the effects of 2-week administration of the following drugs on such "unhealed ulcers" were examined. Aluminium hydroxide (3×600 mg/kg/day) had no effect on the healing of "unhealed ulcers" (*Fig. 3*). The volume and pH of the gastric contents of these animals were much the

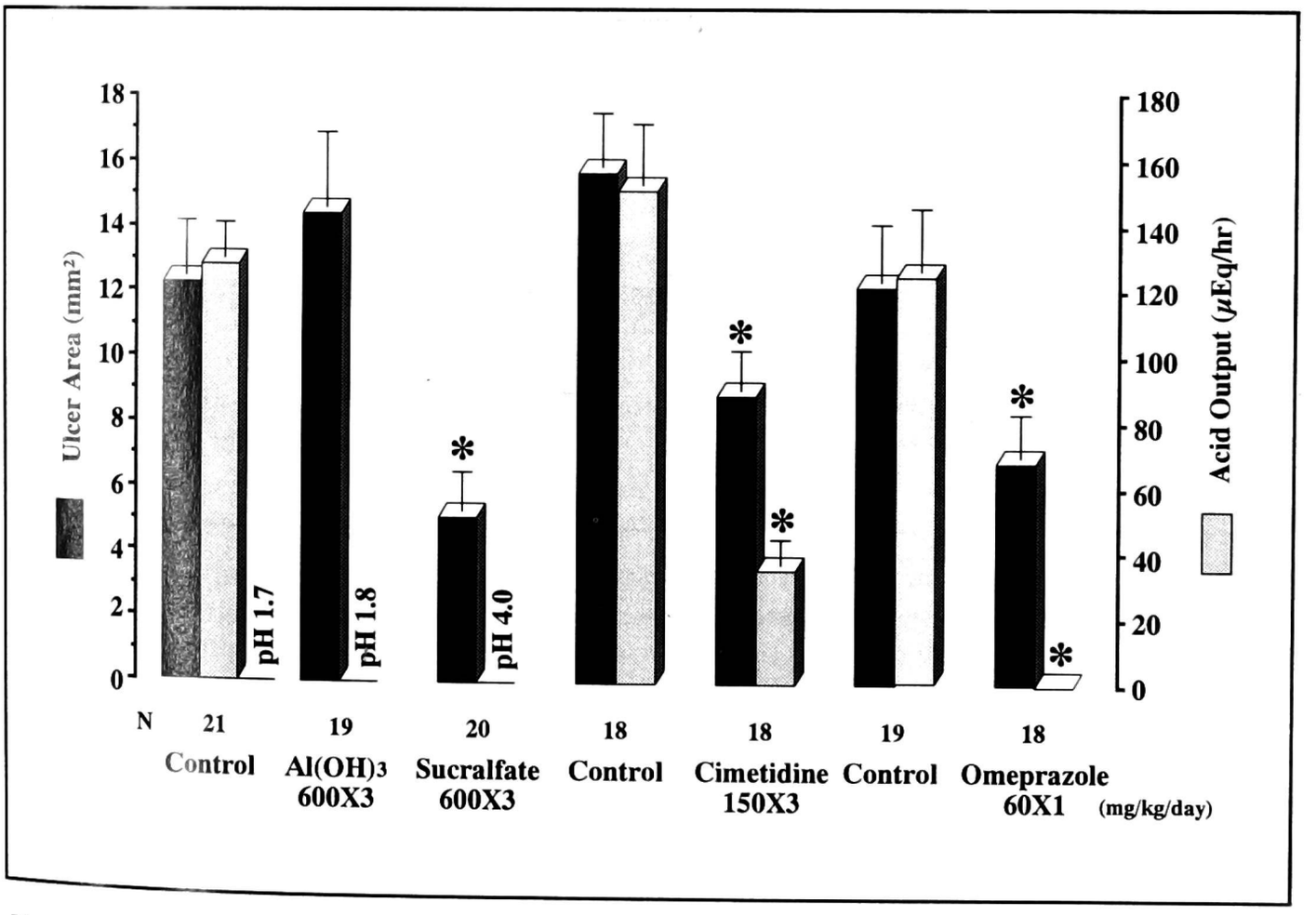

Fig. 3. Effects of drugs on indomethacin-induced "unhealed gastric ulcers" in rats. $Al(OH)_3$, sucralfate, and cimetidine were administered three times daily, while omeprazole was administered once daily for 2 weeks after the end of indomethacin treatment. Gastric acid output and pH were determined the day after the cessation of the drug treatment. Data are presented as means $\pm$ 1 S.E.M. for 18—21 rats. *Significantly different from the control values, $P < 0.05$.

same as those in the control group. In contrast, sucralfate (3 × 600 mg/kg/day) significantly reduced the area of "unhealed ulcers" with 58.8% inhibition. The volume of gastric contents significantly increased to 9.3 ± 0.5 ml/4 hr in the control group) with the pH 4.0 (vs the pH 1.7). Both cimetidine (3 × 150 mg/kg/day) and omeprazole (60 mg/kg/day) significantly reduced the ulcerated area by 43.6% and 44.3% of the control values, respectively. The volume and gastric acid output in the cimetidine- and omeprazole-treated animals were significantly reduced by 48.0% and 35.5%, and 77.0% and 100%, respectively.

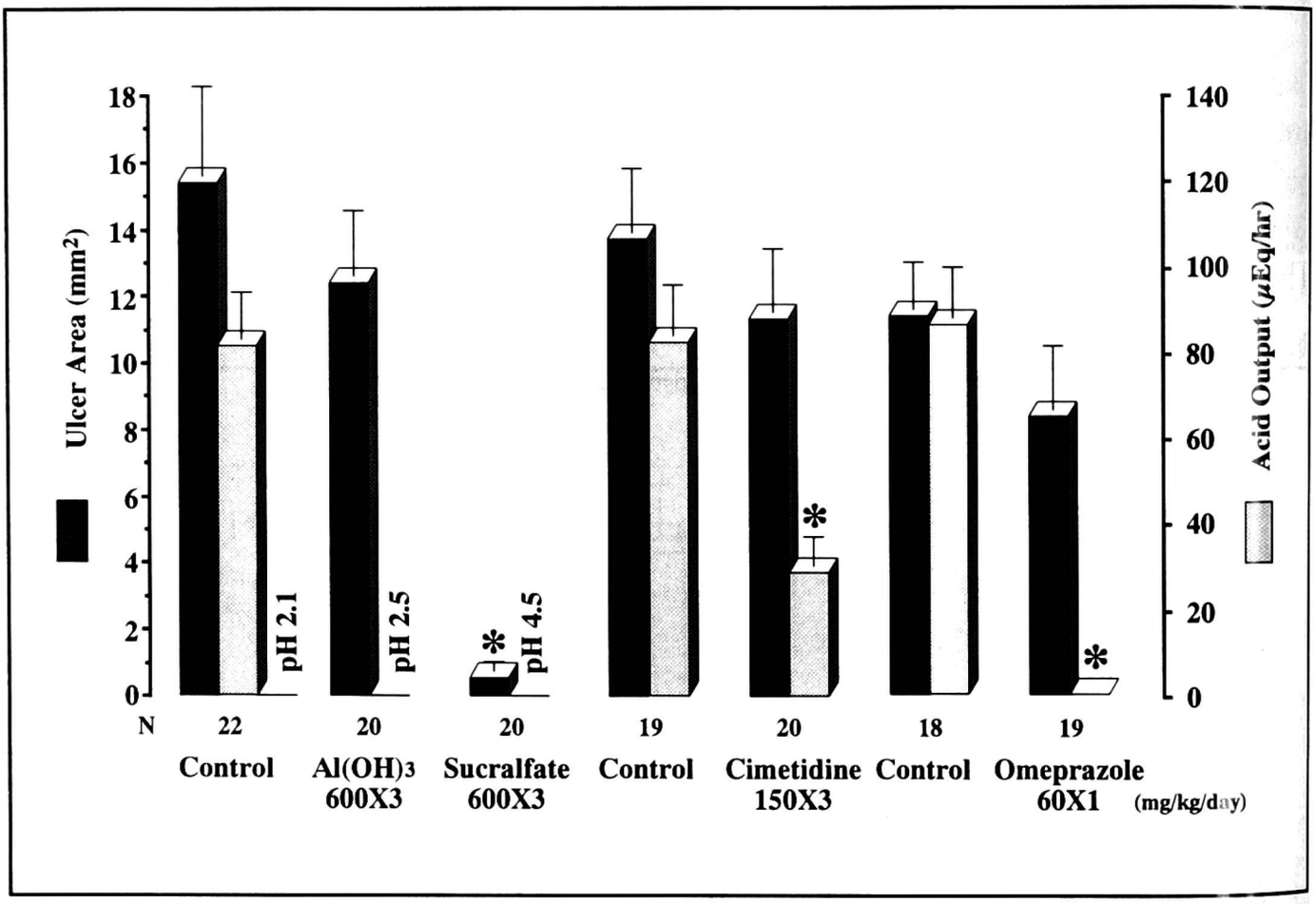

Fig. 4. Effects of drugs on indomethacin-induced "unhealed gastric ulcers" in rats. $Al(OH)_3$, sucralfate, and cimetidine were administered three times daily, while omeprazole was administered once daily for 4 weeks after the induction of "unhealed ulcers". Gastric acid output and pH were determined the day after the cessation of the drug treatment. Data are presented as means ± 1 S.E.M. for 18—22 rats. * Significantly different from the control values, $P < 0.05$.

Effects of 4-wk treatment with various drrugs on "unhealed ulcers"

Similar to the results observed with the 2-wk treatment, aluminium hydroxide (3 × 600 mg/kg/day) had no effect on the "unhealed ulcers" (*Fig. 4*). In contrast, sucralfate extensively reduced the ulcerated area by 96.1%, the incidence of completely healed ulcers being 75% (*Fig. 4, 5A, 6*). The volume of the gastric contents of these animals significantly increased to 8.7 ± 0.9 ml/4 hr

(vs 5.0±0.5 ml/4 hr in the control group) with the pH 4.5 (vs the pH 2.1). It should be noted that both cimetidine and omeprazole only exhibitet a tendency to reduce the ulcerated area (*Fig. 4, 5B*), despite the marked inhibition of

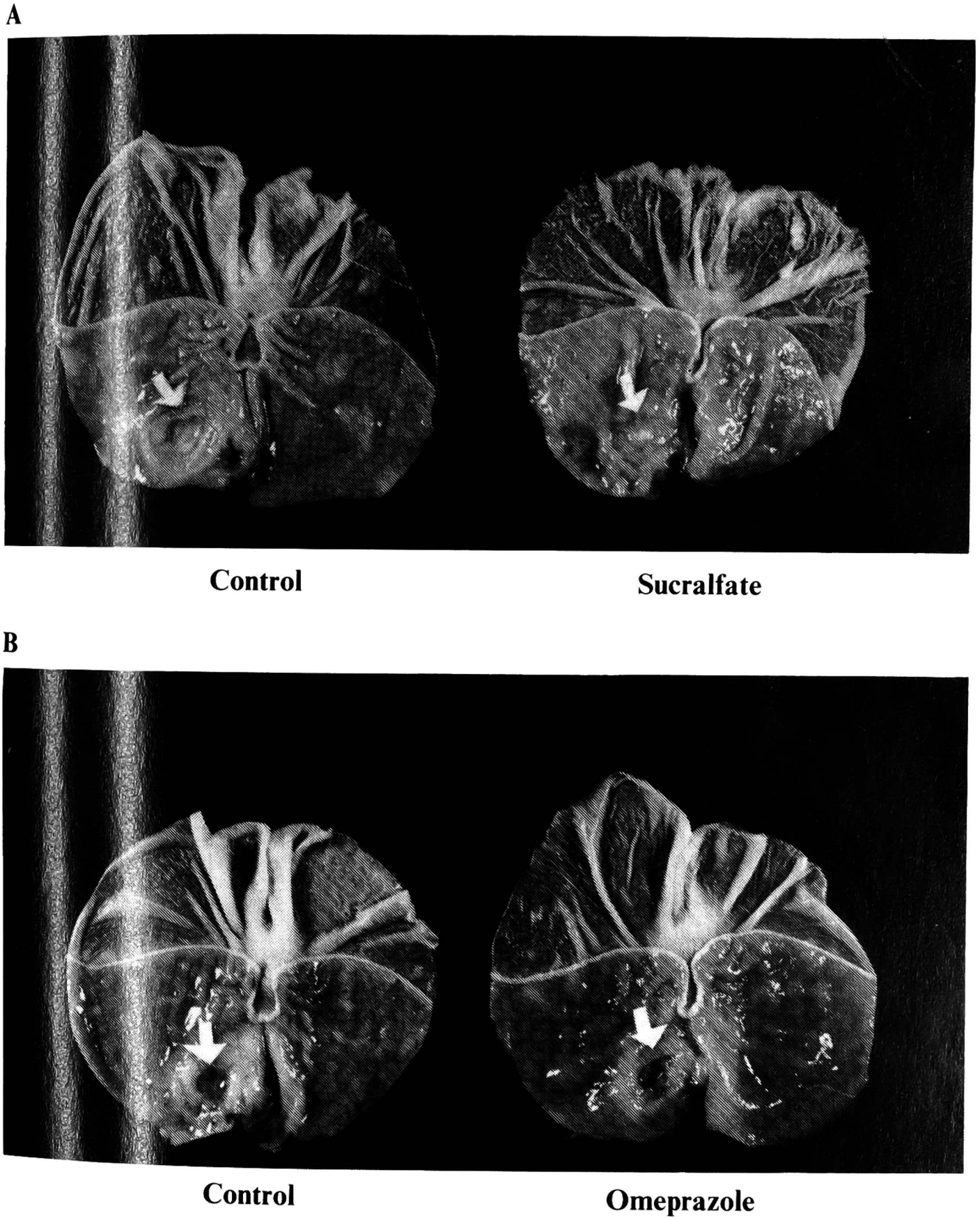

Fig. 5. Effects of sucralfate (A), and omeprazole (B) on "unhealed gastric ulcers" induced in rats. Note that while sucralfate markedly reduced the size of the ulcers, omeprazole had less effect on these ulcers.

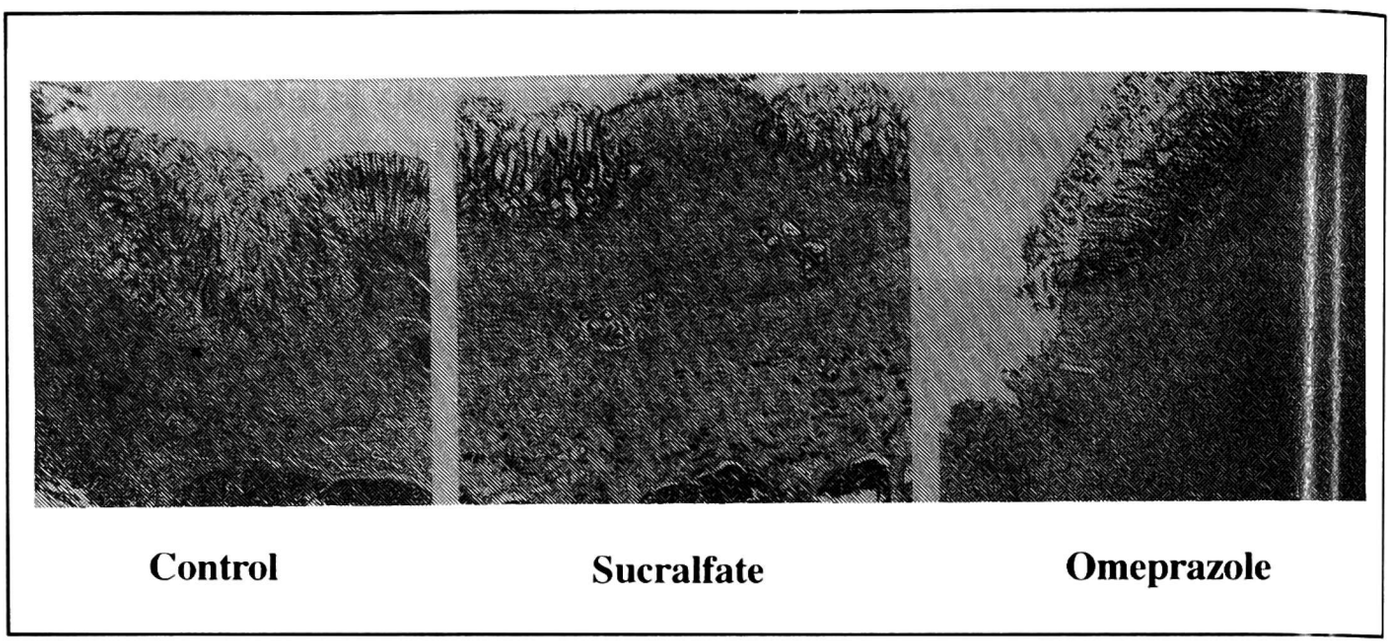

Fig. 6. Histological pictures showing "unhealed gastric ulcers" in rats treated with the vehicle alone, sucralfate (3 × 600 mg/kg/day) and omeprazole (60 mg/kg/day) for 4 weeks, respectively. Note that dense fibrosis was observed in the ulcer base, indicating a lack of healing of the ulcerated area with omeprazole in comparison with the control.

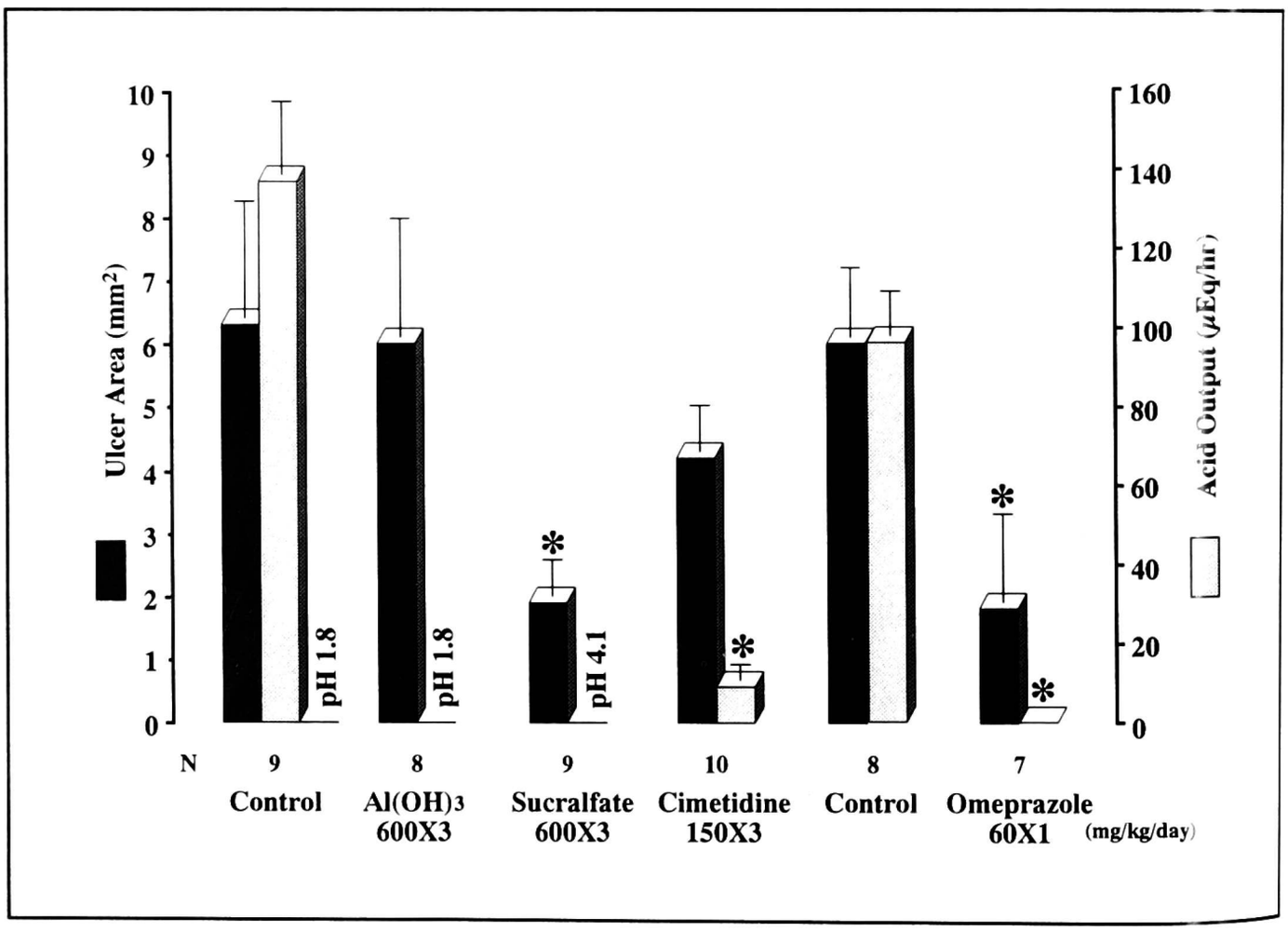

Fig. 7. Effects of drugs on the spontaneous healing of acetic acid ulcers induced in rats. $Al(OH)_3$, sucralfate, and cimetidine were administered three times daily, while omeprazole was administered once daily for 2 weeks after onset of ulceration. Gastric acid output and pH were determined the day after the cessation of the drug treatment. Data are presented as means ± 1 S.E.M. for 7–10 rats. * Significantly different from the control values, $P < 0.05$.

gastric acid secretion. In the case of omeprazole-treated animal, histological studies also confirmed the presence of extensive fibrosis in the ulcer base which is commonly seen in chronic-type ulcers (*Fig. 6*).

Effects of 2-wk treatment with various drugs on spontaneous ulcer healing

Treatment with sucralfate and omeprazole significantly enhanced the spontaneous healing of gastric ulcers by 69.8% and 70%, respectively (*Fig. 7*). The volume of gastric contents in the sucralfate-treated group significantly increased to 11.6 ± 1.2 ml/4 hr (vs 6.8 ± 0.7 ml/4 hr in the control group) with the pH 4.1 (vs the pH 1.8). Both aluminium hydroxide and cimetidine had insignificantly inhibited the gastric acid secretion by 93.3% and 100%, respectively.

Effects of 4-wk treatment with various drugs on spontaneous ulcer healing

In comparison with the 2-week treatment, nearly identical results as to the effects on spontaneous healing were obtained on 4-wk treatment with sucralfate and omeprazole (*Fig. 8*). Again, the volume of gastric contents in the

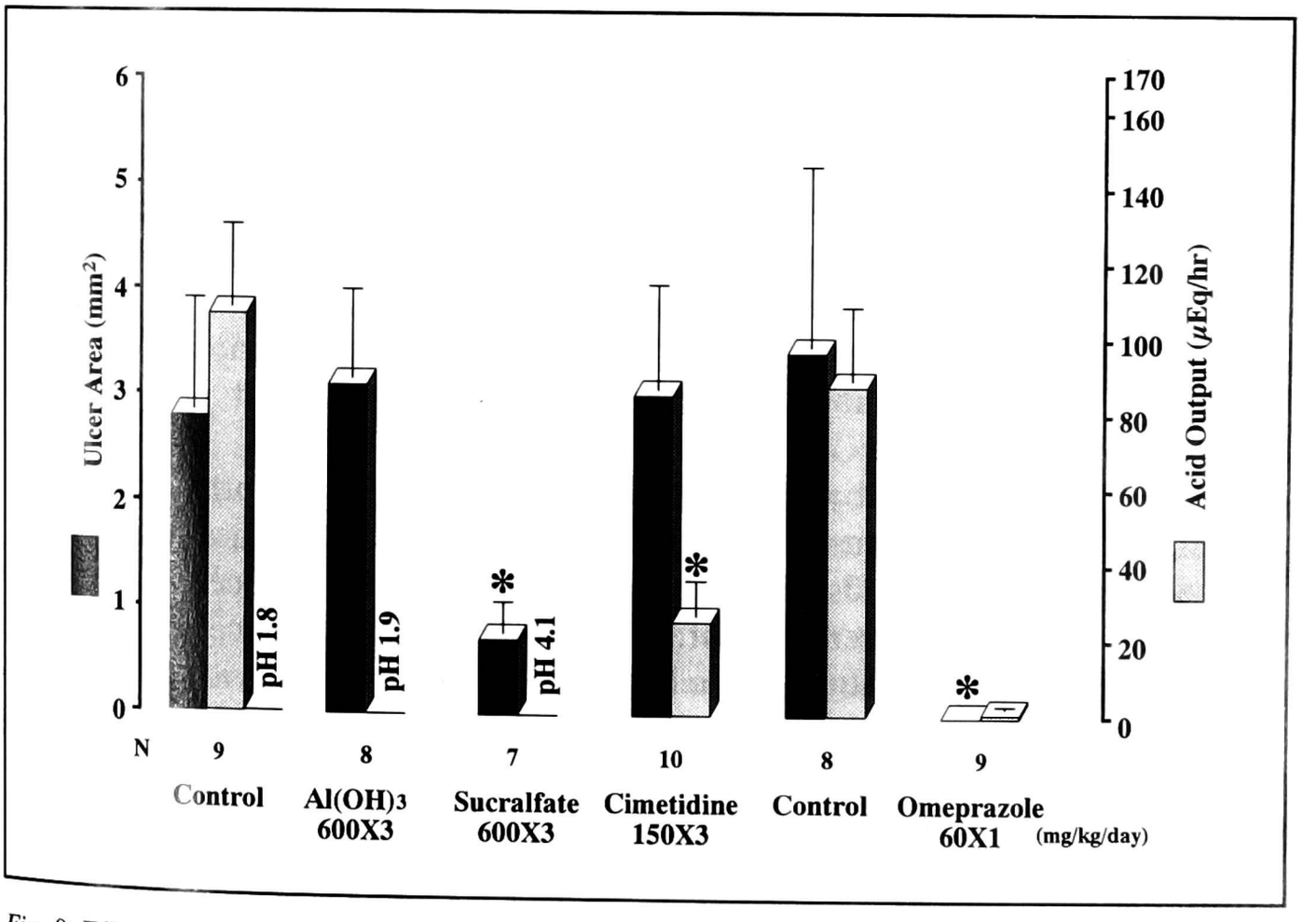

Fig. 8. Effects of drugs on the spontaneous healing of acetic acid ulcers induced in rats. $Al(OH)_3$, sucralfate, and cimetidine were administered three times daily, while omeprazole was administered once daily for 4 weeks after the onset of ulceration. Gastric acid output and pH were determined the day after the cessation of the drug treatment. Data are presnted as means $\pm$ 1 S.E.M. for 7—10 rats. * Significantly different from the control values, $P < 0.05$.

sucralfate-treated group significantly increased to 11.4 ± 1.2 ml/4 hr (vs 5.3 ± 0.8 ml ± 0.8 ml/4 hr in the control group) with the pH 4.1 (vs the pH 1.8). Neither aluminium hydroxide nor cimetidine had an appreciable effect on spontaneous ulcer healing, despite the marked inhibition of gastric acid in the case of cimetidine administration.

DISCUSSION

The present study demonstrated that acetic acid ulcers rapidly heal within 4 weeks after ulceration. Nonetheless, partly-healed ulcers remained the same size for up to 12 weeks, with an incidence of 25—50%. It remains unknown why such small ulcers in the stomach could not totally disappear, as in the case of wounds on the surface of the skin that completely heal. As evidenced by the present study, a potent and long-lasting antisecretory drug, such as omeprazole, markedly accelerates the healing of ulcers. Consequently, continuous gastric acid secretion appears to represent a key element preventing such small ulcers from completely healing over such a long period.

In our previous study, we found that 8-week administration of indomethacin after the onset of ulceration significantly prevented acetic acid ulcers from healing (5). The present study additionally showed that ulcers on 4-week treatment with indomethacin remained unhealed for 12 weeks, with a high incidence, after the cessation of indomethacin treatment. These results indicate that at the end of the 4-week treatment with indomethacin the characteristics of the ulcers were extensively altered, resulting in the persistence of the ulcers, namely "unhealed ulcers". This alteration might have been caused by irregularly-formed connective tissue in the ulcer base that prevented the ulcers from healing (11).

Sucralfate is well known to enhance the healing of both gastric and duodenal ulcers in humans and animals (12, 13). One hypothesis is that the drug electrostatically binds to tissue proteins coating the ulcer crater, thus forming a physical barrier against acid and pepsin (14). Accordingly, this process is generally described as the "band-aid effect". We previously reported that sucralfate accelerates spontaneous ulcer healing (13) and prevents the delayed ulcer healing caused by indomethacin when simultaneously administered for 4 weeks (15). Interestingly, this ulcer healing property of sucralfate was found to be applicable to "unhealed ulcers", it diminishing the ulcer size. Such results strongly indicate that even "unhealed ulcers" are treatable by physically covering the surface of the ulcer crater. It should be noted that the volume of gastric contents significantly increased with the sucralfate treatment. The mechanism of this increase in the gastric volume and the role in accelerated ulcer healing remains unknown. Certainly, the raised pH (approxi-

mately 4.0) of the gastric contents observed in animals treated with sucralfate might be involved in the mechanism underlying the accelerated healing. Nevertheless, it appears unlikely that only the inhibition of acidification is sufficient to heal an "unhealed ulcer". This supposition was derived from the fact that although omeprazole resulted in nearly complete suppression of basal gastric acid secretion for 4 weeks, the drug had an insignificant effect on the healing of "unhealed ulcers". This finding indicates that the increased pH resulting from sucralfate does not contribute to the beneficial effect on the healing of "unhealed ulcers".

Various growth factors, such as epidermal growth factor (EGF), transforming growth factor alpha (TGF_{α}), basic fibroblast growth factor (bFGF), platelet-derived growth factor (PDGF), and VEGF (vascular endothelial growth factor), are expressed in the gastric mucosa, irrespective of the presence of an ulcer, and are postulated to extensively contribute to ulcer healing (16—19). As demonstrated by Konturek *et al.* (16), sucralfate not only binds with EGF, but also possesses the ability to stimulate the expression of EGF and bFGF. Folkman *et al.* (20, 21) provided evidence that the binding of sucralfate with bFGF makes possible the delivery of the growth factor to the ulcerated area, which leads to acceleration of ulcer healing. Ito *et al.* (22) also suggested that sucralfate binds with EGF in the stomach, leading to a prolonged EGF effect on the ulcer base.

Tarnawski *et al.* (23) postulated that the mechanism by which indomethacin delays ulcer healing involves reduced angiogenesis in the ulcer base. Furthermore, sucralfate is also known to stimulate both prostaglandin E_2 synthesis in the gastric mucosa of humans and animals (24), and angiogenesis in an *in vivo* wound healing model (25). Accordingly, sucralfate might restore the reduced angiogenesis in the ulcer base caused by indomethacin to the normal level, most probably by stimulating the expression of VEGF and/or bFGF, as well as PGE_2. We have already confirmed that the PGE_2 level around an ulcerated area returned to the normal level within 1 week after cessation of 4-week treatment with indomethacin (unpublished data). Overall, it is possible that sucralfate accelerates the healing of both fresh ulcers and "unhealed ulcers" through its protein binding activity, stimulation of PGE_2 generation, and transportation of growth factors to the ulcerated tissue. Aluminium hydroxide, simultaneously administered at the same dose with sucralfate, had no effect on either fresh ulcers or "unhealed ulcers", suggesting that the effect of sucralfate is not related to the effect of aluminum on the ulcerated tissue.

It should be noted that "unhealed ulcers" were less sensitive to histamine H_2-receptor antagonists and acid pump inhibitors. We revealed that acid pump inhibitors have a beneficial effect on the healing of both fresh and indomethacin-delayed ulcers (concurrent administration) (5, 26). We also confirmed the effects of omeprazole on spontaneous ulcer healing after 2- or

4-week treatment. Interestingly, 2-week treatment with omeprazole significantly reduced the size of "unhealed ulcers", although to a lesser extent than observed in the case of spontaneous healing. In contrast, 4-week treatment with omeprazole had little or no effect on the healing of "unhealed ulcers". Consequently, it can be said that "unhealed ulcers" are resistant to an acid pump inhibitor. All in all, such phenomena strongly indicate that the mechanism underlying delayed healing is not due to the aggressive action of gastric acid.

It is concluded that 4-week treatment of rats with ulcers with indomethacin results in "unhealed ulcers" that persist for > 12 weeks following the cessation of treatment. Such "unhealed ulcers" appear to be quite sensitive to mucosal protective drugs, such as sucralfate, yet are considerably resistant to antisecretory drugs, including an acid pump inhibitor.

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