Prevention of Postoperative Intestinal Adhesions with Combined Promethazine and Dexamethasone Therapy:

Experimental and Clinical Studies

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INTESTINAL obstruction occurring after abdominal surgery is always a threat to successful convalescence. Colleti and Bossart [7] reported that, in their series, intestinal adhesions were responsible for 90 per cent of small bowel obstructions in the early postoperative period. The incidence of this complication is particularly high following abdominal surgery in infants. Devens [9] observed that following abdominal surgery, the most frequent cause of recurrent intestinal obstruction in the neonate is intestinal adhesions. Review of our own experience at the Children's Hospital of Boston over the past 10 years fully substantiates this report (Table 1). Nearly 25 per cent of all newborn babies undergoing laparotomy for meconium ileus, intestinal atresia or stenosis required a second operation for relief of obstruction due to intestinal adhesions. In the group of babies having small intestinal atresia, small bowel obstruction from adhesions was responsible for 33 per cent of the fatalities. (The remainder of the fatalities were principally due to other severe congenital anomalies).

Research by surgeons and investigators into methods of preventing adhesions has been extensive; two excellent reviews fully document these efforts.[4, 6] Frequently, reports of success have been made, but no method, as yet, has proved consistently useful. A feeling of futility has crept into the surgeon's attitude toward the avoidance of adhesions and hence adhesions have come to be viewed as an inevitable product of surgical trauma which, at best, can be reduced to a minimum by close attention to the classical tenets characterizing good surgical technic. Any new development, to be practical clinically, must be simple, safe and consistently effective. We are reporting investigations from this laboratory into methods of preventing intestinal adhesions which meet most of these criteria.

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Pathogenesis of Adhesion Formation

Postoperative intestinal adhesions originate from the response of the intestinal serosa or parietal peritoneum to trauma, of multiple sorts, inflicted by the operative procedure. The fact that bowel often can undergo extensive trauma without subsequent formation of adhesion makes us believe that some local preventive mechanism is normally active. Hartwell [15] describes such a mechanism which seems logical. He states, "the characteristics of serosal cells being what they are, it is only logical to believe that they prevent adhesions by combining their fibrinolytic power with their epithelial-like function of extending themselves as a solid sheet of cells to cover smoothly any raw surface. This gives them the ability to come between any two ap-

posed musculofibrous surfaces which are stuck together only by fibrin which has not yet been organized by growth of granulation tissue or laying down of collagen. Adhesions are composed of collagen fibers. If fibroplasia appears between two surfaces before motion or before serosal cells grow in to separate them, a permanent adhesion will be formed. If serosal covering of one or both of the apposed denuded surfaces be rapid and permanent, no adhesion will form."

While fibrinolytic activity has not been reported specifically for serosa, Astrup and Permin [1] found that fibrinolysis was a general property of many tissue cells. Recently, this tissue fibrinolytic activity has been shown to be due to cytokinase (a potent tissue activator of plasminogen), which is located in the lysosome fraction of cells and is released during cellular destruction.[27] Dissolution of any blood clot which is free in a peritoneal cavity, rapid and complete absorption of blood introduced into a peritoneal cavity, and clinical observation that a thick fibrinous exudate covering of any bowel can often be absorbed rapidly and completely, without subsequent adhesion formation, all support an assumption that there is some local fibrinolytic activity of high degree.

Trauma to the serosa of bowel during the course of a surgical procedure within the abdomen initiates an inflammatory response. Reactions of body tissues to an inflammatory stimulus are similar, regardless of the nature or site of the stimulus. The characteristic increase in permeability of blood vessels, resulting in an exudation of a protein-rich material through vessel walls (chiefly through the small venules [33]), is well recognized. Histamine was long thought to be solely responsible for the increased vascular permeability occurring during inflammation, but more recent evidence suggests that other factors are also important. These substances (nucleosides, polypeptides and globulins) are grouped together as "permeability factors" [51] and are

TABLE 1. *Incidence and Morbidity of Postoperative Intestinal Adhesions in the Infant (1953–1963)*

Diagnosis	Total Patients	Secondary Lysis of Adhesions	% of Total Mortality due to Adhesions
Intestinal atresia	105	24	33%
Intestinal stenosis	34	5	20%
Meconium ileus	55	7	15%
Total	194	36	23%

products of cellular destruction which resulted from the initial inflammatory stimulus. These "permeability factors" amplify and extend the effect of histamine on blood vessel permeability.

Exudate which has accumulated during the early inflammatory stages undergoes certain changes. Some of it is removed by fibrinolytic activity and resorption.[41] That remaining contains the precursors of collagen and can be transformed into collagen by fibroplasia and differentiation, in a manner analogous to the process of wound repair.[14] In the adult animal, fibroplasia and differentiation begins about 4 days after wounding. But in the young animal this phenomenon starts one day earlier,[22] which may explain why the rate of healing is more rapid in the young animal [22] and may also have a bearing on the greater incidence and severity of intestinal adhesions in the infant compared to the adult. After the 3 or 4 day lag period, differentiation of the exudative materials into collagen by fibroblastic activity proceeds at a relatively rapid rate although the process is not completed for many months.[45]

This sequence of events—inflammatory reaction, exudation, fibroplasia and organization—describes the process by which intestinal adhesions develop following an intra-abdominal operation.

Prophylaxis of Intestinal Adhesions

Considering the pathogenesis of adhesion formation, a successful approach to prevention of adhesions could take one or more forms.

1. Minimizing the initial inflammatory reaction, thereby reducing the amount

of exudate and limiting secondary cellular damage.

2. Promoting the dissolution and early removal of the fibrinous exudate by artificially adding lytic agents to the peritoneal fluid.
3. Delaying fibroblastic organization and collagen formation, thus allowing serosal cells to cover traumatized areas of intestine before mature adhesions form.

1. The initial inflammatory reaction has a very rapid onset and is characterized by small blood vessel dilatation and increased vessel permeability, resulting in exudation and local edema. This early response to a noxious stimulus can be minimized by administration of an antihistaminic.[52] Several hours after the early stage, a delayed, exudative phase occurs.[57] This is thought by some, to be due to *increased formation of endogenous histamine,* and evidence indicates that this phase of inflammation can be inhibited by administration of corticosteroids.[48]

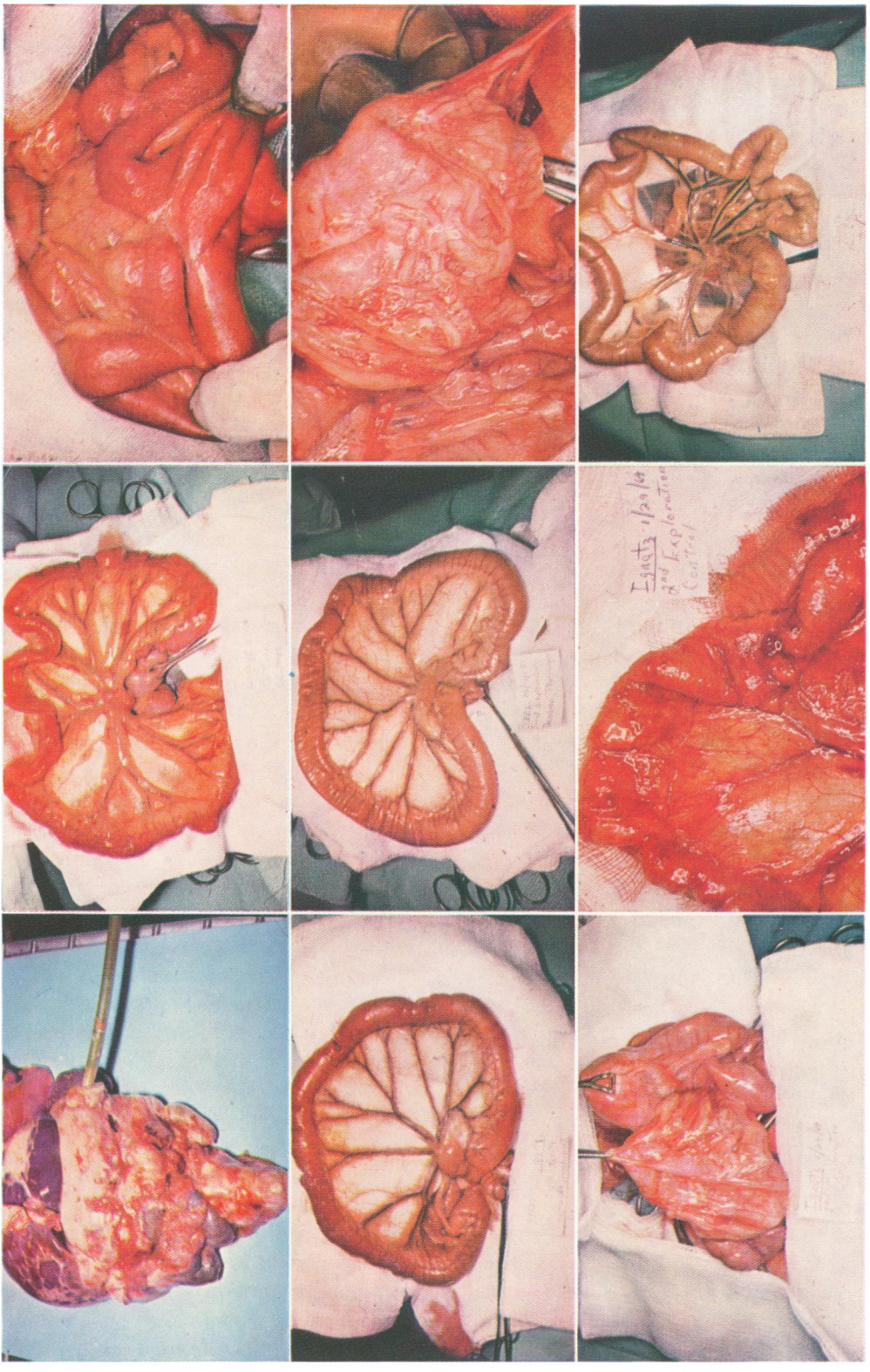
Selection of a drug which minimizes the early phases of inflammatory reaction should be based on certain considerations. Promethazine * possesses several properties which make it most desirable. First, it inhibits the increase in vascular permeability induced by histamine and blocks the reaction resulting from all the nucleosides, peptides and globulins tested by Spector.[49] Second, promethazine blocks the *release* of histamine from the mast cell, in contrast to other antihistamines which act by *stimulating* the release of histamine, depleting the mast cell.[59] Finally, promethazine protects the cellular lysosome system against a variety of insults, thereby reducing the degree of secondary cellular damage that follows the release of intracellular enzymes.[24]

Treatment with corticosteroid hormones considerably reduces exudation resulting from an inflammatory stimulus.[3] Another property of adrenal steroids appears to limit secondary damage of the inflammatory response. To some extent this may also result from the protective effect of corticosteroids on the lysosome system.[24] However, other effects of the corticosteroids also seem important in this regard. Eyring and Dougherty[11] suggest that when tissue is damaged, material is released which causes an increase in the permeability of the cellular membrane. This permeability change causes the affected cells to take up sodium and water, swell, and even burst. More products of cell destruction are thereby released, giving rise to more destruction. Available evidence[11] indicates that adrenocortical hormones possess the capability for stabilization of the cell membrane in the presence of these permeability factors, affording protection to the cell, thereby reducing the extent of secondary cellular destruction.

2. Previous studies from this laboratory have focused on the use of fibrinolytic activators to promote dissolution of fibrinous exudate.[55] While preliminary results indicated that adhesion formation might be lessened, complications from hemorrhage attending the use of the fibrinolytic agents limited their clinical use. Heparin has also been reported to be useful,[4] but, again, hemorrhagic complications were experienced during clinical trials.

3. An inhibitory effect of antihistaminics on fibroplasia has been reported,[2] resulting in greatly diminished granulation in response to talc introduced into the abdomen or pericardium. The inhibitory effects of adrenal steroids on fibroblastic migration, proliferation and organization are well documented. While a dose-response relationship was not defined, Kaufman, Mason and Kinney[25] found that the inhibitory effects of hydrocortisone on the migration of fibroblasts in tissue culture was *directly proportional* to a *wide range* of steroid concentration in the culture medium. Holden and Adams[19] reported that fibroblastic proliferation in tissue culture was markedly reduced by hydrocortisone (20 μgm./ml.)

* Promethazine (Phenergan®), Wyeth Laboratories. Dexamethasone (Decadron®), Merck, Sharp & Dohme.



in the culture medium. However, by increasing the concentration to 50 μgm./ml., an *additional* 50 per cent reduction in proliferative activity could be attained. The growth of granulation tissue in an experimental wound was found by Ragan *et al.*[44] to be inhibited by moderate doses of cortisone, and *complete suppression of the connective tissue response could be obtained by the use of massive amounts of the drug.* These studies support the belief that massive doses of steroids might elicit responses that are not apparent when lesser amounts of drug are used.

Antihistamines [23] and adrenocortical steroids [8, 31, 58] have been used individually to prevent intestinal adhesions. To the best of our knowledge, the combined use of the drugs has not been recorded. From a consideration of the pathogenesis of adhesion formation it would seem that a synergistic effect of the two drugs might be expected.

Two points seem worth emphasizing. First, the use of massive doses of steroids has certain theoretical advantages. Second, since adhesion formation begin within minutes after surgical trauma, an effective concentration of the drugs should be present at the time when tissue damage sets off the inflammatory reaction. Optimal protection can only be achieved by treatment before, during and after operation.

The goals of this study were to develop methods to:

1. prevent formation of adhesions in the highly susceptible infant undergoing abdominal surgery
2. inhibit the reformation of adhesions following surgical division of those which had appeared after some previous operation.

Methods and Results of Experiments

In order to evaluate the efficacy of a number of drugs to prevent adhesion formation, preliminary studies were carried out in a large number of rats. The technic [33] consisted of implanting a piece of rat liver homograft, 1.5 × 1.5 cm., freely into the peritoneal cavity of a recipient rat. Within 12 hours adhesions developed between the homograft and the omentum and intestines of the recipient. These adhesions are quite extensive after 48 hours. We found that dexamethasone would inhibit considerably the formation of such adhesions. Promethazine also lessened the extent of adhesion formation. Diphenhydramine was much less effective than promethazine. A combination of dexamethasone and promethazine, in the absence of peritoneal sepsis, consistently prevented adhesion formation for 48 hours.

From the information gained from rat studies, the effectiveness of a *combination* of dexamethasone (Decadron) and promethazine (Phenergan) in preventing intestinal adhesions was studied. In each of 90 adult mongrel dogs, the entire free surface of the distal 60 cm. of ileum was scrubbed 20 times with a stiff nylon brush, using sterile technic. This produced an excoriation (Fig. 2a), which simulates and greatly amplifies the trauma bowel might receive during a human operation.

Twenty of these 90 animals were treated according to the following schedule: dexamethasone and promethazine 1 mg./Kg. intramuscularly, 6 and 3 hours preoperatively; the same dose intraperitoneally, diluted in 50 ml. of saline; and 1 mg./Kg. of each drug intramuscularly every 4 hours for 24 hours postoperatively (giving the first postoperative medication about 2 hours after operation). The 70 control animals received only 50 ml. of saline intraperitoneally at the time of laparotomy. Both groups received procaine penicillin (300,000 u) intramuscularly every day for 3 days.

Ten of the 20 treated and 35 of the 70 control animals were explored 7 days after operation, and the remainder of each group were explored after 4 weeks. The extent of adhesion formation at exploration was graded as none, minimal (a single adhesion of omentum to bowel, or bowel to bowel) and moderate to severe (Table 2). The four animals in the treated group who had minimal adhesions underwent surgical di-

TABLE 2. *Adhesions Following Initial Scrub*

	None	Minimal	Moderate to Severe
Treated	16	4	0
Control	0	7	63

vision of these adhesions and a second course of treatment exactly like the first. At exploration 2 weeks later there were no residual adhesions in these animals.

All 70 untreated dogs in this experiment were divided into two groups, and each animal underwent surgical division of any intestinal adhesions (under sterile conditions). Forty-three of 70 dogs received dexamethasone 1 mg./Kg. and promethazine 1 mg./Kg. intramuscularly 6 and 3 hours preoperatively, the same dose intraperitoneally in 50 ml. saline at the time of laparotomy, and again 1 mg./Kg. of each drug intramuscularly every 4 hours for 24 hours postoperatively. Twenty-seven of 70 animals were given only 50 ml. saline intraperitoneally at the time of adhesion division and were given no further treatment. All 70 animals received procaine penicillin (300,000 u) intramuscularly every day for 3 days postoperatively (Table 3). Twenty-five of 43 treated dogs were free of adhesions at exploration 1 to 6 weeks after surgical division of their adhesions. Fourteen of 43 treated animals had minimal adhesions, and four of 43 dogs had moderate to severe adhesions at subsequent exploration. Of 27 dogs in the control group, subsequent inspection showed that 25 had exceedingly tough, dense adhesions and 2 had minimal ones.

TABLE 3. *Adhesions Reforming after Surgical Division of Existing Adhesions*

	None	Minimal	Moderate to Severe
Treated	25	14	4
Control	0	2	25

Representative pictures of treated and control animals in both series of experiments are shown in Figures 2, 3 and 4.

In another series of experiments, 12 dogs underwent division of small bowel, following which an anastomosis was made by a single layer Halsted technic, using 4-0 silk sutures. All of these animals received dexamethasone and promethazine as outlined for the previous studies. The animals were sacrificed 2 weeks after operation and the anastomosis evaluated. In no instance was there evidence of anastomotic leakage.

Clinical Studies

We utilized the method outlined in our experimental studies in 27 patients; 22 were babies and young children, five were adults. There were two changes from the experimental protcool. For newborn infants, doses of promethazine were reduced to 0.5 mg./Kg. intramuscularly every 4 hours following operation because of a sedative effect from higher dosage of the drug. For adults, standardized doses of the drugs (irrespective of patient weight) were used. Twenty

FIG. 1. Autopsy specimen from an infant with ileal atresia. This demonstrates massive intestinal adhesions that followed initial primary repair, and secondary surgical division of adhesions. This is the picture that all too commonly faces the surgeon dealing with neonatal abdominal surgical problems.

FIG. 2A. Dog experiment. Appearance of the ileum, immediately following vigorous scrubbing of bowel.

FIG. 2B. Two weeks after Figure 2A, showing the adhesions which formed in this animal which was not treated with drugs.

FIG. 3A. Dog experiment. Denuded appearance of the distal ileum after it has been scrubbed with a stiff brush.

FIG. 3B. Appearance of intestine two weeks after Figure 3A. This animal had received dexamethasone and promethazine in doses indicated in the text. There are no adhesions.

FIG. 4A and 4B. Dog experiments. Intestinal adhesions that developed in an animal whose distal ileum was scrubbed, and who was not treated with drugs.

FIG. 4C and 4D. 4C. Shaggy, ragged appearance of intestines after division of adhesions shown in Figures 4A and 4B. The abdomen was closed and drug therapy instituted. 4D. Appearance of intestines 4 weeks after 4C. The serosal surfaces are smooth and free of adhesions.

mg. of dexamethasone and 25 mg. of promethazine were given intramuscularly 6 hours and 3 hours preoperatively, the same dose in 50 ml. saline intraperitoneally, and repetition of this dose every 4 hours for 24 to 36 hours postoperatively, giving the first dose about 2 hours following operation.

Seven patients were treated because of obstruction from existing intestinal adhesions. All seven underwent exploration and lysis of adhesions, and all were treated with the drugs as described. Five did very well postoperatively, with no further evidence of obstruction. One patient (an infant) had had obstruction for 3 weeks before exploration and lysis of severe adhesions; she died 5 days after operation of inanition and pneumonia; at autopsy no adhesions were found. A seventh patient, 6 years old, with massive small intestinal infarction due to midgut volvulus, required intestinal resection as well as lysis of adhesions. A small bowel anastomosis was constructed which subsequently (10 days postoperatively) developed a fistula. This fistula was believed to have resulted from the use of intestine with questionable viability for the anastomosis.

Twenty patients came to operation for the first time, but were believed to represent a very high risk for formation of adhesions after an abdominal procedure; ten were newborn infants. One baby with cystic fibrosis and meconium ileus had a Mikulicz resection of small bowel and died 2 weeks postoperatively of pulmonary complications. The abdomen was completely free of adhesions at postmortem examination. The remaining nine babies all had an uneventful postoperative course. The ten other patients were all older children and adults, and their postoperative course was very satisfactory.

Non-absorbable sutures were used in the abdominal closures of these patients and the skin sutures were left in for 12 to 14 days. No wound complications were observed.

Discussion

Interest in the use of enormous doses of corticosteroids has been increasing, particularly in the areas of tissue transplantation [34] and shock.[30] Melby *et al.*[38] found that 10 to 20 mg./Kg. of cortisol was necessary to prevent an elevation in serum glutamic oxaloacetic transaminase level that occurred routinely when *E. coli* endotoxin was injected into untreated animals. Recently, Lillehei, Longerbeam, Block and Manax [30] reported that use of hydrocortisone in the treatment of experimental endotoxin or hemorrhagic shock was most effective when doses of 50 mg./Kg. or more were used.

Since the total duration of treatment employed in our animal and clinical studies was only 36 hours, no complications from adrenal inhibition or peptic ulceration were anticipated or observed, experimentally or clinically.

Studies are currently underway regarding the short and long-term effects of treatment with dexamethasone and promethazine on wound healing. Use of non-absorbable sutures minimizes the importance of delayed wound healing and we have routinely closed all wounds in animals and patients with silk sutures. Observations of Prudden,[43] Lattes,[28] and Pappas [42] that cartilage powder and collagen film specifically reverse the inhibitory effects of corticosteroids on wound healing are also pertinent. The possibility exists that we may be able to inhibit selectively inflammation and fibroplasia in one area of the body, and yet promote healing in a desired area by the local addition of collagen film or cartilage powder.

Summary

A method for the prevention of postoperative intestinal adhesions has been presented, based on consideration of the pathophysiology of adhesion formation. By the use of an antihistamine, promethazine (Phenergan^{R}) and an adrenocortical hormone, dexamethasone (Decadron^{R}), the in-

flammatory phase that follows trauma to intestinal serosa can be minimized, and the organization of inflammatory exudate into fibrous adhesions can be delayed. This delay allows serosal cells to grow over the denuded areas of bowel and thus cover any raw fibromuscular surfaces which otherwise could be the seat of adhesion formation. Results of an experimental study in dogs and a series of 27 patients have been very encouraging. Further observations on humans are indicated.

Two points must be emphasized:

1. Since adhesion formation begins within minutes after any peritoneal injury, prevention of adhesions requires a high level of drug saturation at the time the injury is made.

2. *Large doses* of the drugs are required to insure maximum benefit. We have used, experimentally, a schedule of 1 mg./Kg. of each drug, given intramuscularly 6 and 3 hours preoperatively, with the dose repeated in 30 to 100 ml. of saline intraperitoneally as the abdomen is being closed, and intramuscularly every 4 hours for 24 hours to 36 hours postoperatively. For small babies the postoperative dosage of promethazine is reduced to 0.5 mg./Kg. to minimize soporific affects. For adults, standardized dosage schedule (independent of weight) appear acceptable.

Addendum

Since this report was submitted, a total of 81 patients, ranging in age from newborn to 89 years, have been treated according to the schedule outlined. The results have been very satisfactory, and no complications related to treatment have occurred except the probable oversedation of a newborn infant who received promethazine 1 mg./Kg. instead of 0.5 mg./Kg.

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