Indomethacin-Induced Intestinal Inflammation

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Indomethacin induces inflammation of the small-intestinal mucosa leading to ulceration in patients. In rats we examined this untoward drug effect by measuring changes in de novo *macromolecular synthesis and morphology during exposure to indomethacin given as a single oral dose of 15 mg/kg. Indomethacin alone induced diffuse jejunoileal mucosal inflammation accompanied by spotty ulceration. These lesions were not observed at 2 and 6 hr after administering the drug but were apparent by 24 hr. By 72 hr the intestinal inflammation had intensified, and there were multiple perforating ulcers, extensive adhesions, and peritonitis in the moribund animals.* De novo *DNA synthesis was increased approximately fourfold by 24 hr and ninefold by 72 hr; RNA synthesis was nearly doubled by 24 hr and nearly trebled by 72 hr; protein synthesis increased about fourfold at 24 hr and eightfold at 72 hr. Both the histological lesions and the macromolecular synthetic changes induced by indomethacin were prevented by 16,16-dimethyl prostaglandin E_2 and by broad-spectrum antibiotics but not by dexamethasone, prednisolone, or colchicine. Neither ligation of a mesenteric arterial branch nor administration of vasopressin induced the intestinal inflammatory lesions seen with indomethacin. The predominant mechanism involved in indomethacin ulceration of the gut appears to be acute inflammation rather than ischemia.*

Indomethacin is a nonsteroidal drug with antiinflammatory, antipyretic, and analgesic properties. An untoward effect of indomethacin therapy is gastrointestinal bleeding and ulceration (1–8). Robert has reported that these lesions can be prevented in animals by administration of prostaglandins (9). Several mechanisms of prostaglandin cytoprotection against indomethacin-induced ulcers may be involved, including inhibition of gastric acid secretion (8, 10–12), compensation for endogenous prostaglandin deficiency induced by indomethacin (9, 13, 14), stimulation of the synthesis of intracellular cyclic AMP (15), and reestablishment of the integrity of the mucosal cell membrane in terms of its impermeability to H^+, water, electrolytes, and noxious agents (16, 17).

Indomethacin-induced intestinal lesions in rats occur in the jejunum and ileum. The lesions consist initially of white nodules and hemorrhagic segments palpable from the serosal surface. Subsequently massive adhesions of the abdominal viscera form in response to the perforating lesion and the rats die from peritonitis and septicemia (7, 9).

In cutaneous systems, E-type prostaglandins markedly stimulate DNA, RNA, and protein synthesis as measured by incorporation of radiolabeled precursors (18, 19), whereas prostaglandins significantly inhibit DNA, RNA, and protein synthesis in cultures of mouse leukemia lymphoblasts (20). Little has been reported about prostaglandin effects on the synthesis of these substances in gastrointestinal tissues (21).

The main purpose of our investigation has been to study macromolecular synthesis in rat intestinal mu-

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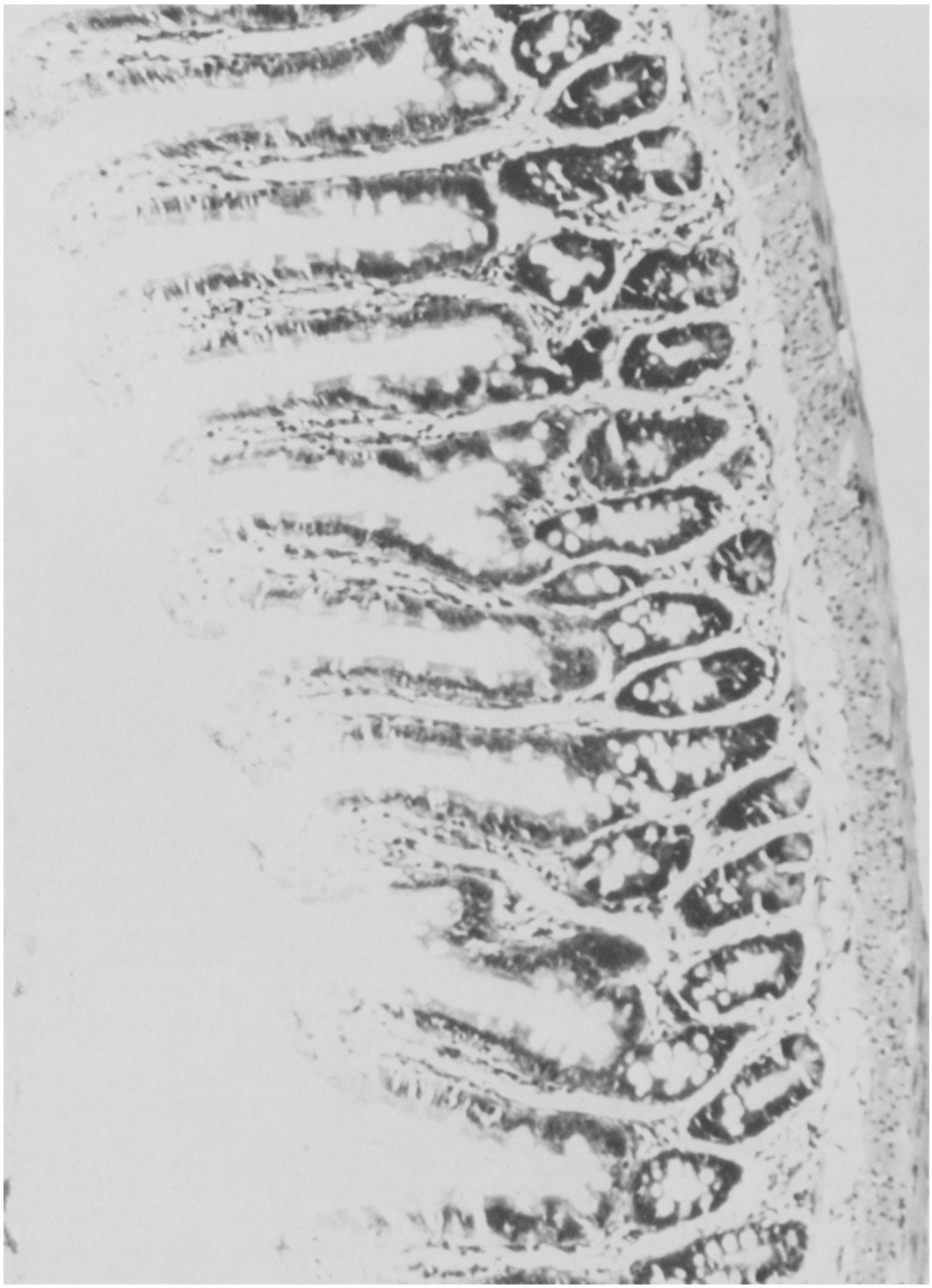

Fig 1. *Light micrographs of rat small intestine at various times after administration of indomethacin.* (A, this page) At 6 hr following indomethacin there is no change from normal (× 160). (B, facing page) Shows the lesion at 24 hr. The mucosa is edematous with an inflammatory exudate, and at two antimesenteric sites (labeled A and B on this photomicrograph) there is complete ulceration of the mucosa extending through to the muscularis of the bowel (× 40). (C, page 752) Shows, in contrast to Figure 1A above, at the same magnification, the lesion at 24 hr with edema and an inflammatory infiltrate into the wall of the small intestine (× 160). (D, page 753) Shows the lesion at 72 hr where there has been perforation of the wall, adhesion of adjacent loops, and extension of the inflammation into the adipose tissue of the peritoneum (× 40).

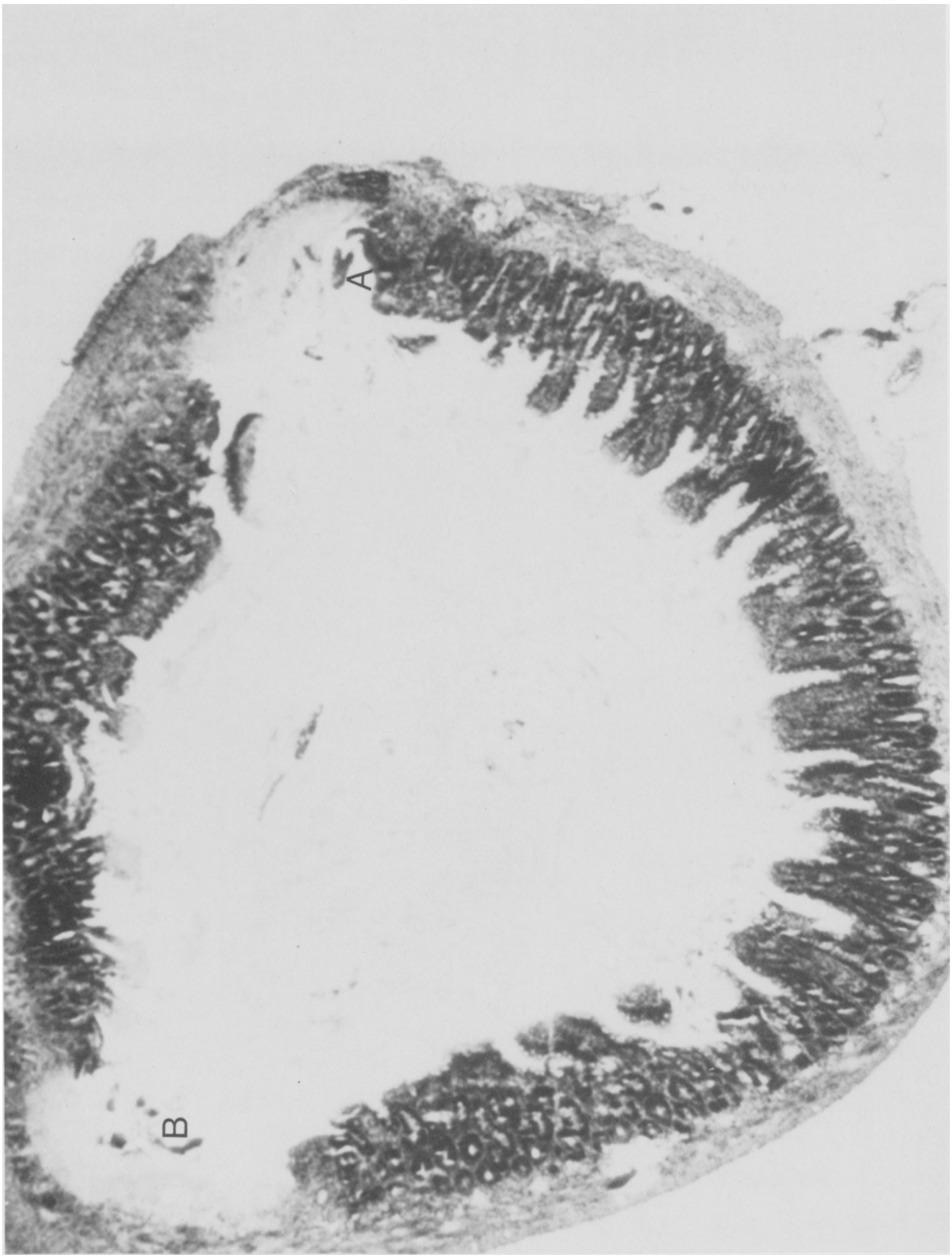

Fig. 1B

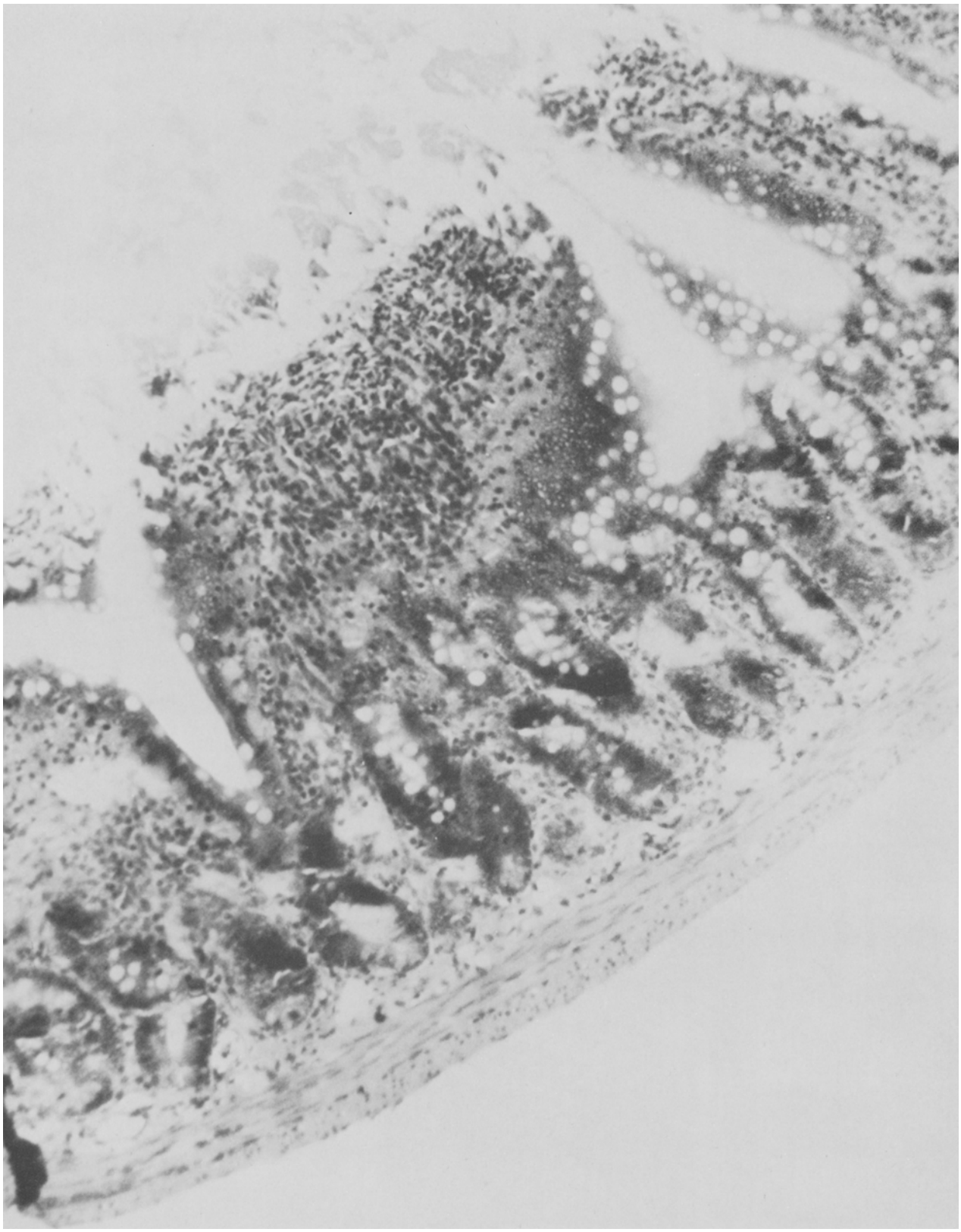

Fig. 1C

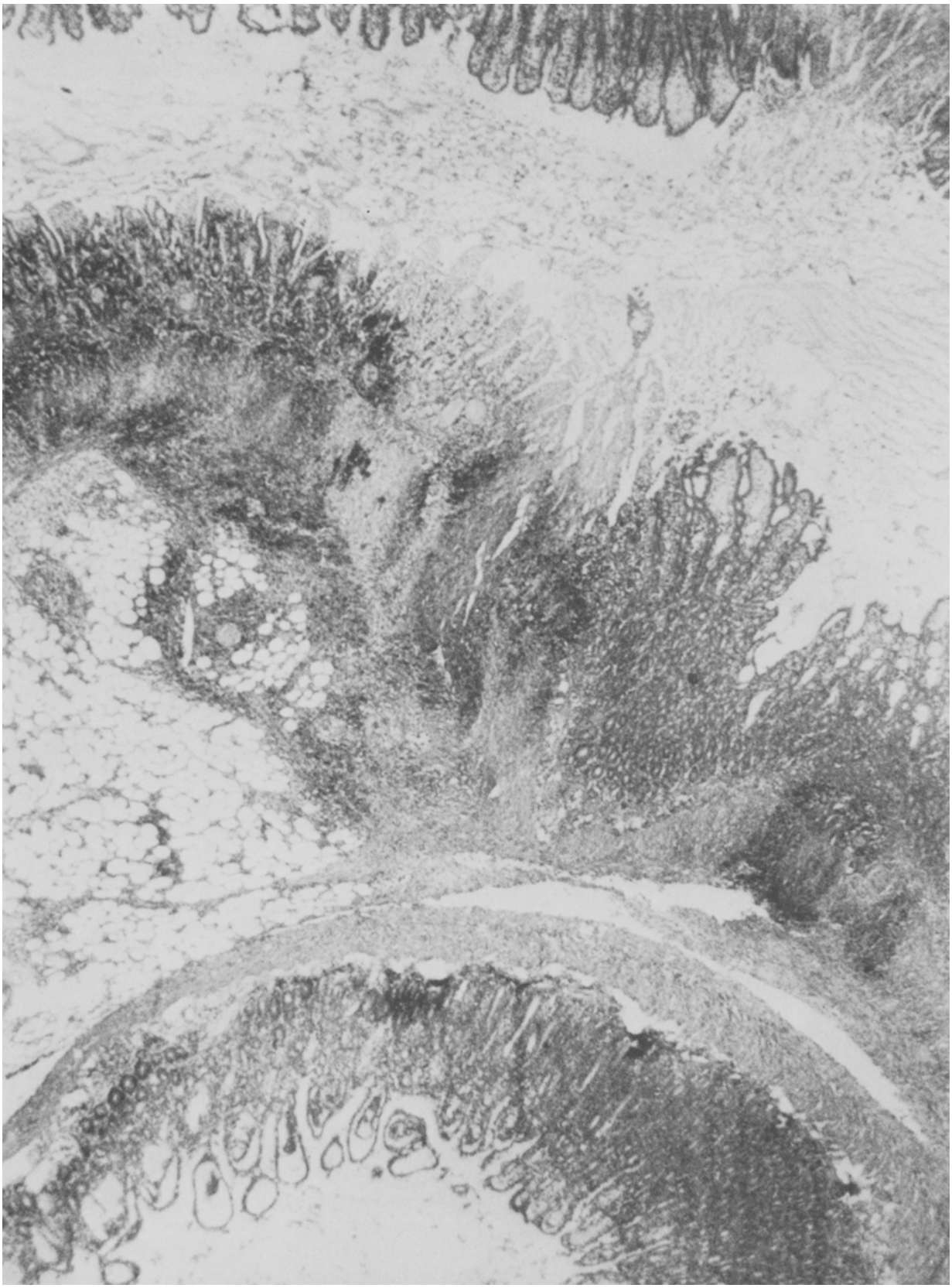

Fig. 1D

cosa during the course of indomethacin ulceration and cytoprotection by prostaglandins.

MATERIALS AND METHODS

Wistar female rats weighing 200–300 g were chosen for this study since this strain is sensitive to the ulcerogenic effect of indomethacin.

Indomethacin (Merck Sharp & Dohme), 16,16-dimethyl prostaglandin E_2 ($dmPGE_2$), kindly supplied by Dr. John Pike of The Upjohn Company and a broad-spectrum antibiotic combination (Gibco; penicillin–streptomycin, polymixin "B" sulfate, and neomycin) were the drugs used in our experimental rats and the drug vehicle V-100 (Upjohn) was administered to control rats. Indomethacin was suspended in V-100, the rest of the drugs were diluted with V-100, and all the drugs were given to the rats orally by a feeding needle. Control rats were fed only a single dose of V-100. Rats in the test group were given 15 mg/kg of indomethacin. The dose of $dmPGE_2$ was 0.3 mg/kg and that for the antibiotic combination was: penicillin and polymixin B sulfate, 20,000 U/kg each; and streptomycin and neomycin, 20,000 μg/kg each. $dmPGE_2$ or antibiotics were given to separate groups of rats twice daily for three days. In another two groups of animals, after the first dose of $dmPGE_2$ or antibiotics, a single dose (15 mg/kg) of indomethacin was administered, and the twice daily pattern of $dmPGE_2$ or antibiotics was continued for the next three days. Thus, for the major portion of our study there were six groups of rats including the control group, with six rats in each group. After three days, rats were sacrificed for examination of the gut and for tissue incubation.

An additional 30 rats were divided into five equal groups and were sacrificed at the following times after administration of a single dose (15 mg/kg) of indomethacin: 2, 6, 24, and 72 hr; the fifth group was not given the drug and served as control animals. Intestinal tissue was excised from these rats for assay of *de novo* synthesis of DNA, RNA, and protein in a study of the time course of changes evoked by indomethacin.

Three pieces of jejunoileal tissue of about 200 mg wet weight were taken from each rat. Each tissue portion was minced in 2 ml of 199 Hanks' salt medium (Gibco) adding either 2 μCi/ml of 6-[^{3}H]thymidine (specific activity 27 Ci/mmol) as the DNA tracer, 5-[^{3}H]orotic acid (specific activity 20 Ci/mmol) as the RNA tracer, or [U-^{14}C]protein hydrolysate (specific activity 10 mCi/mmol) as the protein tracer. The minced tissue pieces were incubated in a 37° C water bath for 30 min, shaken, and further uptake was arrested by addition of 2 ml of ice-cold 0.4 N PCA with 5 mM of the carrier for thymidine, orotic acid, or the amino acid mixture.

The incubated tissue pieces were homogenized in a glass piston homogenizer. After homogenization, two washes with ice-cold 0.2 N PCA at 500*g* centrifugation were carried out for 10 min each to remove excess isotope. The modified Schneider procedure was adapted for the fractionation of nucleic acids and protein. The RNA fraction was extracted from the washed pellet by hydrolysis with 0.3 N KOH at 37° C for 90 min. Further hydrolysis by 10% PCA at 100° C for 10 min allowed collection of the DNA fraction. The protein fraction was the pellet left after DNA extraction.

The nucleic acids and protein content were estimated by both chemical and radioisotopic assays. The chemical assay measured the total pool of nucleic acids and protein in the tissue in terms of μg per unit of wet weight of tissue. Orcinol reagent was used for RNA determination (yeast RNA being the standard), and diphenylamine reagent was used for DNA measurement (calf thymus DNA being the standard). Lowry's procedure was employed for protein estimation (BSA was used as the standard). Since the overlap contamination among fractions was less than 10%, the determination of RNA, DNA, and protein contents was carried out solely on the fractions.

The radioisotopic assay was used to determine the newly synthesized macromolecules as counts per minute per unit wet weight of tissue during the 30 min of incubation. An aliquot of each sample was mixed with PSC scintillation fluid (Amersham/Searle) and counted in a scintillation detector (Nuclear-Chicago Mark I). In these determinations the contamination among fractions was taken into consideration because the overlapping radioactivity was as high as 30% compared to the fraction. The newly synthesized RNA was determined from the counts of the RNA and DNA fractions of the tissue which had been incubated with [^{3}H]orotic acid. The newly synthesized DNA was estimated as counts from the RNA and DNA fractions of the tissue which had been incubated with [^{3}H]thymidine. The newly synthesized protein was considered to be represented by the sum of the counts from the RNA, DNA, and protein fraction of the tissue which had been incubated from the [^{14}C]amino acid mixture.

Histological sections were prepared in the preceding experiments using representative areas of the small bowel. Sections were stained with hematoxylin and eosin.

RESULTS

A single dose (15 mg/kg) of indomethacin produced severe intestinal lesions in the jejunum and the cephalic part of the ileum and followed a time course. There were no gross lesions at 2 and 6 hr after indomethacin was given. At 24 hr after administration of indomethacin, there was a general loss of appetite in the rats, the intestinal content was black in color, and small nodules were palpable in the adjacent mesentery. By 72 hr the gross abdominal findings consisted of massive adhesions between adjacent loops of gut, discrete hemorrhagic lesions in the intestinal wall, and mesenteric nodules. At this time the peritoneum was filled with fluid, the eyes were pale, the body weight had decreased by approximately 10–20%, and the rats appeared moribund. $dmPGE_2$ and antibiotics prevented the aforementioned indomethacin-induced lesions and symptoms, although diarrhea was prevalent in these two groups (indomethacin + $dmPGE_2$ or antibiotics). The body weights of these protected

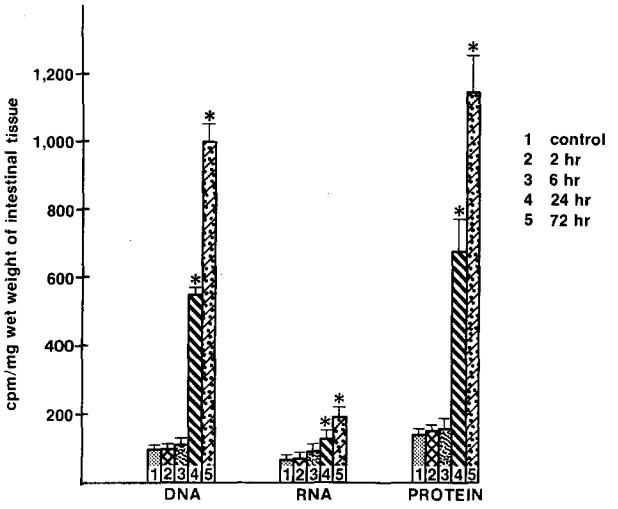

Fig 2. The time course of changes in *de novo* macromolecular synthesis following administration of indomethacin in 5 groups of rats. Asterisk indicates $P < 0.05$.

rats decreased only 3–6%, and animals appeared healthy compared to rats receiving indomethacin alone. Rats in the two groups receiving $dmPGE_2$ or antibiotics alone experienced diarrhea but appeared healthy and were without lesions.

Interestingly, indomethacin did not produce comparably severe lesions in adult Sprague–Dawley male rats (250–350 g). One third of this strain of rats (6 animals) resisted indomethacin and survived without intestinal lesions.

Light microscopic observation of intestinal tissue revealed no changes at 2 and 6 hr after indomethacin alone. By 24 hr after administration of indomethacin, there was diffuse acute inflammation in the villi. The sections also showed ulceration at various points in the circumference of the bowel (Figure 1). By 72 hr there was intense widespread inflammation, with perforation in many bowel wall sites and evidence of frank peritonitis (Figures 1A–D).

There was no significant change in total tissue content of DNA, RNA, and protein in rats treated with indomethacin alone, indomethacin combined with $dmPGE_2$ or antibiotics, or either of the latter two agents alone compared with control rats. These findings are consistent with the presence of a large macromolecular pool which contains a small population of newly synthesized molecules. Hence, the chemical assay is not sufficiently sensitive to detect *de novo* synthesis, and radioisotopic assay must be used to determine significant variation among groups of rats receiving different drugs.

In rats administered indomethacin alone *de novo* DNA, RNA, and protein synthesis was significantly stimulated by indomethacin at 24 and 72 hr but not at 2 or 6 hr (Figure 2). Although $dmPGE_2$ and antibiotics alone did not significantly alter *de novo* synthesis of macromolecules, both of these drugs prevented the increased biosynthesis induced by indomethacin (Figure 3). Furthermore, both antibiotics and $dmPGE_2$ prevented development of the indomethacin-induced inflammatory lesions of the gut (Figure 4).

In the preceding experiments the indomethacin-induced increases in *de novo* synthesis of RNA appear to have been less than the increases in synthesis of DNA or protein (Figure 2 and 3). This apparent lesser sensitivity of new RNA synthesis to indomethacin may have been due to degradation of RNA by a local lysosomal RNase, since indomethacin decreases tissue prostaglandin content,

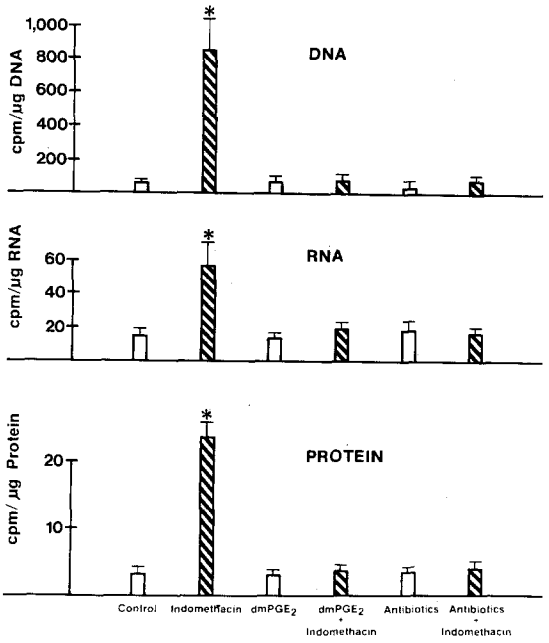

Fig 3. Comparison of effects of indomethacin, indomethacin + $dmPGE_2$, indomethacin + antibiotics, $dmPGE_2$ alone, and antibiotics alone on *de novo* synthesis of DNA, RNA, and protein in rat gut. Asterisk indicates $P < 0.05$.

Fig 4. Appearance of the gut wall 72 hr after administration of indomethacin combined with a regimen of dmPGE$_2$. There is a minimal inflammatory infiltrate into the villi but no evidence of edema or ulceration. This figure should be contrasted with Figure 1D (× 160).

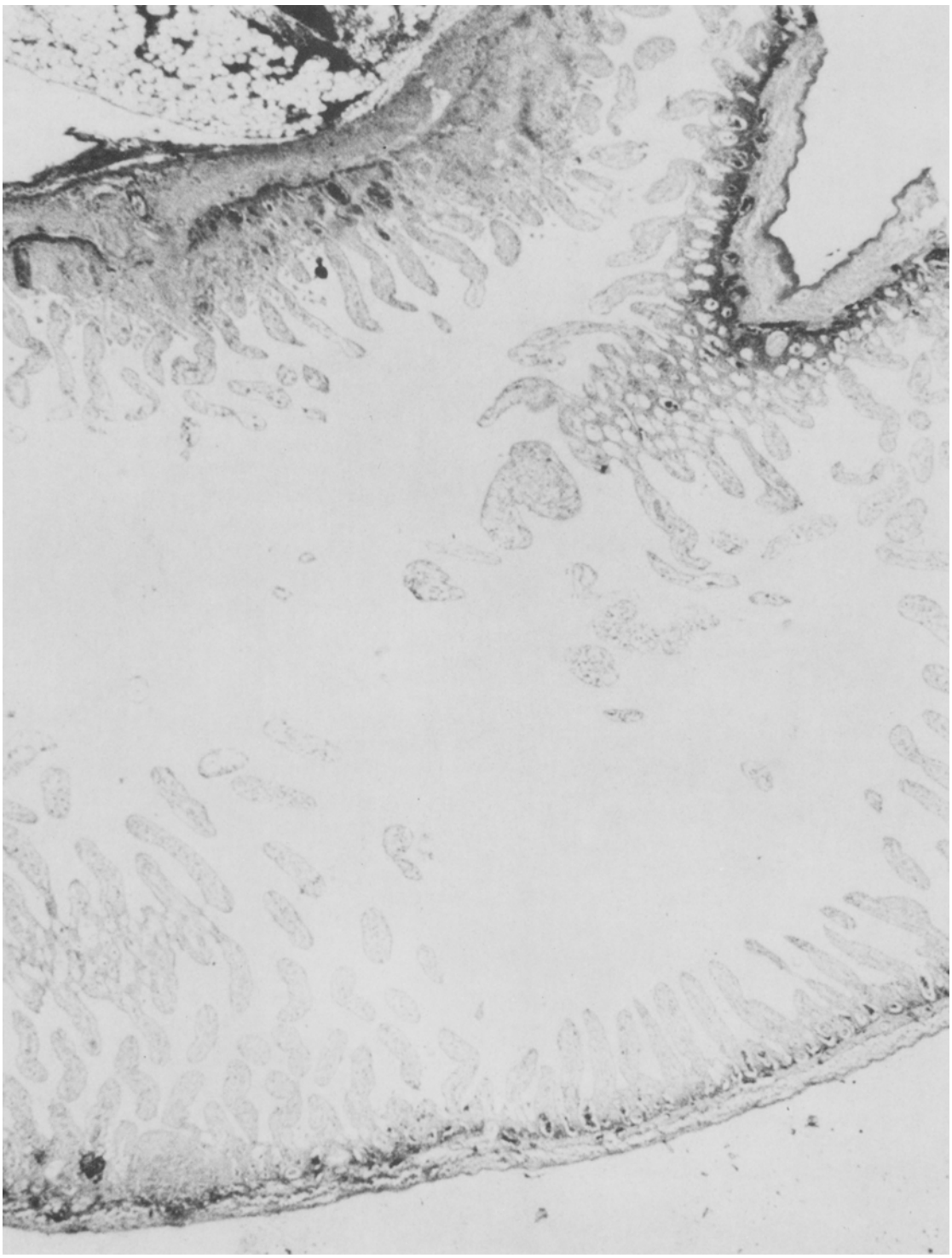

Fig 5. Appearance of the gut wall 18 hr after ligation of its nutrient artery. There is complete necrosis of the mucosa with many cell ghosts remaining and a minimal inflammatory infiltration in the submucosa. This figure should be contrasted with Figure 1B.

TABLE 1. EFFECTS OF LIGATING A BRANCH OF THE SUPERIOR MESENTERIC ARTERY AND OF VASOPRESSIN ON *DE NOVO* SYNTHESIS OF DNA IN THE GUT WALL

Rat Group	*[³H]Thymidine uptake (cpm/mg wet wt)*	*P value compared with control*
Control	122 ± 16 (SE)	
Mesenteric ligation	2679 ± 976	< 0.01
Vasopressin	120 ± 10	N.S.

and prostaglandins act via cyclic AMP to stabilize lysosomal membranes (34). In addition, radiolabeled orotic acid (or uridine) uptake provides a less sensitive estimate of macromolecular synthesis than does uptake of thymidine or amino acids (35).

In view of the rapid development of intestinal wall necrosis with indomethacin and the reported vasoconstrictor action of this drug (22), we performed experiments on two additional groups of six rats each to assess a possible ischemic mechanism in the intestinal lesion. In the first group a major branch of the superior mesenteric artery was ligated under anesthesia via laparotomy, the incision was closed, and the animals were sacrificed 18 hr later. Histological examination of the black-colored intestinal wall revealed the findings of massive ischemic necrosis without the inflammatory elements observed 24 hr after indomethacin (Figure 5). Tissue assays of the ileal wall for *de novo* production of DNA revealed a dramatic increase in this synthesis compared with control, and no significant increase was observed in an area of the upper gut which had not been subjected to ischemia (Table 1). In a second group of rats, we injected vasopressin intraperitoneally every 6 hr in the dose of 10 U/kg for 1 day to evoke intestinal vasoconstriction and we killed the animals 24 hr later. No gross or histological lesions were noted and no increase in newly formed DNA was found in these animals (Table 1).

Finally we explored possible protective effects of two potent steroidal antiinflammatory drugs and an antimitotic agent. Animals were pretreated for two days with prednisolone (5 mg/rat each day, subcutaneously), dexamethasone (1 mg/rat each day, subcutaneously), or colchicine (0.5 mg/rat twice daily orally) before administering indomethacin. These agents failed to prevent either the jejunoileal lesions or the increase in macromolecular synthesis at 72 hr after indomethacin (Table 2).

DISCUSSION

The small-intestinal lesion of the rat induced by large doses of indomethacin is of interest for several reasons. First, indomethacin is ulcerogenic in human subjects (1–4), the drug is widely used, and the mechanism of this toxic effect of indomethacin is uncertain. Indomethacin is also an inhibitor of the endogenous biosynthesis of prostaglandins, and the indomethacin-induced lesion is prevented by administration of prostaglandins, as Robert has demonstrated (9). Indomethacin is a weak electrolyte which is absorbed from the gut into the enterohepatic circulation, and it has been found that the jejunoileal lesions can be prevented by ligation of the common bile duct (7, 23). Our object in the current study was to observe changes in intestinal wall macromolecular biosynthesis as a correlate to the development of gross lesions of the ileum in order to gain insight into the pathophysiological mechanisms of indomethacin-induced ulceration.

Macromolecular synthesis may be related to prostaglandins via cyclic AMP. Pratt and Martin (24) reported that the level of cyclic AMP in embryonic rat palate was inversely related to the rate of DNA synthesis as well as to cell division. In leukemia cell culture, Yang et al (20) found that prostaglandins significantly inhibited the rate of incorporation of [³H]thymidine, [³H]uridine, and [³H]leucine. In the lens of the rat, Sallmann and Grimes (25) demonstrated that the amount of radioactive precursor incorporated per cell was reduced to half by prostaglandins. In malignant cells, Jaffe (26) observed that indomethacin stimulated replication by 23% and the stimulatory effect of indomethacin was reversed by

TABLE 2. EFFECTS OF PREDNISOLONE, DEXAMETHASONE, AND COLCHICINE ON 72-HR INDOMETHACIN-INDUCED SMALL-INTESTINE LESIONS AND *DE NOVO* DNA SYNTHESIS

Rat group	*[³H]Thymidine uptake (cpm/mg wet wt)*	*Intestinal lesions*
Control	92 ± 12	None
Prednisolone + indomethacin	1982 ± 603*	Present
Dexamethasone + indomethasone	367 ± 158*	Present
Colchicine + indomethacin	574 ± 116*	Present

*Significant ($P < 0.05$) difference from control.

the addition of prostaglandin E_1. In separate studies we have observed that the inhibitory effect of indomethacin on energy-dependent transport of sodium across the gastric mucosa is reversed by $dmPGE_2$ and by dibutyryl cyclic AMP (27). Furthermore, prostaglandins stimulate adenylyl cyclase in the gastrointestinal mucosa (28, 29). Our present findings agree generally with the aforementioned reports. The intestinal lesions we induced with indomethacin were accompanied by great increases in *de novo* synthesis of DNA, RNA, and protein. A prostaglandin protected the jejunum and ileum against development of the lesion and prevented elevation of the macromolecular synthetic rate. Nevertheless, we interpret the increase in synthesis of nucleic acids and protein as a reflection of the acute inflammatory processes surrounding the ulceration in the wall of the gut, such as invasion of the area by leukocytes, tissue cells, increased local metabolism, etc. It seems most likely that the events responsible for the indomethacin ulcer remain unknown and that the changes in incorporation of radiolabeled components are secondary to the onset of acute inflammation.

Our efforts to separate the process of ulceration from the increase in macromolecular synthesis were generally unsuccessful. Indomethacin induced both events and both were prevented by $dmPGE_2$ and antibiotics. Other antiinflammatory agents and colchicine failed to protect against indomethacin ulcers and failed to stop *de novo* synthesis of the macromolecules, although the response of DNA synthesis to indomethacin seemed to be obtunded by dexamethasone and by colchicine. In other series of rats we have observed some variability in the magnitude of the increase in synthesis of DNA with indomethacin alone. Nevertheless, it is possible that larger doses of these drugs might have significantly reduced the response to indomethacin. On the other hand, gangrene of the bowel following arterial ligation did stimulate macromolecular synthesis without mimicking the gut lesion.

The role of intestinal bacteria in the development of the lesions is also uncertain. Robert has found that indomethacin will not induce jejunal or ileal ulceration in gnotobiotic rats, and the broad-spectrum antibiotics prevent the onset of the lesion (23). We confirmed the latter observation. Our speculation would also assign a secondary role to endogenous bacteria in the development of a drug-induced ulcer.

A more direct mechanism in the genesis of the indomethacin ulcer could be a vascular phenomenon. Indomethacin has been shown to reduce gastric mucosal blood flow (30) and E-type prostaglandins are intestinal vasodilators (31). Exploration of this possibility in our rat model was not fruitful, however. Neither arterial ligation nor the constrictor drug, vasopressin, duplicated the indomethacin lesion, although the former procedure stimulated DNA synthesis. Furthermore, the lesion observed with lethal intestinal ischemia in human subjects is a hemorrhagic necrosis quite unlike the lesions we observed with indomethacin (32).

It seems more probable that both the pathophysiological mechanism of indomethacin ulceration and of prostaglandin cytoprotection initially involve mucosal epithelial intracellular metabolic pathways. Both agents are lipophilic and readily penetrate the interior of cells to reach vulnerable enzymes. In the gastric mucosa the prostaglandins activate adenylyl cyclase, stimulate energy-dependent sodium transport, and inhibit acid secretion (29, 33), whereas indomethacin inhibits epithelial sodium transport (27). Prostaglandins also stabilize lysosomal membranes (34). Profound effects on intracellular energetics and cell membranes are probably involved in the damaging or protective actions of drugs such as indomethacin or prostaglandins.

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