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Histopathology of Duodenal Mucosal Lesions Produced Experimentally By Chemical Vasoconstrictors and The Soothing Effect of Increased Microcirculation

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SUMMARY

In this trial, the effects of epinephrine, norepinephrine and vasopressin on duodenal mucosa was studied histopathologically following their direct intra-arterial administration in rats, rabbits and dogs. In addition, probable preventive action of dextran 40 as a stimulant of microcirculation was tested in rabbits and dogs.

Vasoconstrictors caused mild to severe hyperemia, petechial and ecchymotic hemorrhages and small or larger necroses of duodenal mucosa in experimental animals. The Dextran 40 was mixed into the vasoconstrictor solutions in saline to test the probable soothing action, and the results proved that the increased microcirculation was very effective to prevent the mucosal tissues from necrotizing by vasoconstriction.

Keywords: *Vasoconstriction, Duodenum, Hemorrhage, Necrosis, Microcirculation, Rat, Rabbit, Dog.*

ÖZET

KİMYASAL VESYOKANTRİCTÖRLERLE OLUŞTURULAN DENEYSEL DUODENAL MUKASOL LESYONLARIN HİTOPETOLOJİSİ VE ARTMIŞ MİKROCİRCULATİONYANIN YATIŞTIRICI ETKİSİ

Bu çalışmada, sıçan, tavşan ve köpeklerde adrenalin, noradrenalin ve vazopresin gibi damar büzücülerin direk arter içi verildiğinde duodenal mukoza üzerindeki etkileri histopatolojik olarak incelendi. Ayrıca dekstran 40 ile mikrosirkülasyonun arttırılmasından sonra damar büzücülerin neden olduğu histopatalojik bozuklukların azalıp azalmayacağı araştırıldı.

Vazokonstriksiyon ile deney hayvanlarında duodenum mukozasında sırası ile hiperemi, değişen büyüklükte kanamalar ve koagulatif nekrozlar şekillendi. Tavşan ve köpeklerde vazokonstriktörlerin dekstran 40 ile birlikte verilmesi halinde nekrotizan etkilerin azaldığı gözlendi.

Anahtar Kelimeler: *Vazokonstriksiyon, duodenum, hemoroji, nekroz, mikrosirkülasyon, rat, tavşan, köpek.*

Gastric and duodenal mucosa has an active blood supply and rich vascularisation in addition to its very high epithelial regeneration potential (1). However, the same tissues may be easily damaged as the result of vascular spasms, atherosclerosis, thromboembolism, congestive heart failure and/or some blockage on the portal circulation. The main cause of these damages is the trophic or functional disorders due to the disturbed blood supply for mucosal tissues (2). In these focalareas because of the back diffusion of HCL both the electrolyte balance and the protective secretion of the cell are

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disturbed. The mucosal epithelium and submucosal mesenchymal tissues with disturbed electrolyte balance are degenerated and necrotized. In this process, degenerated or necrotized cells are more sensitve to the proteolytic action of gastric pepsin or intestinal proteases and trauma. These cells than may easily fall into the lumen, leaving a typical ulcer behind on either stomach or duodenal mucosa (1,2).

On the other hand, normal or increased blood supply to bring more food and oxygen to those disturbed mucosa, is considered as an esssential factor to prevent or to treat the ulcerations. The increase in microcirculation is considered as a major factor in the treatment or prevention from gastric or intestinal ulcerations (3.4).

MATERIALS AND METHODS

In the experiment, 70 male albino rats with an average body weight of 380 gr., 24 rabbits with an average body weight of 3.5 kg., and 12 mongrel dogs with an average body weight of 15.0 kg. were used.

The rats were divided into 7 groups with 10 animals in each, and first 6 groups of rats were anesthetized with Nembutal Sodium (Abbott) or penthotal (Abbott) before the injection of 25 gamma/kg Epinephrine, 25 gamma/kg Norephrine and 0.01 IU/kg Vassopressin in 0.1 cc/kg saline. The injections were given directly into the pancreaticoduodenal artery. After 24 hours the first three groups treated with the vasoconstrictors, and control group of rats were overdosed by the same anesthetics to perform necropises and to observe the gastrointestinal pathology. The last three groups were killed 5 days after and evaluated the same way to observe the effect of the elapsing time on the pathology. The specimens were collected from pyloric and duodenal region.

The rabbits were divided into 6 groups each containing 4 animal. Following the anesthesia with the same drugs, the first three groups were treated with the same vasoconstrictors at equal doses, and the last 3 groups were injected with equal doses of same drugs in 1 cc Dextran 40 (Baxter) simultaneously. The drug administrations were again done direct injections into pancreaticoduodenal artery. All animal sacrificed by the end of 24 hours following injections, to observe the lesions and to collect the specimens for histopathology.

The dogs were also divided into 6 groups with 2 animals in each, before anesthetizing by Ketalar (Padeko) together with Rompun (Bayer). The first 3 groups were given only vasoconstrictor drugs, while the last 3 received the same compounds in 2 cc Dexstran 40 simultaneously, via direct injection into pancreaticoduodenal artery. All of the treated dogs were overdosed by the same anesthetics, to assess the degree of pathological changes.

All collected specimens were fixed in 10 % formalin, and processed by conventional techniques. Tissues were sectioned at 6 micron and the sections stained with Haematoxylin and Eosin (5).

RESULTS

In the first three groups of rats, vasoconstriction by epinephrine, norepinephrine and vasopressin caused varied strength of hyperemia, different sized hemorrhages including petechiae, ecchymoses and even larger suggulations of blood, and mild to severe ischemic or anoxic coagulative necroses (Figure I) of duodenal mucosa, in a day following the administration of the drugs. However, these pathologic findings were much less severe in the last 3 rats groups of sacrificed at 5 days. As the result of high regeneration potential, the restoration of mucosa lost by anoxia did not take long time. The control rats did not exhibit any lesion. The severity of induced pathology is summarized in Table I.

Table I: The severity of duodenal lesions in the rats

Group	Used drug	Dosage	Hyperemia	Hemorrhage	Necrosis
1	Epinephrine	25 gamma/kg	+++	+++	+++
2	Norepinephrine	25 gamma/kg	+++	+++	+++
3	Vasopressin	0.01 IU/kg	++	-	++
4	Epinephrine	25 gamma/kg	+	-	+
5	Norepinephrine	25 gamma/kg	+	-	+
6	Vasopressin	0.01 IU/kg	+	+	-
7	Saline	0.1 cc/kg	-	-	-

Mild (+) . Moderate (++) . Severe (+++)

Table II: The severity of duodenal lesions in the rabbits.

Group	Used Drug	Dosage	Hyperemia	Hemorrhage	Necrosis
1	Epinephrine	25 gamma/kg	++	+	+
2	Norepinephrine	25 gamma/kg	++	++	+++
3	Vasopressin	0.01 IU/kg	+	+	+
4	Epinephrine + Dextran 40	25 gamma/kg+1 cc	+	+	-
5	Norepinephrine+ Dextran 40	25 gamma/kg+1 cc	+	+	-
6	Vasopressin+ Dextran	0.01 IU/kg+1 cc	+	+	-

Mild (+) , Moderate (++) , Severe (+++).

In the rabbits, first group treated with epinephrine and third group that received vasopressin showed hyperemia, hemorrhages and mild or limited necroses, while those treated with norepinephrine had more severe hyperemia, hemorrhages and deeper coagulative necrosis in duodenal mucosa (Figure II,III). Those rabbits treated with the same vasoconstrictors mixed with 1 cc Dextran 40, exhibited only hyperemia and some small foci of bleeding in duodenal mucosa (Table II).

The necrosis were present in only those dogs treated with norepinephrine (Figure IV), while the groups taking epinephrine and vasopressin had only mild hyperemia and a few petechiae in the mucosa. The animals treated with the same drugs in 2 cc Dextran 40, were prevented much more significantly, and epinephrine caused no change, while vasopressin produced hyperemia only, and norepinephrine induced hyperemia and small hemorrhages but no necrosis (Table III).

DISCUSSION

Direct relationship between the trophic and functional disorders and mucosal circulation is very important, and studies concerning the blood supply and circulation in the gastric mucosa are being conducted for long time. Cheung et al . (6), have demonstrated that formation of acute erosions on the gastric mucosa in dogs were the result of decreasing rate of blood circulation that causes the reabsorption of secreted hydrogen ions. Kerr et al . (7), showed that the selective application of vasopressin in dogs is capable of markedly limiting and reducing the blood supply of the gastrointestinal tract. Many functions of stomach is partially controlled by Gastrin releasing peptide, acting on the autonomic nerves of the gastric mucosa, and this peptide is secreted and controlled by adrenal catecholamines. This may be understood by looking at the parallel action of increased plasma level of catecholamines. especially that of epinephrine, and increased mucosal blood circulation. On the contrary, a decrease in the circulation, causes reduction in the acid secretion by gastric glands (3,4). On the other hand, there is a nonlinear correlation between the increase in the circulation by Pentagastrin stimulation and the increase in the acid secretion by the gastric mucosa . although that acid secretion does not stop by the reduction of blood supply(8)

Any slowing or blocking in the blood circulation results in formation of marked histopathological changes ranging from mild hyperemia to severe hemorrhages and large necrosis of the mucosa as we have noticed in our studies . Similar findings were reported as the formation of duodenal segmental necrosis following the use of cyanoacrylate in the treatment of bleeding duodenal ulcers (9). Other reports confirming this point of view were published by Lloyd, Touloukion. Emanuel, (10-12), that determine the ischemia, as the primary factor in the etiology of intestinal perforation in newborn children.

Table III: The severity of duodenal lesions in the dogs.

Group	Used drug	Dosage	Hyperemia	Hemorrhage	Necrosis
1	Epinephrine	25 gamma/kg	+	+	-
2	Norepinephrine	25 gamma/kg	+	+	+++
3	Vasopressin	0.01 IU/kg	+	+	-
4	Epinephrine+Dextran 40	25 gamma/kg+2 cc	-	-	-
5	Norepinephrine +Dextran	25 gamma/kg+2 cc	+	+	-
6	Vasopressin+Dextran 40	0.01 IU/kg+2 cc	+	-	-

Mild (+) , Moderate (++) , Severe (+++) .

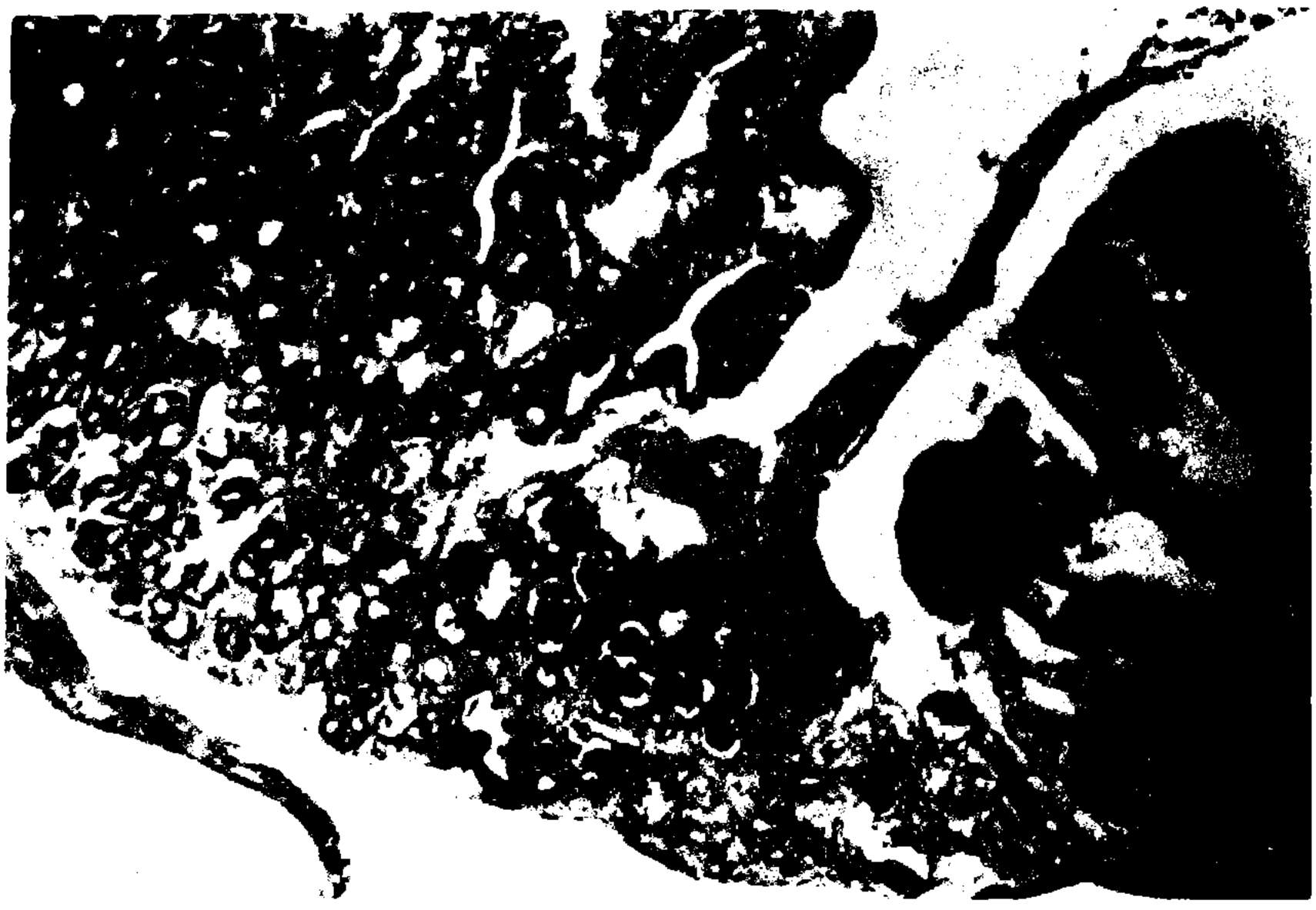

Figure I. Hyperemia, hemorrhages and coagulative necrosis of duodenal mucosa of a rat after vasoconstriction. H.E., x160.

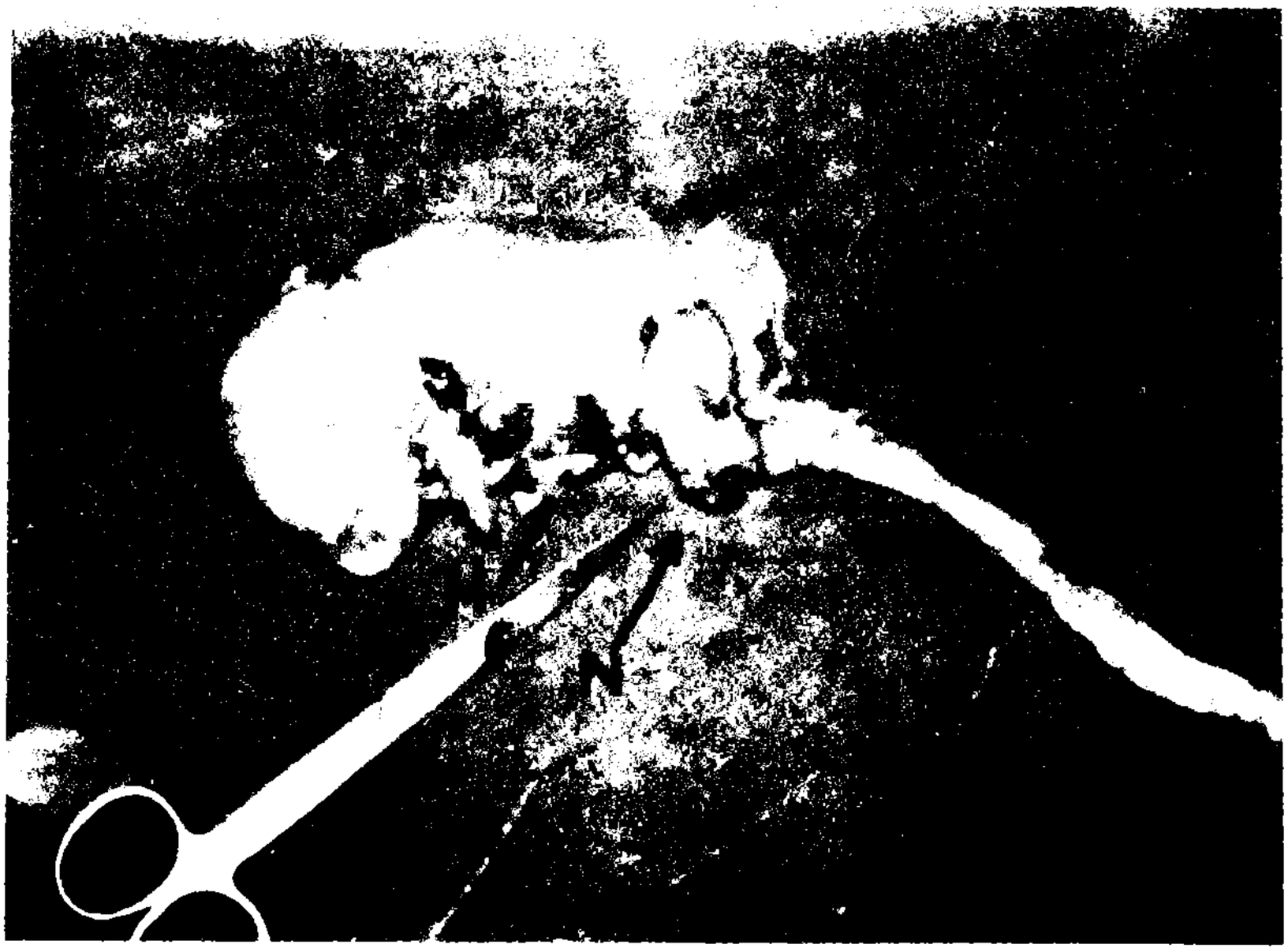

Figure II. Hemorrhages following vasoconstriction (H), and large coagulative necrosis (N) of pylorus.

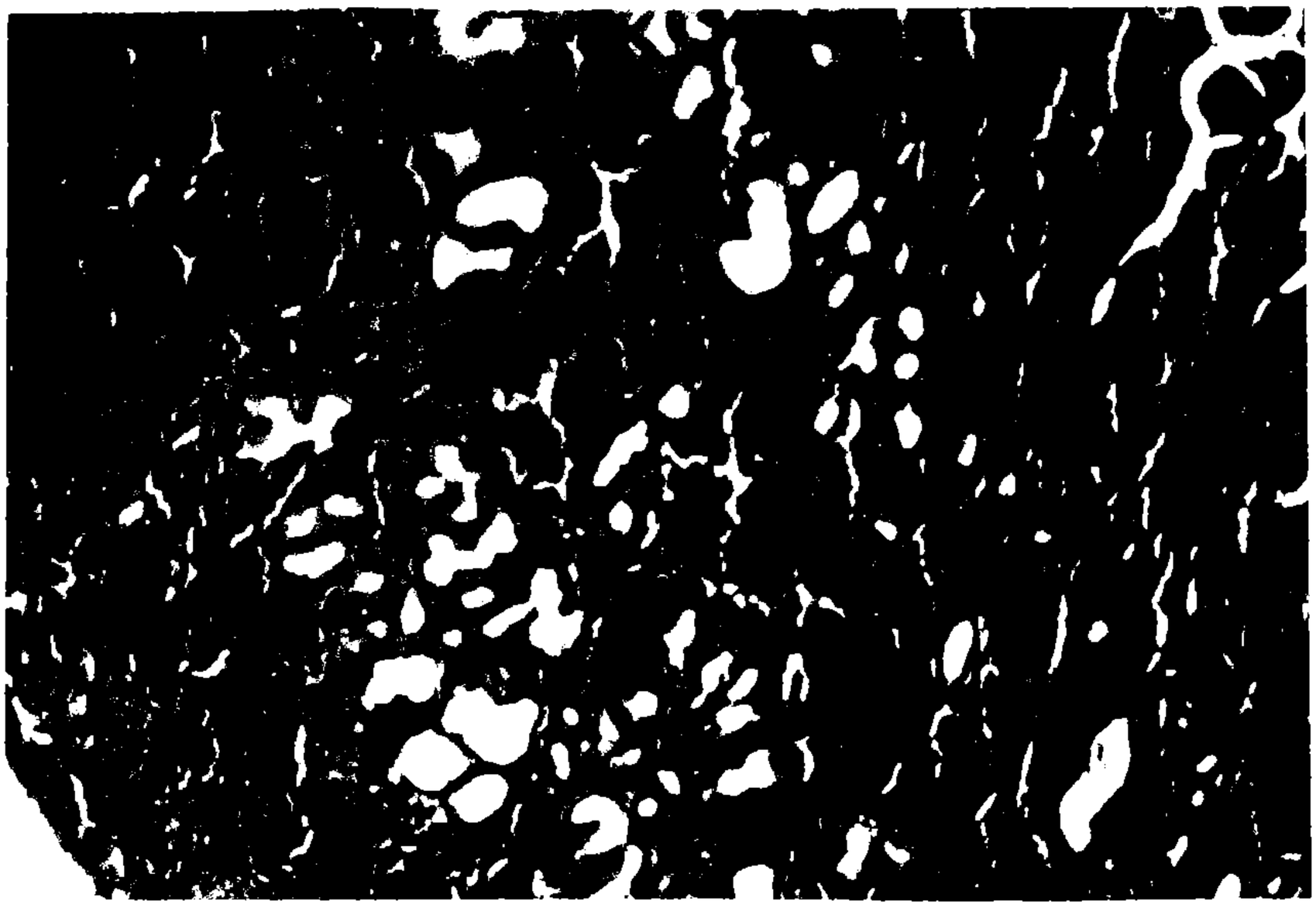

Figure III. Large hemorrhages in the duodenal submucosa of rabbit after vasoconstriction. H.E., x160.

Figure IV. Formation of severe necrosis in the dog duodenum with vasoconstriction. H.E., x160.

Cranioneural system also has an important role in the regulation of gastrointestinal systemic functions . Hovewer, without the additive peripheral factors, this role is not capable of producing duodenal ulcer. This may be explained by studies with 1-Methyl-4-Phenyl-1,2,5,6-Tetrahydropyridine (MPTP) which is a known dopominergic neurotoxin (13,14).

Ischemia is a primary factor in the pathogenesis of duodenal ulcer. The disturbance of acid secretion, loss of mucus covering and protecting gastric mucosa are also important. However, an interesting question is the occurence of some ulcers in certain spots, rather than all over the stomach or duodenum, that are equally affected by acid secretion. As an answer to this question, one might think the cumulative action of local predisposing factors including thromboembolism, atherosclerosis, vascular spasms or local hemorrhages all produce or lead to focal circulation disorders (15-19). Our gross and histopathologic observations are strongly supporting this idea.

The indomethacin or histamin induced ulcers are reported to heal almost completely in fifteen days after injections (20,21). In rats, the healing started and in some cases quite progressed after the fifth day post injections of epinephrine, norepinephrine and vasopressin. The results showed that rat intestinal mucosa has a strong regeneration and reperation potential, and ulcers start healing as early as five days after their induction.

In rabbits and dogs, the protective action of Dextran 40 with its microcirculatory augmentation effect were very obvious. Wahl and Butterfield (22), tried to increase the microcirculation by Pluoronic F-68, a compound increasing the plasma volume, in the rats with tied pylorus, and they showed that this technic was very effective in preventing ulcer formation. In our study, epinephrine, norepinephrine and vasopressin which are powerful vasoconstrictors were added into Dextran 40 which is also a plasma volume expander drug. After the direct injection of this mixture into pancreaticoduodenal artery, we were able to demonstrate the marked reduction in their necrotizing activity by increasing the local microcirculation. The most important effects of Dextran 40 are to increase the plasma volume, the antithrombotic activity and regulation of local blood circulation (23-27). This compound expands the blood volume and circulation together with dilatation of capillaries simultaneously.

In the prearteriolar section, after use of vasoconstrictors capillary hydrostatic pressure decreases, while the transcapillary movement of water and salt increases.The ratio between precapillary and postcapillary resistance also decreases, and this reduction slows microcirculation disturbing the tissues since the oxygen and food intake becomes restricted accordingly (28-30). Due to the increase in need for oxygen and food, the inactive capillaries are opened , and the blood supply in the area is enriched. Increased blood volume starts forming small lacunes and causing coagulations that lead to severe thromboembolisms and disturbed tissue perfusion with local acidosis result in precipitation of proteinous substances into such areas (31-34). The histopathological evaluation of these changes may be summarized as the occurence of hyperemia, varied sized hemorrhages and mild to severe coagulative necroses of gastrointestinal mucosa.

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