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EXPERIMENTAL DATA TO THE PATHOGENESIS OF GASTRIC HAEMORRHAGE

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Introduction

Ever since *Hunter* (1772) numerous researches have been concerned with the digestive effect on living tissues of gastric juice. The problem has many a clinical implication. The pathogenesis and healing of peptic ulcer; perforation of gastric ulcer into the pancreas, liver, gall bladder, etc.; the course of gastric perforation; the effect on adjacent tissues of the gastric contents flowing out after perforation; the ulcer developing following anastomosis; the effect on vessels of gastric juice with special reference to the genesis of gastric haemorrhage; are some of the features of clinical interest involved in this problem.

Problematics

As early as 1772, *Hunter* was concerned with the effect on living tissues of gastric juice. He thought that every living cell was capable of resisting gastric digestion. This view, however, has been refuted by *Claude Bernard*, *Pavy*, *Mathes*, *Katzenstein*, *Dragstedt*.

Claude Bernard (1859) demonstrated that if the leg of a living frog was placed into a gastric fistula of a dog, the leg became digested. Using a similar method, *Pavy* repeated the experiment with the rabbit ear.

Price and *Lee*, starting from the fact that after gastric perforation practically any organ in the abdominal cavity may become exposed to the effect of gastric juice, have studied the effect on various abdominal organs of gastric juice. Their method consisted in making an aperture in the wall of the stomach, through which the living abdominal organs to be tested could be introduced into the gastric cavity. The studies covered the mesenterium, the intestines, the spleen, the gall bladder, the pancreas, the kidney, the connective tissue, the gastric wall and, finally the lung tissue. (The latter may be affected following aspiration of gastric contents.) It was found that the organs and tissues intro-

duced through the aperture into the gastric lumen were rapidly and completely digested up to the level of the gastric wall, but not farther. If the tissues or organs were placed tangentially into the level of the aperture, i. e. if the defect was only covered by the organ to be tested, the gastric juice did not exert its digestive action. The literature concerning this point is, however, somewhat contradictory. (In this connection we refer to the papers by *Holz*, *Licini*, *Teitze*, *Takáts*, *Morton* and *Dragstedt.)*

In order to elucidate the problem, we have carried out the following experiments.

Experiment 1. The effect of gastric juice on the intestinal mucosa was examined (Fig 1). A circular window about 5 cm in diameter was cut into the anterior wall of the stomach.One section of intestine was mobilized together with its mesenterium containing the pertinent vascular and nervous network. The intestine was then cut open opposite the mesenterium and the aperture in the gastric wall was so covered with it that the mucosa faced the gastric cavity and within th e stomach only mucose membranes were in contact.

Two months later the animal was killed. Microscopic examination of the implanted area revealed that the implanted section of small intestine (Fig. 2 a) was normal in structure, with no signs indicative of digestion on it.

Experiment 2. Price and *Lee* carried out deep implantation with small intestine. We have repeated these experiments and obtained similar results. In Fig. 3 it is shown that a section of small intestine, 10 to 15 cm in length together with its mesenterial connections was so placed into the stomach that it formed an arc. The animal was killed 14 days later and the intestine was found to have been digested in an area about 3 cm. in diameter (Fig. 4, between a—a.) In this way between the stomach and the intestine a communication was formed, in other words a spontaneous arastomosis developed *(Csillag—Jellinek).*

The result of this experiment confirmed the statements made by *Dragstedt*, *Price* and *Lee*. It was shown that the intestinal mucosa implanted into the stomach wall in the level of the gastric mucosa is not digested by gastric juice, while the intestine protruding into the cavity of the stomach becomes dissolved. These facts explain why there are contradictions in the literature. t may be assumed that at the beginning the experimentators did not devote attention to the fact whether the implanted tissue protruded into the gastric cavity or was level with the wall of the stomach.

Numerous experiments were carried out to determine the effect of gastric juice on living tissue (mesenterium, intestine, appendix, gall bladder, pancreas, sections of liver, kidney, isolated gastric wall, lung tissue, skin).

In the only *in vitro* experiment, the one carried out by Dragstedt, the effect of gastric juice on blood vessels was examined. *Dragstedt*, starting from *Claude Bernard*'s experiment in which the leg of a living frog was placed into the gastric fistula of a dog, has studied this problem *in vitro*. Flasks were filled with gastric content and then sealed with a rubber cap. The cap was perforated and the hind leg of a frog was allowed to hang into the juice in the flask. First the skin was digested, by the end of the first hour, then, after 2 hours, the fascia, after 5 hours the muscle and, finally, the blood vessels. Was the frog leg previously ligated, the digestion process was accelerated.

To our best knowledge, no *in vivo* studies have been made of the effect of gastric juice on blood vessels. To conduct such experiments was the primary aim of the present study.

The first question was whether on exposure to gastric juice it is the vein or the artery which becomes first digested or perforated. It seemed plausible that the first to fall victim to the digestive action of gastric juice will be the vein with its thin wall, and only later will the artery be affected. If it were actually so, why is then gastric haemorrhage usually arterial?

The second question was, how is it possible that a vessel exposed to the action of gastric juice does not perforate? We have succeeded in finding a more or less satisfactory answer to both of these questions.

Experimental

A total of 25 dogs without selection, mostly males, were used in the experiments. Operation was performed under ether anaesthesia and under aseptic conditions. Prior to operation the dogs given 40 mg of morphine and 0,5 mg of atropine. On the first postoperative day they were allowed to drink water, on the second day they were offered soup, and on the third day vegetables. No pre-operative preparations were made. Several series of experiments were carried out.

In series 1 the abdominal aorta was introduced into the stomach. The operation, performed on four dogs, consisted of the following steps. Upper median laparatomy was made. The intestines were pulled to the left and the infrarenal section of the aorta was exposed, its branches ligated and divided. The isolated section of the aorta, about 6 cm in length, was thus exposed. The posterior wall of the stomach was pulled down through the aperture of the mesocolon. Near to the major curvature a vertical incision about 6 to 7 cm in length was made in the gastric wall. The cardial margin of the incision was made to slip through under the exposed section of the aorta and was satured to the pyloric margin. In this way the section of aorta lay free in the stomach (Fig. 5 a), exposed to the action of gastric juice. The abdominal wall was closed by layers. Three of the 4 dogs used in the experiments developed haematemesis and died with a sudden death 16, 70 and 90 hours, respectively, following the operation. The fourth dog was killed after 3½ hours and examined histologically.

At autopsy the stomach was opened on its anterior aspect, near to the minor curvature. A small amount of thin, liquid blood and a clot of about a child's head in size were found in the gastric cavity. There were some blood clots in the intestines. The intragastric section of the aorta was covered with clustered clots. In areas not covered by clotted blood the surface of the adventitia was split up into fibres. A sound was introduced into the aorta from above the diaphragm and, in each of the three dogs, a small hole, somewhat larger than the head of the sound, could be detected near to the upper site of entry, in the intraventricular section. The defect was fo und to be covered, or surrounded, by clottedblood.

After fixation, sections were prepared from the aorta-stomach complex in the direction of the course of the vessel, i. e. transversally to the longitudinal axis of the stomach. Examining the bridgelike section of aorta that had reposed in the stomach, and also the adjacent gastric tissue (Fig. 6) it was found that, in contrast with the uniform thickness of the upper wall, the lower vascular wall was uneven and markedly thinned at its middle, as compared to other sections of the vessel. At the site of the thinning, clotted blood was seen in the vascular lumen.

In Figs. 7 and 8 a section of a vessel from another case of this series is shown. Vascular changes induced by exposure to gastric juice are variable. The above mentioned figures illustrate one type of these changes. Right, the thickened vascular wall is clearly visible (Fig. 7 a), with its

smooth muscle, within which there is oedema. The fibres of the adventitia are homogenized (b), nuclear staining is partly absent, on the surface there is clotted blood. In the lumen (d) a few red cells are visible. In contrast with the Right wall, the left wall exhibits marked changes (e). This wall has become thin, its cellular structure is indistinct. Part of the vascular wall is homogeneous and the thinning is gradual from down to top in the figure. Thus, the vascular wall has necrosed in its entire width and at a site there is a defect in it, giving rise to haemorrhage.

The necrosis develops gradually. In Fig. 8 another section of the above vessel is shown. The vascular wall opposite the homogenized, necrosed a one still shows the shadows of muscle fibres (b). The nuclei, however, did not stain. Fibrinous inhibition and complete homogenisation have not yet taken place. In the vascular section marked with (b) a few leucocytes are also present.

It was, accordingly, established that the cause of the haemorrhage is a necrosis of the vascular wall leading first to thinning, then to rupture of the vascular wall.

Series 2. The inferior vena cava was introduced into the gastric cavity. The operative procedure was similar to that described for the aorta and it was performed on three dogs. As it had been anticipated, no lethal haemorrhage developed. One of the dogs was killed on the 21st postoperative day.

Microscopic examination of the longitunidal section of the vessel reveals a narrowness of the vessel at the site where it enters the stomach, (Fig. 9 a) and its complete obliteration at the level of the muscle (b). In the direction of the previous lumen the layers exhibit gradual hyalinization. From this it could not be established with certainty whether the obliteration resulted from the organisation of a thrombus or in consequence of the fusion of the opposite walls due to inactivity *(Mechratra)*, induced eventually by an infraction of the vessel. To avoid infraction, in one case the vein was enclosed in a rigid rubber tube in which a window had been cut to permit the gastric juice to come into contact with the vascular wall. The vein was not perforated in this case, either. Five days after the operation the dog succumbed to peritonitis due to a gastric decubitus caused by the rubber tube.

From the results of series 1 and 2 the conclusion was drawn that the artery is apparently less resistant to the action of gastric juice than is the vein. In order to confirm this, the following experiment was performed.

Series 3. By the method described the aorta and the vena cava were simultaneously introduced into the gastric lumen. (Fig. 5 b. in five dogs.) 40, 47, 48 and 100 hours following the operation, respectively, the dogs died of perforation of the aorta. The vena cava remained intact in every case.

By a similar method the splenic artery and vein were introduced into the gastric lumen. The artery perforated and caused a lethal bleeding on the 14th and 2½nd post-operative day, respectively. The vein remained intact in both cases.

Histological examination revealed in these cases that the aorta underwent changes similar to those described above, while changes in the veins were insignificant. The collagen fibres of the venous adventitia exhibited swelling with leucocytic infiltration. In the media the elastic fibres showed intensive basophilia. In the muscular coat there was only a slight hydropic degeneration. In two cases the veins were filled with thrombi.

In the case of lineal vessels, too, the haemorrhage occurred from the artery and not from the vein (Fig. 10). The arterial coat was necrotic and infiltrated with leucocytes. At one site there was a small vessel branching off from the artery and running toward the surface, where it divided into two tiny branches (Fig. 10, n). In this small vessel homogenisation of the vascular wall, fibrinoid necrosis similar to that usually occurring with ulcers, as well as fibrinoid thrombus formation was present.

The evidence obtained in series 1, 2 and 3 appeared to indicate that the wall of veins was unusually resistant to the digestive action of gastric juice. This is the more striking if the thickness of the arterial and venous walls are compared.

The other question to which we sought an answer was whether a vessel exposed to the digestive action of gastric juice would be capable of resisting dissolution and would not perforate. In order to elucidate this question a further series of experiments was carried out.

In *series 4* a circular window about 3 cm in diameter was cut into the posterior gastric wall near to the major curvature and this window was circularly sutured onto the aorta or onto the inferior vena cava. Thus, practically the tissue defect in the gastric wall was mended with

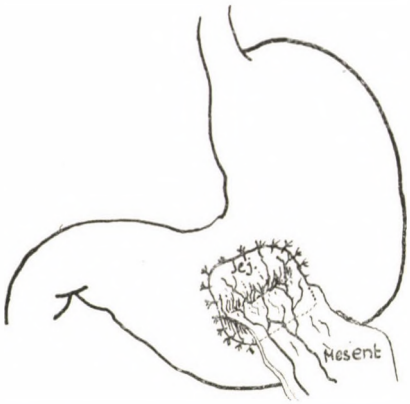

Fig. 1. Diagrammatic presentation of the operation. The window cut into the anterior aspect of the stomach was so covered with a section of jejunum complete with its mesenterium that the mucosa faced the gastric cavity

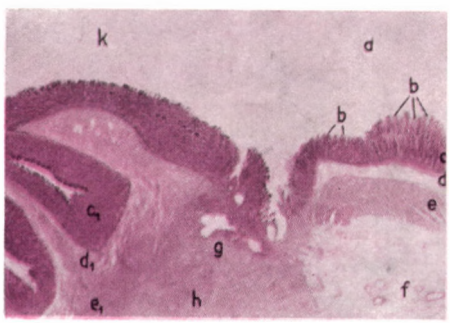

*Fig. 2.** Histological section from the preparation in Fig. 1. *a)* intestinal mucosa ; *c)* tunica mucosa ; *d)* submucosa ; *e)* muscularis mucosae ; *f)* subserosa ; *g)* foreign body granulation ; *h)* cicatrized tissue between two muscle layers ; *i)* dilated glands ; *k)* gastric mucosa ; *cl)* tunica mucosae ventriculi ; *dl)* submucosa ; *el)* muscularis

*The histological sections shown in the photographs have been stained with haematoxylin-eosin.

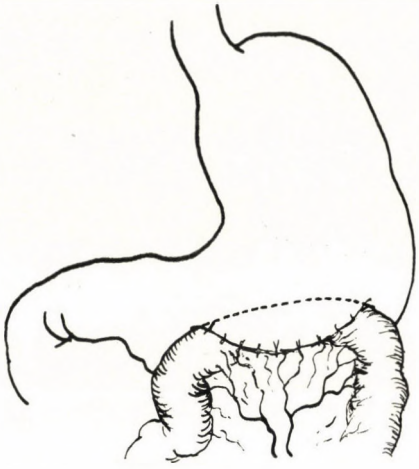

Fig. 3. Diagrammatic presentation of the section of small intestine traversing the gastric lumen

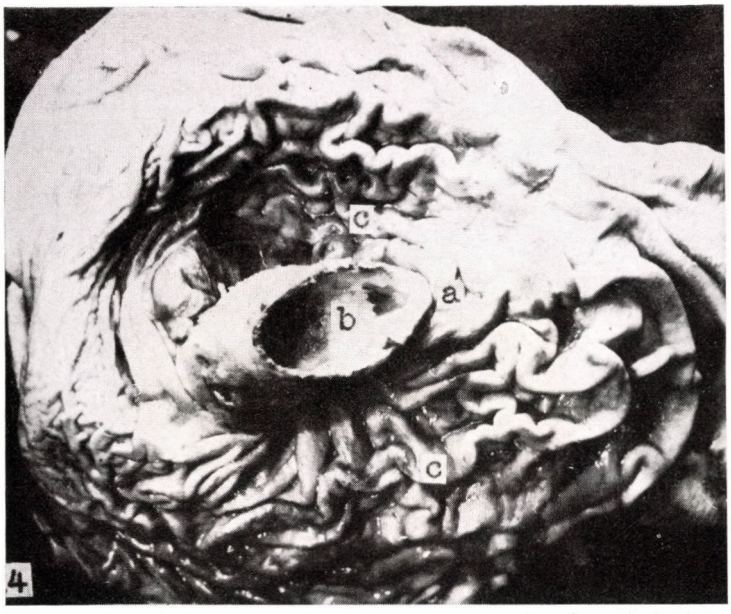

Fig. 4. Autopsy finding of case shown in Fig. 3. The section of intestine traversing the gastric lumen was digested (a—a); *b)* lumen of small intestine, before and after the letter «b» the efferent and afferent sections are distinctly visible. *c)* Gastric mucosa spread out after cutting up the intestine

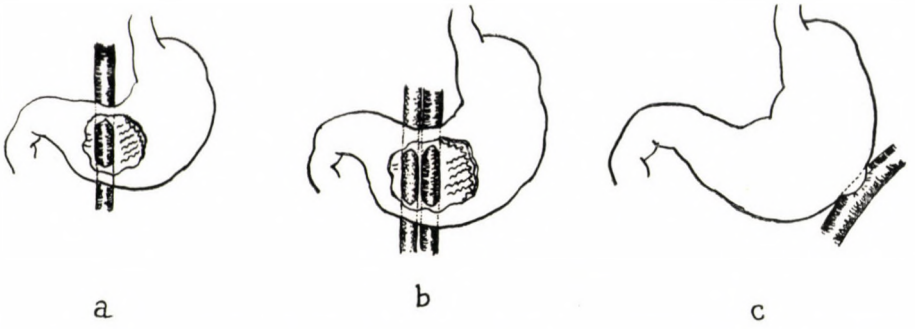

Fig. 5. a) aorta traversing the stomach; *b)* aorta and vena cava traversing the stomach *c)* stomach sutured tangentially onto the aorta

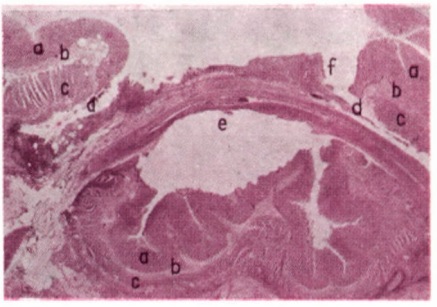

Fig. 6. a) gastric mucosa; *b)* submucosa; *c)* muscle layer; *d)* tissue defect in gastric wall, through which the aorta traverses the gastric cavity (the aorta: *e), f)* clotted blood covering the surface of the aorta; above *e)* a thrombus in the vascular lumen

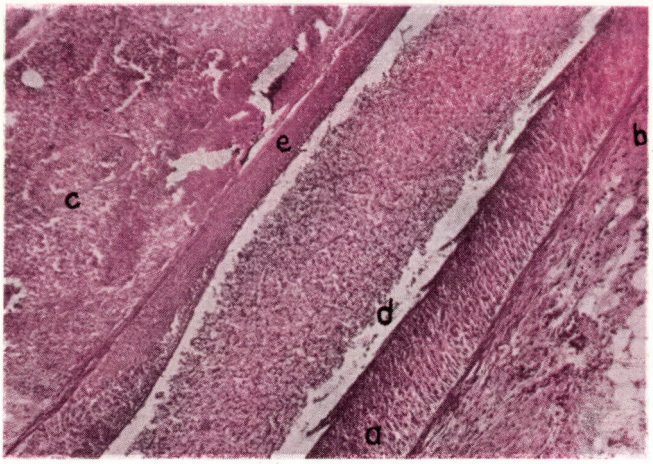

Fig. 7. a) relatively intact oedematous vascular wall ; *b)* homogenized adventitia ; *c)* clot on the surface of the vessel ; *d)* vascular lumen ; *e)* the opposite wall of the vessel, gradually thinning and necrosed

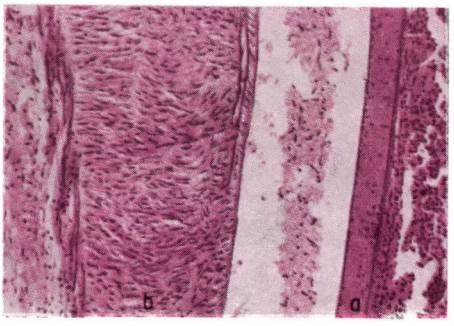

Fig. 8. a) necrosed, thinned vascular wall ; *b)* opposite vascular wall. The muscle fibres are homogenized, there are a few leucocytes in the wall. At the surface clotted blood, in the lumen erythrocytes can be seen

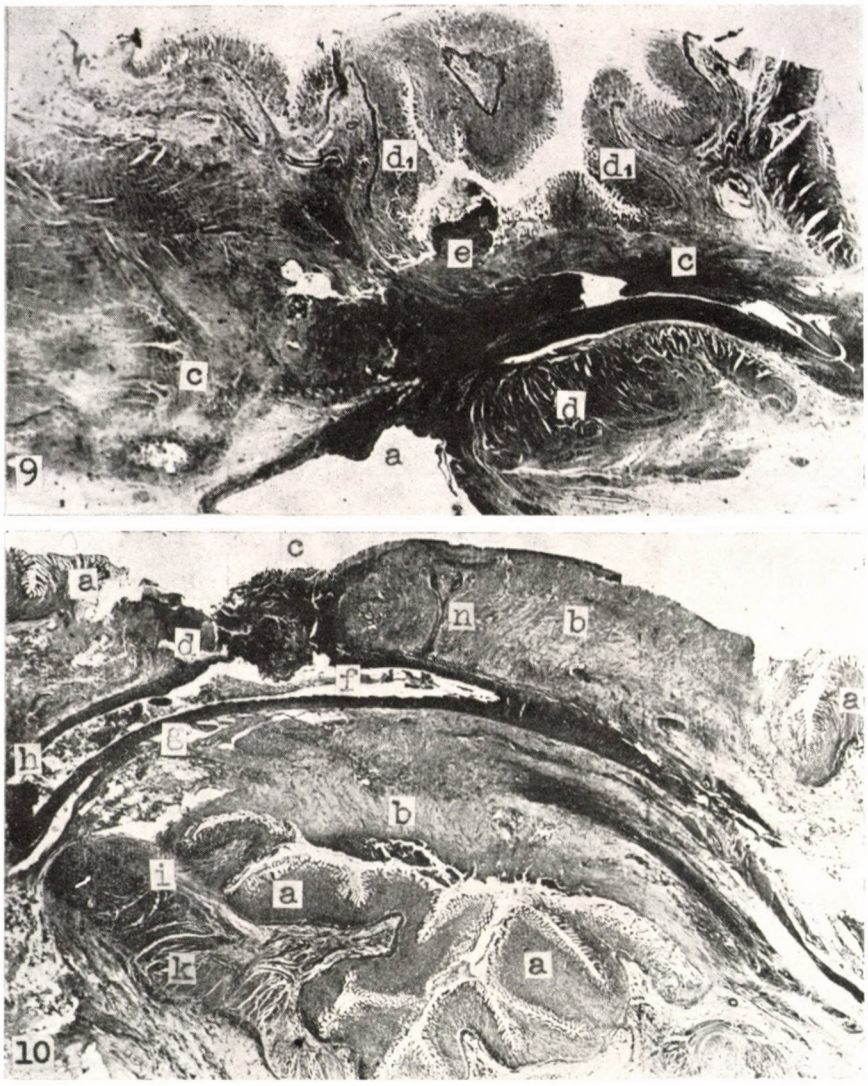

Fig. 9. Histological appearance of a vein traversing the gastric cavity. *a)* funnel-like narrowing of the venous lumen and complete occlusion of same in the level of the muscle layer; (d) gastric mucosa; *c)* cicatrized tissue; *e)* necrotic tissue between the two mucosae

Fig. 10. Lienal artery traversing the gastric cavity. *a)* gastric mucosa; *b)* connective tissue enclosing the vessel, with necrosed areas on the surface; *c)* thrombus obliterating the lumen; *d)* thinned and ruptured lumen, filled with thrombus; *f)* vascular lumen; *g)* lower, and *h)* upper, vascular wall; *i)* gastric submucosa; *k)* muscularis; *n)* tiny vessel branching off from lienal artery

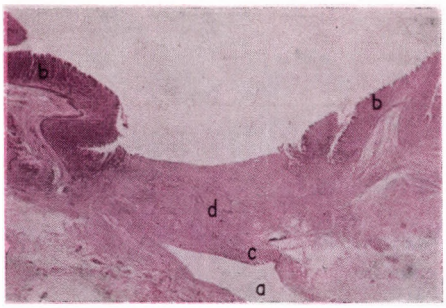

Fig. 11. Histological appearance of a tangential vascular implantate. *a)* lumen of vena cava ; *c)* adventitia of same ; *d)* the cicatrizing granulation formed above it, simulating an ulcer when seen from the gastric cavity ; *b)* gastric mucosa next to ulcer

aortic or venous wall tissue (Fig. 5, c). The vascular walls so implanted did not protrude into the cavity of the stomach, but were tangentially levelled with the rest of its wall. None of the 4 dogs so operated developed a haemorrhage.

At autopsy, gross examination of the operation area revealed in the gastric mucosa a tissue defect with a cicatrized base, similar to an ulcer and about 2 cm in diameter. With the naked eye no haemorrhage could be detected, neither could a vessel be discerned in the gastric cavity or in the area of operation. Introducing a sound into the vessel it was, however, revealed that the vessel (aorta or vena cava) ran at the base of the «ulcer».

Fig. 11 shows the relation between vessel and gastric wall as seen under the microscope. The vessel is shown in its transversal section (a); to the vascular margins gastric mucosa is attached in both sides (b). The defect in the gastric mucosa is bridged over by vascular wall. Under high power the vascular adventitia appears to be thickened (c) in the area of the window. On the inner surface of the macroscopic ulcer there is some necrotic tissue under which cicatrizing granulation tissue (d) can be seen. The latter continues without any distinct border into the vascular adventitia. The aortic and venous patterns were similar.

We have had a total of 18 evaluable cases. In 7 cases the animals died in consequence of technical errors (peritonitis, lethal haemorrhage after we have failed to ligate minor vessels when making an operature in the gastric wall, etc.)

Discussion

The experimental evidence obtained in the various series clearly show that of the vessels introduced into the gastric cavity it was always the artery that perforated.

One of the causes of perforation is the histological change which takes place in the arterial, but not in the venous, wall. If such a change occurs in the venous wall, it is only very slight. The arteries exhibit grave regressive changes, manifesting themselves partly with vacuolar degeneration of the muscle and partly with swelling of the elastic fibres. Such a grave and extensive lesion to the arterial wall initiates defensive activity in the organism in the form of thrombus formation.

In many a case of rupture, if the vascular lumen is narrow, the organism attempts to cover the defect with a thrombus and so to delay for some time lethal haemorrhage. In such cases the distribution of blood in the intestines will be sectional, due to the periodic bleeding. The vascular injury however becomes more and more extensive and finally a lethal haemorrhage develops.

Thus, in addition to the arterial bleeding, a decisive role is played by the actual pressure prevailing in the vessels. In the veins an eventual lesion of the wall causes no significant functional disturbance, because in such cases the affected section may be protected adequately by a thrombus. This protection suffices for a vein but not for an artery, especially not for the aorta.

The above findings completely agree with data in the literature concerning gastric haemorrhage in man caused by ulcer. On the basis of our results it may be stated that the artery is less resistant to the digestive action of gastric juice than is the vein and in our experiments lethal haemorrhage always occurred from an artery.

This statement confirms the clinical observations on gastric haemorrhage. The authors, *Ivy*, *Markoff*, *De Busscher*, *Boyd*, *Dietriech*, *Illingworth* and *Dick*,

Cole, *Elman* etc., are, practically without exception, of the opinion that gastric haemorrhage due to ulcer is arterial in origin. «It is known that the haemorrhage is mostly arterial» wrote *Hetényi*.

Haemorrhage originating from veins has naturally also been described. It is however infrequent and usually originates from major veins following penetration. Lethal haemorrhage from the lienal vein has been reported by *Schlikker*, *Finsterer*, and from the renal vein by *Merkel*.

Our experiments explain why haemorrhage is often the first symptom of ulcer. In the case of rapid arrosion the situation is namely very similar to that created in our experiments, where bleeding occurred as early as 16 hours after placing the vessel into the gastric cavity.

Our experiments contribute, in addition, some data to the problem of gastric digestion in general. We could confirm the findings by *Price* and *Lee* that only such organs or living tissues as protrude deeply into the gastric cavity will be digested. In our experiments only the arteries introduced in the form of an arc into the cavity of the stomach were digested, while vessels tangentially stitsched to the gastric wall showed no change whatsoever. In this, as *Price* suggested, gastric mucin might have a role, covering the organs implanted into the gastric wall and thus protecting them from the digestive action of hydrochloric acid and pepsin.

In the study reported we have endeavoured to examine the effect on vessels of gastric juice. To our knowledge, no such experiments have been carried out. One experiments have contributed some data to the pathogenesis of gastric haemorrhage, the arterial origin of which could be confirmed.

Summary

In dog experiments the effects on the intestinal mucosa, serosa and on blood vessels of gastric digestion have been examined. Functioning arteries and veins were placed into the cavity of the stomach. It was found that the vessels underwent digestion, perforated, so that lethal haemorrhage ensued, but the bleeding was always from the artery and not from the vein.

Evidence has been obtained that the vascular wall is digested only if it protrudes into the cavity of the stomach. If the exposed vessel is placed tangentially into the level of the gastric wall, the gastric juice will fail to digest it.

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ЭКСПЕРИМЕНТАЛЬНЫЕ ДАННЫЕ К ПАТОГЕНЕЗУ ЖЕЛУДОЧНОГО КРОВОТЕЧЕНИЯ

И. ЧИЛЛАГ, Р. ГЕРГЕЙ и Х. ЕЛЛИНЕК

Авторы проверяли в опытах над собаками действие желудочного пищеварения на слизистую и серозную оболочки и исследовали действие желудочного пищеварения на кровеносные сосуды. Авторы проводили через полость желудка артерию и вену, сохранившие свои функции. Из экспериментов выяснилось, что сосуды перевариваются, издырявливаются и смерть наступает следствием обезкровливания, однако, смертельное кровотечение происходит всегда из артерии, а не из вены.

Авторы выявили, что желудочный сок переваривает сосуд только в том случае, если он находится в полости желудка. Если свободно расположенный кровеносный сосуд находится в тангенциальном положении на одном уровне с желудком и в этом состоянии подвергается действию желудочного сока, то он не переваривается.

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