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PREVENTION OF PORTAL DEATH BY MEANS OF HYPOTHERMIA

(AN EXPERIMENTAL STUDY)

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In cases of thrombosis, injury or tumours involving the portal vein, ligation of the vessel for a shorter or longer period is, of necessity, one of the major and ever present problems the surgeon must face.

As early as 1856, *Ore* [25] had reported that in rabbits ligation of the portal vein was fatal within a short period of time. In 1877, *Claude Bernard* [6] had described the symptoms elicited by the ligation of the portal vein. It has been stated that when portacaval anastomosis was performed *(Eck,* [11], *Pavlov,* [26]) and the portal vein ligated for a period exceeding 30 minutes, the outcome of the operation was fatal in every case. *(Large, Preshaw,* [19], *Csillag, Jellinek, Novák,* [8]).

In 1875, *Soloviev* [33] was the first to report that in cases where the branches of the portal vein had been ligated previously and the main trunk itself was ligated only after collaterals had developed *(Ito* and *Omi* [16], *Neuhof* [23], *Torcigliani* [36], *Sappey* [31], *Josselin de Jong* [17], *Hedri* [14], *Oehlecker* [24], *Kusnetzow* [18], *Ore* [25], *Claude Bernard* [6], *Childe, Milnes, Holswade, Gore* [5], *Colp* [7]) the dog would survive.

Acute strangulation of the portal vein is inevitably lethal in both man and animal. Attempts made at delaying portal death and to ensure an at least temporary survival have been numerous. Aortic compression *(Senn, Dahlgreen, Thöle* [35]), infusion *(Borszéky* and *Báron* [3]) and transfusion of blood *(Mallet-Guy, Device, Galgolphe* [21]) and finally removal of the entire gastrointestinal tract together with the spleen *(Elman* and *Cole* [12]) have been the methods used to attain this end.

The actual cause of death has been attributed to anaemia *(Elman* and *Cole* [12], *Boycel* [4], *Tappeiner* [34], *Ranschoff* [30]), to toxaemia *(Elman* and *Cole* [12], *Peck* and *Grover* [27]), to impairment of hepatic function *(Schiff* [32] and to neurogenic factors *(Burdenko* [35], *Thöle* [35]).

In the experiments to reported attempts were made at elucidating some concerning the strangulation of the portal vein and avoiding death due to that procedure. The experiments, leading to the discovery of an entirely successful method, were performed in 3 series.

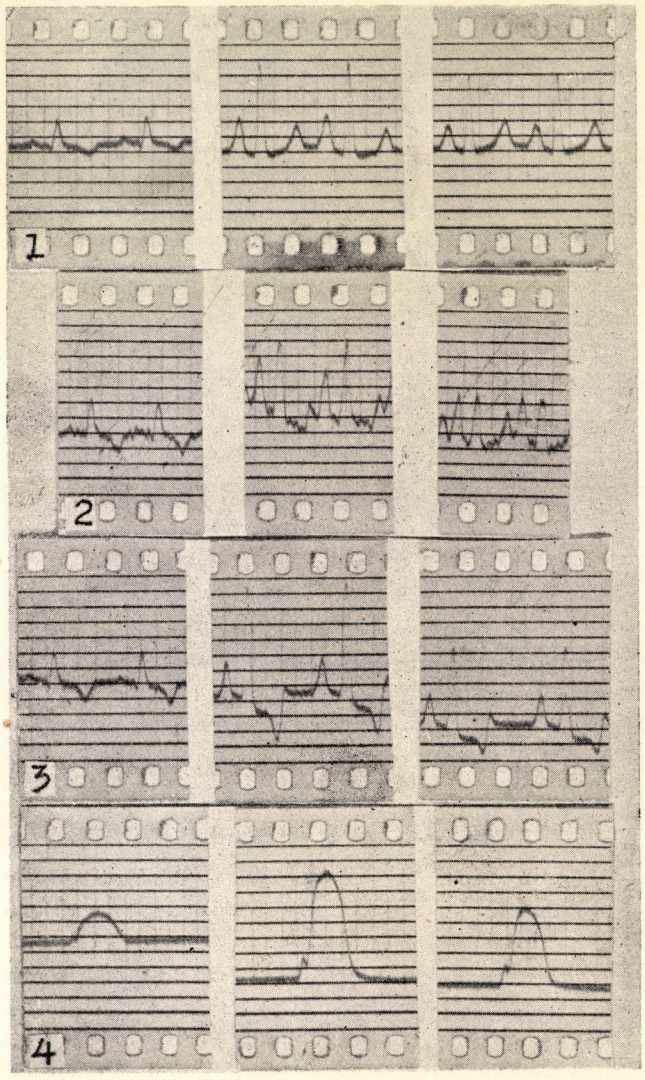


Fig. 1. ECG. before opening of abdomen: Sinus rhythm, low amplitudes in lead I., T^{I} neg. T^{II} pos., low, T^{III} pos. $ST^{I, II, III}$ in the isoelectric line.

Fig. 2. ECG. at 24 minutes following ligation of portal vein. Sinus rhythm, P^{I} flat, $P^{II, III}$ high, peaked, T_{I} neg., $T^{II, III}$ pos., very low, $ST^{II, III}$ markedly depressed.

Fig. 3. ECG. at 44 minutes following ligation of portal vein. Sinus rhythm, P^{I} low, $P^{II, III}$ high, peaked, $T^{I, II, III}$ neg., ST^{I} isoelectric, $ST^{II, III}$ markedly depressed.

Fig. 4. ECG. at 50 minutes following ligation of portal vein. Automatic ventricular systoles, at rata of about 8 per min., no P waves visible, the base of the ORS complex widened (0,17 sec), no T waves.

In the first series, 6 dogs were used. The portal vein was ligated for 20 to 40 minutes, as described in another paper *(Csillag, Novák, Jellinek* [8]). None of the animals survived the operation.

In the second series the portal vein was ligated in 9 dogs.

Of the 9 experiments in this series, one is described in some detail. Prior to opening the abdominal cavity, I-II-III lead electrocardiograms were made and the blood pressure recorded by cannulating the right femoral artery. During the experiment electrocardiograms were taken at intervals of 4 to 6 minutes and the blood pressure was continuously recorded. In addition, blood from the portal vein and the inferior vena cava was tested for clotting prior to, and 6 and 20 minutes after ligating the portal vein.

Only 4 characteristic electrocardiograms are shown. (Figs. 1 to 4.)

Evaluation of the experiment

Following ligature of the portal vein, blood pressure declined gradually.

Blood pressure prior to ligature					160 mm	Respiration	regular
6 min.	after	ligature		.....	120 mm	«	«
14	«	«	«	.....	70 mm	«	«
20	«	«	«	.....	30 mm	«	«
24	«	«	«	.....	20 mm	«	«
34	«	«	«	.....	20 mm	«	«
39	«	«	«	.....	10 mm	«	«
44	«	«	«	.....	0 mm	«	ceased.

In the ECG taken at 14 minutes there was already evidence of a depressed ST interval.

At 44 minutes, when blood pressure and breathing were no more recordable, very marked changes appeared in all three leads on both the T wave and the ST interval.

At 48 minutes the atrium was paralyzed, the ventricular rate was very slow, but regular.

At 55 minutes 1 or 2 automatic ventricular systoles were still detectable, in spite of the fact that blood pressure had not been recordable for 9 minutes and the animal ceased breathing.

Cardiac function deteriorated parallel with the decrease of blood pressure. Clinical death ensued 44 minutes after clamping the portal vein, while, according to the electrocardiograms, after 55 minutes.

Clotting times were as follows.

Prior to clamping the portal vein, portal vein blood, 2 to 5 minutes, vena cava inferior, 2 to 5 minutes.

6 minutes after clamping portal vein blood 1—3,5 min., vena cava inferior blood 1—4 min.

20 minutes after clamping portal vein blood 1—1,5 min., vena cava inferior blood 1/2—1 min.

In addition to this detailed analysis, in the following a general evaluation of the 9 experiments is presented.

Clamping of the portal vein was accompanied by rapidly developing collapse in every case. If the clamp was not released, the blood pressure decreased to 0 and the animal died in 31 to 55 minutes, with no respiration and blood pressure recordable during the last 5 to 10 minutes. The first changes to occur in the ECG appeared on the ST interval, then on the T wave, and increased parallel with the collapse. During the last 5 to 10 minutes signs of cardiac failure, such as complete atrio-ventricular dissociation, atrium paralysis with ventricular automatism, marked bradycardia, ventricular fibrillation were demonstrable by electrocardiography. In the 5 experiments where clamping was released at 15, 17, 18, 30 and 32 minutes, respectively, the blood pressure did not decrease further and remained at the reduced level (40, 50, 60 mm) for some time, then began to increase, but never returned to the initial level (120—170 mm). This increase of blood pressure lasted for from 15 to 41 minutes, when another wave of collapse followed, the pressure decreased and became unrecordable in 16, 24, 56, 90 and 135 minutes, respectively, and the animal died. The ECG changes were identical with those described above.

The experiments have shown that clamping of the portal vein is accompanied by a collapse fatal within a short time. If clamping is released within 30 minutes, the collapse is temporarily relieved, though for not more than 45 minutes, but the second episode of collapse which follows causes further deterioration and, finally, complete failure, of heart function. None of the 9 animals survived the first or the second collapse. Parallel with the deterioration of the state during the collapse, marked ECG changes present themselves which prove irreversible. In this series nothing was done to prevent or relieve the collapse.

In the third series hypothermia was employed, starting from the observation that it has succesfully been used in cardiac surgery (*Lewis* and *Taufic* [20]), and that cooled experimental animals tolerate occlusion of the inferior or superior venae cavae for a longer period of time. It may be assumed that in such cases a reduced rate of metabolism may play some role.

Of Hungarian authors, *Horváth* [15] in 1871, *Aszódi Z.* [1] in 1921, *J. Pólya* [29] in 1942 and *I. Csillag, I. Novák, E. Egedy, H. Jellinek* [10] in 1953 were concerned with hypothermia.

In this series the body temperature of the dogs was decreased to 23° to 28° C before clamping the portal vein for periods of 45 to 51 minutes. The 7 dogs

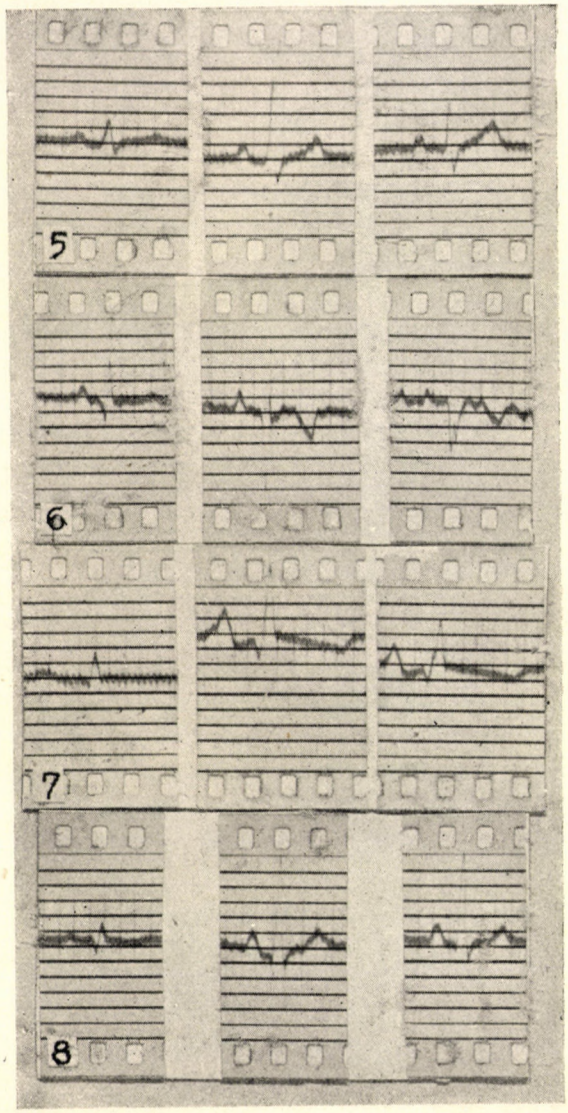


Fig. 5. ECG before ligation of portal vein. Sinus rhythm, low amplitudes in lead I. T pos., low, $T^{II, III}$ pos. $ST^{I, II, III}$ in the isoelectric line.

Fig. 6. ECG. at 28 minutes following ligation of portal vein. Sinus rhythm, P waves peaked, R^{I} higher, $R^{II, III}$ very low. T^{I} pos., low, $T^{II, III}$ neg. $ST^{I, II, III}$ isoelectric. The animal was shivering.

Fig. 7. ECG at 55 minutes following ligation of portal vein, (10 minutes after release of ligation and rewarming). Sinus rhythm. P^{I} low, $P^{II, III}$ high, peaked, R^{I} low, $R^{II, III}$ high, T^{I} flat $T^{II, III}$ slightly neg. ST^{I} isoelectric, $ST^{II, III}$ deflected and slightly elevated.

Fig. 8. ECG 14 hours after ligation of portal vein, 13 hours after release of ligation. Sinus rhythm, low amplitudes in lead I., positive P waves. $R^{II, III}$ high, T^{I} low, $T^{II, III}$ positive. $ST^{I, II, III}$ isoelectric.

of this series all survived the operation. Prior to inducing hypothermia, the animals were anaesthetized with 2 ml of morphine and intratracheal ether, with a specially devised apparatus *(Csillag, Novák* [9]). The body temperature of the dogs was reduced to 28° C in 30 to 60 minutes. Cooling was performed in ice-water, and warming up by immersion into water of 31° to 45° C for about 60 minutes. Room temperature varied between 25° and 30° C. Within a few hours after warming up the dogs could walk about.

One of the 7 experiments of this series is described in detail.

4 characteristic electrocardiograms are presented. (Figs. 5 to 8.)

On cooling, the body temperature decreased to 27° C and the dog shivered. 20 minutes after immersion into the warming bath rectal temperature rose to 32° C, shivering diminished and the animal began to waken. Two hours later it walked about and 14 hours later it fed normally.

The experiments made on 7 dogs to study the ligation of the portal vein under hypothermia may be evaluated as follows.

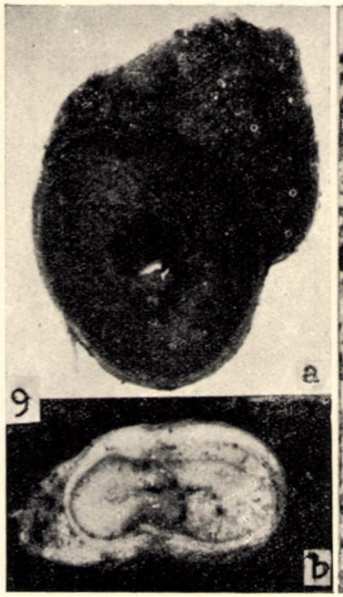
When clamping of the portal vein was performed in hypothermia, the dog survived an obstruction of the portal blood flow lasting 45 to 51 minutes. There was a delay in the appearance of electrocardiographic changes, which were of a lesser degree than in the previous group and presented themselves simultaneously on the ST interval and the T wave. After the clamp had been taken off, anaesthesia was discontinued and the animal was rewarmed. Soon afterwards respiration and heart function became normal and the dog could walk about within 2 to 3 hours. Next day, some 14 to 16 hours after the intervention the animal behaved normally, it took food, moved about in a normal manner, and no pathological change was present on the electrocardiogram.

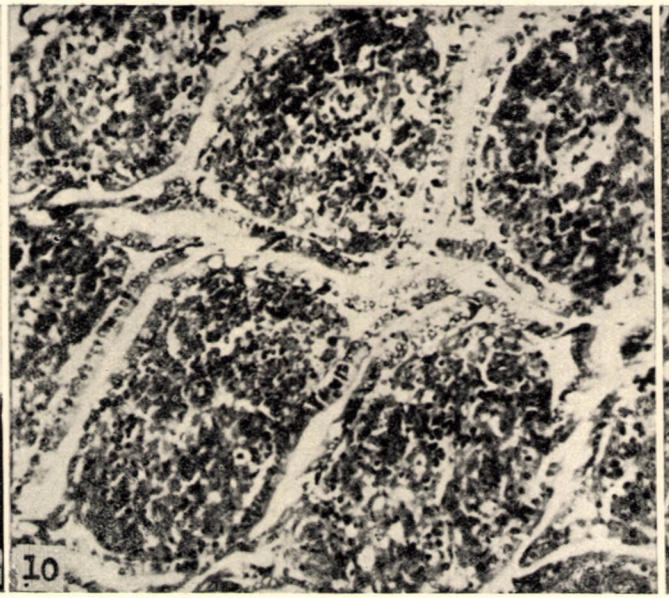
We could detect no lesion attributable to the clamping of the portal vein if this occurred in hypothermia, although in animals with a normal temperature the procedure caused death in every case. This means that by reducing the body temperature for the period of portal obstruction we succeeded in keeping the animals alive. Normothermic animals were autopsied immediately after death. Of the dogs with hypothermia 3 were sacrificed 1 hour after rewarming, 4 at later points of time, the last one was killed on the 90th day.

The two groups (hypothermic and normothermic) exhibited characteristic and clearly distinguishable differences at autopsy. The changes within the individual groups were similar and differed only in the extent or degree of the lesions. For this reason from each group only one representative case will be described in detail.

In the animal to be reported from the normothermic group (No. 1), the portal vein was clamped for 45 minutes and then released. 9 minutes later the dog succumbed with the usual symptoms.

The most marked changes were detectable in the intestines. With the exception of two thirds of the colon, the intestines were dark livid, the mesen-





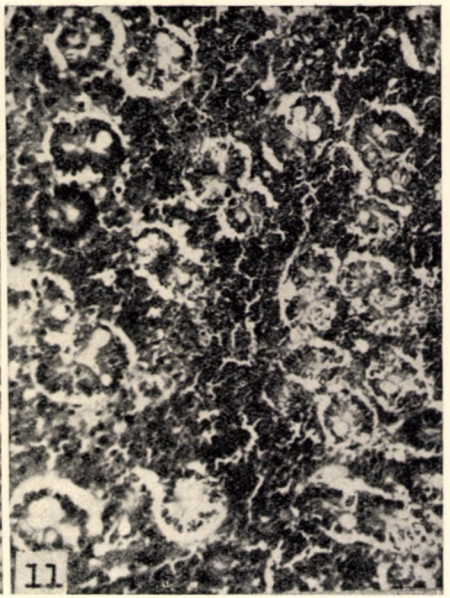


Fig. 9. Segment of intestine from not hypothermized (a) dog. Segment of intestine from hypothermized (b) dog.
Fig. 10. Gross section of intestinal villi from a non-hypothermized dog. Note diffuse haemorrhage in stroma.
Fig. 11. Mucosa from a non-hypothermized animal. The interglandular spaces are distended, filled with blood.

tery was markedly swollen, oedematous, with extensive haemorrhages, particularly in the areas adjacent to the intestines. In some areas the haemorrhages were confluent, making the fatty tissue hardly recognizable. (Fig. 9.)

In the gastric serosa, especially in the pyloric region, greatly dilated blood vessels could be seen, and at sites haemorrhages.

The spleen was livid and dilute blood oozed from its cut surface. The surface and the cut surface of the liver offered a variegated picture, with pale areas up to 3 cm in diameter, and signs of livid congestion. The kidneys were dark livid and markedly congested.

The right ventricle of the heart was greatly dilated. Other organs showed no gross changes.

Histology. The intestinal changes were extensive and irreversible. Haemorrhage was present in all layers of the intestinal wall, being so extensive in the submucosal layer that the mucosa was practically separated from the muscle-layer in which it displaced the fibres. In the mucosa, in the axis of the villi, the connective tissue was obscured by blood; the epithelium was, however, unaffected. The structure of the connective tissue in the axial part was recognizable only at some sites. Lieberkühn's glands were also displaced. The intestines contained clotted blood. (Fig. 10 and 11.)

Thus, both gross and microscopical examination revealed in the intestines haemorrhagic infarction which, although in its early stage, was nevertheless irreversible.

The vessels of the gastric mucosa were almost completely congested, filled with erythrocytes. The mucosal vessels were also dilated, just as the subserous vessels. The sinuses of the spleen were markedly distended, with haemorrhages destroying the tissue visible at sites. The liver cells contained only reduced amounts of glycogen; some of the hepatic sinuses were greatly dilated, hyperaemic, while in other areas they were empty, anaemic. Renal vessels and glomeruli were hyperaemic, with few haemorrhagic areas detectable in the cortex. Apart from marked hyperaemia extending to the capillaries there were no microscopic changes demonstrable in the heart.

Ligation of the portal vein in hypothermia (No 1 H) in a dog killed by an overdose of the anaesthetic 1 hour after rewarming offered the following picture.

The vessels of the intestinal serosa were somewhat more distinct than usual. There were no other changes detectable in the intestinal wall.

In the mesenterium slight oedema was present but no haemorrhage.

The liver was dark livid, a great amount of dark blood was discharged from the cut surface. Other organs showed no changes.

Histology. The vessels of the intestinal mucosa appeared slightly congested. There was no haemorrhage in any of the layers. The lymph spaces of the submucosal layer were distended and filled with a substance staining homogeneously with eosin. There were no pathological changes present in the other organs.

Comparing the findings in the two groups reveals the most conspicuous differences in the intestinal changes and in the impairement of hepatic circulation. In the cases without hypothermia, intestinal haemorrhagic infarction (Figs. 9, 10, 11) was one of the causes of death and probably also of the fatal collapse. The intestinal changes were in full agreement with the data in the literature (*Pick*, *Neuhof* [28], [23]), and their seriousness was to a certain extent dependent on the duration of clamping. Beyond a certain time, however, every layer of the intestinal wall becomes involved.

In the animals with hypothermia there was no infarction and the intestines exhibited a normal structure (Fig. 9). In a few instances there was marked congestion present, in one case slight haemorrhages could be detected in the intestinal follicles; these changes, however, were of a very small extent. No haemorrhage occurred in the mesentery. It seems that the neuro-vascular-changes, effects of hypothermia (vascular spasm) also participate in the prevention of intestinal changes. This is suggested also by the nature of the hepatic changes.

In cases with no hypothermia, anaemic foci and areas resembling Zahn-type infarctions were detectable in the liver. A reduction of the hepatic blood flow explains the anaemia, with the anatomical relations responsible for the localization of the anaemic areas (*Mallory* [22]). The Zahn-type infarctions were probably due to a decrease in pressure in the portal vein and to reflux from the vena cava (*Filep*, *Cohnheim* and *Litten* [13]). In the cases with hypothermia there was marked cyanosis in the liver, probably owing to a reflux from the vena cava subsequent to ligation of the portal vein, and to the increased flow resulting after the clamp had been released and the trapped blood of the portal vein had entered the liver. A short time (60 minutes) after operation this may manifest itself in the form of marked congestion.

The lymph vessels in the intestines were greatly dilated in the animals with hypothermia. In cases without hypothermia the vasodilatation, being probably a secondary consequence of congestion, was less evident.

Depending on the site of ligation, the spleen presents various pictures. The sinuses are empty if the portal vein has been ligated below the splenic vein, since the stored reserves of blood enter the circulation. When it is above the splenic vein that the ligation has been applied, the spleen is congested, since no evacuation is possible through the obstructed splenic vein.

On the basis of the patho-anatomical findings, ligation of the portal vein leads to death, with intestinal infarction and subsequent collapse, i. e. with irreversible anatomical changes. The development of these anatomical changes could successfully be prevented by hypothermia and in this way it became possible to avert the death of the experimental animals.

Summary

Experimental evidence accumulating over a century has unequivocally shown that ligation of the portal vein for more than 30 minutes is always fatal (portal death). This could be confirmed in two of 3 series of experiments. In the third series the body temperature of dogs was reduced to 23°—28° C prior to ligating the portal vein. The animals survived clamping of that vessel for more than 30 minutes in every case. According to autopsy findings, ligation of the portal vein leads to death by causing intestinal infarction, i. e. an irreversible anatomical change. The development of this irreversible change could successfully be prevented by hypothermia and thus it became possible to avert the death of the animals. The experiments were controlled by electrocardiography.

REFERENCES

1. **Aszódi, Z.:** (1921) Beitrag zur Kenntnis der chemischen Wärmeregulation der Säugetiere. Biochem. Ztschr. *113.* p. 70—89. 2. **Blakemore:** (1948) Portacaval shunt in the surgical treatment of portal hypertension. Ann. Surg. *128.* 4. 3. **Borszéky** and **Baron:** (1913) Treatment of haemorrhage during liver-operation. Orvosi Hetilap *LVII.* 45. p. 825—827. (Hungarian only). 4. **Boyce:** (1914) The Role of Liver in Surgery (Chapt. X) Springfield, 111. 5. **Child, Milnes, Holswade** and **Gore:** (1950) Sudden and complete occlusion of the portal vein in the Macaca Mulatta monkey. Ann. Surgery *132* p. 475—495. 6. **Claude Bernard:** (1877) Leçons sur le diabète et la Glycogenèse Animale, Paris. 7. **Colp:** (1926) Surg. Gynec. and Obst. *43.* p. 627. 8. **Csillag, I., Jellinek, H.** and **Novák, I.:** (1953) A new method of restoring defects in the wall of great abdominal veins. Acta Morph. Hung. *III.* 2. 9. **Csillag, I.** and **Novák, I.:** (1952) Simplified narcotisator. Orvosi Hetilap XCIII. No. 50. p. 1943. (Hungarian only). 10. **Csillag, I. Novák, I. Egedy, E.** and **Jellinek, H.:** (1953) Prevention of portal death by means of hypothermia. Congress of Surgery. Budapest. Coloured film. 11. **Eck, N. V.:** (1877) Vojens. Med. 12. **Elman** and **Cole:** (1934) Haemorrhage and shock as causes of death following acute portal obstruction. Arch. Surg. *28.* p. 1166—1175. 13. **Filep, A.:** (1919) Obstruction of the portal vein and its effects on the liver. Magyar Orvosi Archivum. *20.* p. 200—206. 14. **Hedri E.:** (1952) Hepatic lobectomy in case of primary cancer. Magyar Sebészet. *V.* 2. p. 170—172. (Hungarian only). 15. **Horváth, A.:** (1871) Zur Abkühlung der warmblütigen Tiere. Ztschr. Med. Wissensch. *531.* 16. **Ito** and **Omi:** (1901—2) Dtsch. Ztschr. Chir. *62.* 17. **Josselin de Jong.:** (1932) Über die Folge der Thrombose im Gebiet des Pfortader. Arch. Klin. Chir. *173.* p. 663. 18. **Kusnetzow:** (1900) Roussk. Vratch. 32—33. (Russ.) 19. **Large** and **Preshaw:** (1950) The Eck fistula. J. Int. de Chir. *X./3.* p. 139—146. 20. **Lewis** and **Taufic:** (1953) Closure of atrial septal defects with the aid of hypothermia experimental accomplishments and the report of one successful case. Surg. p. 52—59. 21. **Mallet—Guy, Device** and **Galgolphe:** (1950). Étude expérimentale de l'interruption brusque du courant portal. Lyon Chirurg. *48.* p. 852—929. 22. **Mallory:** (1950). cit. Zalka. Path. Anat. Comp. 23. **Neuhof:** (1913) Experimental Ligation of the Portal Vein. Surg. Gynec. Obst. *16.* p. 481—488. 24. **Oehlecker:** (1932) Leberveränderungen bei Verschluss des linken Astes der Pfortader. Arch. klin. Chir. *173.* p. 663. 25. **Oré M.:** (1856) C. R. Ac. Sci. *42.* 497. 26. **Pavlov** et al.: (1893) Schmiedebergs Arch. *32.* 161. 27. **Peck** and **Grover:** (1952) Cardiovascular responses to acute ligation of portal vein. Arch. Surg. *4.* p. 665—680. 28. **Pick:** cit. Neuhof. 29. **Pólya, J.:** (1942) Crymotherápia. Orvosi Hetilap. 16. p. 30. (Hung.) 30. **Ranschoff:** (1908) Cause of Sudden Fall in Blood Pressure While Exploring the Common Bile Duct. Ann. Surg. *48.* p. 550. 31. **Sappey:** (1940) Kirschner—Nordmann: Die Chirurgie. *VI.* p. 125—126. 32. **Schiff:** cit. Neuhof. 33. **Soloviev:** cit. Neuhof. 34. **Tappeiner:** (1872) Über den Zustand des Blutstroms nach Interbindung der Pfortader. Arb. a. d. physiol. Anst. zu Leipzig. 35. **Thöle, Burdenko, Senn, Dahlreen:** cit. Borszéky and Báron. 36. **Torcigliani:** (1950) Anaemia cronica da salassi dopo chiusura della vena porta. Rass. di Fisiopath. *XXII.* p. 1—2.

ПРЕДОТВРАЩЕНИЕ »ВОРОТНОЙ СМЕРТИ« ПУТЕМ ПРИМЕНЕНИЯ ГИПОТЕРМИИ (ГИБЕРНИЗАЦИИ)

И. Чиллаг, Х. Еллинек и Э. Эгеди

Резюме

Уже столетие различные исследователи утверждают на основе экспериментальных данных, что зажим воротной вены в течение 30 минут ведет к смерти (»воротная смерть«). Авторы подтверждали этот факт двумя сериями собственных опытов. В третьей серии опытов авторы сначала охлаждали подопытных собак до тех пор, пока температура в прямой кишке не достигла 23–28° С, и только тогда они зажимали воротную вену. Животные выдержали зажимание воротной вены во всех случаях даже дольше 30 минут. По данным патологоанатомических исследований, зажимание воротной вены ведет к смерти при явлении инфаркта желудочно-кишечного тракта, то есть при необратимых анатомических изменениях. При помощи охлаждения удалось предотвратить эти анатомические изменения и таким образом сохранять в живых подопытных животных. Авторы проверяли приведенные случаи также при помощи электрокардиографии.