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Easy to say, hard to do[1]. To the anniversary of two fundamental discoveries. Part 3

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Abstract

On the eve of the anniversaries of two historical events: the 145th anniversary of the experiments in which Eck's fistula was performed and the 55th anniversary of the successful clinical approbation of the selective distal splenorenal anastomosis, a retrospective analysis of the key historical stages in the development of portal hypertension surgery was performed: from the first attempts to describe the anatomy of the hepatic vascular system, explaining its purpose in the body, the development of direct portacaval anastomosis, and the widespread use of selective splenorenal anastomoses, to the Transjugular Intrahepatic Portosystemic Shunt procedure and orthotopic liver transplantation. Meantime, the emphasis has been focused on the most colorful characters of researchers and clinicians who passed this path. The expediency of an integrated approach in solving the problems of portal hypertension with the development of both fundamental and applied clinical and organizational

[1] From Latin: Facĭle dictu, difficĭle factu

aspects has been substantiated. It is shown that the discoveries born from summarizing the results achieved by numerous researchers have contributed to a better understanding of this field of medicine, have become a solid foundation for what we have today and are a reliable platform for a successful start into the future.

Keywords: history of medicine, portal hypertension, surgical treatment

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BRTO, balloon occluded retrograde transvenous obliteration

TIPS, transjugular intrahepatic portosystemic shunt

Introduction

“There are moments when, in order to highlight and understand the present, it is useful to turn over a few forgotten pages in the history of medicine, and perhaps not so much forgotten as unknown for many”

N.N. Burdenko

September 2022 was marked by two historical events that had had a huge impact on the development of surgery for portal hypertension, a hemodynamic anomaly in the form of a chronic elevation in pressure in the vessels of the portal venous system, leading to potentially life-threatening complications. The mere mention of portal bleeding evokes absolutely opposite emotions in doctors who have ever faced it on their professional path: from a heady premonition of the opportunity to effectively apply their knowledge and clinical experience to a sticky fear

of fatal hopelessness and hopelessness in their attempts to save the patient's life. Until finally 145 years ago, at the St. Petersburg Imperial Medical and Surgical Academy, a young Russian doctor Nikolai Vladimirovich Eck, for the first time in an experiment after transecting the portal vein, did not connect its distal end to the inferior vena cava. Eck 's fistula, which today we would call a total portacaval shunt, by means of which "blood from the portal vein could be directed directly into the general circulation without any danger to the body" immortalized the name of the author, enabling surgeon-hepatologists to walk confidently along the tortuous historical way of portal hypertension surgery. Fifty-five years ago, ninety years after N.V. Eck, W. Dean Warren, Robert Zeppa and John J. Fomon at the University of Miami School of Medicine and Jackson Memorial Hospital (Miami, Florida, USA) proposed a then-new selective splenic shunting operation in situ, marking the beginning of an era of effective surgical treatment of patients with portal hypertension using a selective distal splenorenal shunt, which allowed not only to save the spleen and left kidney, but also provided a decrease in pressure and flow volume through the gastroesophageal veins, as well as maintained portal venous perfusion of the liver and constant venous hypertension in the intestinal tract with postoperative prevention of post-shunt encephalopathy and acute liver failure.

In anticipation of the approaching anniversaries of these two historical events, we took the liberty of reminding ourselves of the long and thorny path of portal hypertension surgery. The dramatic history of portal hypertension surgery from the first attempts to describe the anatomy of the liver vascular system, explain its purpose in the body, the development of a direct portacaval fistula, the widespread use of selective splenorenal anastomoses prior to the TIPS procedure, and orthotopic liver transplantation is full of bright events, unforgettable impressions and

deep respect for those researchers and clinicians who have worked in this field.

At the turn of the third millennium, ironically, when bypass surgery was convincingly demonstrated as a therapeutic alternative for the treatment of portal hypertension, the indications for distal splenorenal shunting decreased markedly, and the number of surgeons having the skills to perform it decreased. The secret turned out to be simple: new players appeared on the scene. Minimally invasive endoscopic ligation and stenting procedures, X-ray interventional vascular surgery for transjugular intrahepatic portosystemic shunting, and finally the coming of age orthotopic liver transplantation have left little room for shunt surgery for variceal bleeding [1–5]. That is why in the third part of the historical review we will talk about the most striking alternative areas of high-tech surgery for portal hypertension in the 21st century, the wide clinical use of which is impossible without a continuously progressive development of scientific and technological progress, improvement of technical tools and pharmacological support.

Part III. From selective shunt to liver transplant

“Every era has its own tasks, and their solution provides human progress"

Heinrich Heine

In 1986, Alexander G. Scherzinger (b. in 1942), a disciple of M.D. Patsiora, one of the pioneers of endoscopic sclerotherapy and endoscopic ligation of the esophageal and gastric varices in gastroesophageal bleeding, (Fig. 1) proposed an endoscopic classification of esophageal varices, which was the most adapted to the needs of clinical practice and made it possible to almost accurately predict the risk of bleeding in the vast majority of patients. Dilatation of veins up to 3 mm

corresponds to grade 1, dilatation of up to 3-5 mm corresponds to grade 2, and the one of 5 mm or more correspond to grade 3 esophageal varices [6].

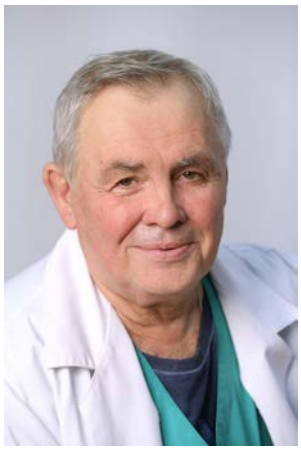

Fig. 1. Alexander Georgievich Shertzinger (born in 1942). Available at: https://med.ru/ru/sercinger-aleksandr-georgievic)

In 1999, the President of the Asia-Pacific Association for the Study of the Liver and founder of the Asia-Pacific School of Hepatology Shiv Kumar Sarin (b. in 1952) (Fig. 2) identified 4 types of gastric varices in his classification [7], namely, A. Gastroesophageal varices: type 1 (GOV1) are gastroesophageal varices extended to the esophageal veins along the lesser curvature of the stomach; type 2 (GOV2) are gastroesophageal varices extended to the esophageal veins along the gastric fundus. C. Isolated gastric varices: type 1 (IGV1) are those in the area of gastric fundus; type 2 (IGV2) are those in other parts of the stomach.

Fig. 2. Shiv Kumar Sarin (born in 1952). Available at: https://usaindiachamber.org/Dr-Shiv-Kumar-Sarin.php

In the 1970s in Cape Town (South Africa), the group John Terblanche (b. in 1935) (Fig. 3), based on research by F. Crafoord, P. Frenckner [8], brought the technique of endoscopic sclerotherapy of venous varices back to clinical practice [9]. Prospective randomized trials showed that endoscopic sclerotherapy gives better results compared to medication therapy [10, 11].

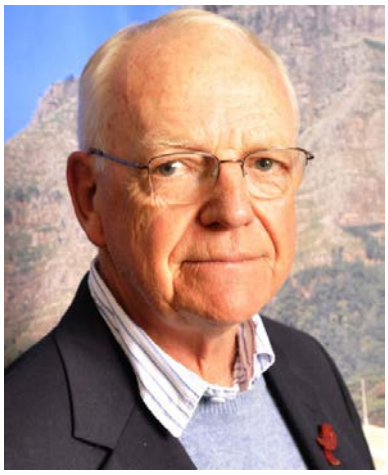

Fig. 3. John Terblanche (born in 1935). Available at: https://www.news.uct.ac.za/article/-2021-02-24-memories-of-stuart-saunders-a-true-friend-and-a-great-colleague

At the same time, a transplant surgeon J. Michael Henderson (Fig. 4) (b. in 1945), the Head Physician of the Medical Center of the University of Mississippi (USA) showed that the results of sclerotherapy in preventing recurrent variceal bleeding were no different from surgical shunting. Despite the use of new sclerosing agents, erosion and ulceration of the esophagus remained a potential complication of endoscopic sclerotherapy, as F. Crafoord and P. Frenckner noted as early as in 1939 [8]. A high risk of rebleeding required careful monitoring of these patients and a repeated endoscopic treatment [12].

Fig. 4. J. Michael Henderson (born in 1945). Available at: https://expertfile.com/experts/jmichael.hendersonmd/j-michael-henderson-md

John Terblanche attempted ligating venous varices under general anesthesia using a rigid esophagoscope [10]. In 1989 Greg van Stiegmann (b. in 1949) (Fig. 5) during his internship at the Department of Surgery, Groote Schuur Hospital run by John Terblanche, improved the technique by offering elastic rings as ligatures for ligation of bleeding esophageal venous varices. Upon returning to Denver, Colorado, Greg van Stiegmann adapted the procedure, which he had regularly used to ligate varicose hemorrhoidal veins by means of a rigid rectoscope before to ligate

esophageal varices with a flexible endoscope. To do this, he developed and manufactured a prototype of a stainless steel device at his own expense in the university machine workshop [13].

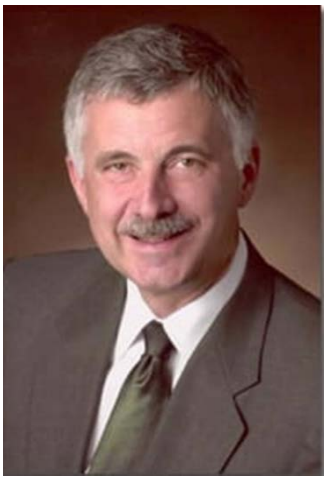

Fig. 5. Greg van Stiegmann (born in 1949). Available at: https://www.vitals.com/doctors/Dr_Gregory_Stiegmann.html

Greg van Stiegmann ligation device allowed only one elastic ring to be placed at a time. In 1997, Zet Saeed from Houston (Texas, USA) improved the device; and after that it became possible to place six elastic rings in it. That allowed ligating six venous varices in the esophagus during one endoscopy session [14].

One of the convinced enthusiasts of widely using clinical endoscopy in the treatment and diagnostic program of patients with portal hypertension was Alexander Evgenievich Borisov (1948–2012) (Fig. 6). In A.E. Borisov's opinion, today there is no reason to restrain a powerful wave of implementing endoscopy and advanced technologies in such a challenging clinical area as the treatment of portal bleeding. By using endoscopic techniques, a wide range of diagnostic tasks can be solved: establishing the fact of bleeding, the source of hemorrhage, as well as predicting the expected risk of recurrent bleeding. It is the high predictive

value of endoscopic parameters that serves as the main argument in favor of the widest possible use of esophagogastroscopy in this group of patients [15].

Fig. 6. Alexander Evgenievich Borisov (1948-2012). Available at: https://www.livelib.ru/author/733938-aleksandr-borisov

According to Roberto Giuseppe de Francis (b. in 1945) (Fig. 7), local endoscopic therapy in combination with vasoactive drugs aimed at the eradication of varicose veins, is today the "gold standard" at the initial treatment stage for acute esophageal-gastric bleeding. However, in 10–20% of clinical cases, ligation cannot be performed due to massive bleeding, or the high likelihood of early recurrence of bleeding. Mortality in such patients reaches 30–50% [16].

Fig. 7. Roberto Giuseppe de Franchis (born in 1945). Available at: https://easl.eu/easl-recognition-award/

For these patients, Angels Escorsell (Fig. 8) proposed two different approaches. First, if bleeding is minor and the patient has a relatively good liver function, endoscopic therapy may be attempted again. If the bleeding is severe or the second attempt has failed, it can be temporarily controlled with a self-expanding nitinol stent [17, 18].

Fig. 8. Angels Escorsell. Available at: https://www.laveu.cat/afons.cfm/id/599972/angels-escorsell-metgessa.htm

The first such stent, intended, however, for the surgical elimination of esophageal stenosis was installed by Jan Danis (1952–2010) (Fig. 9) in the Department of Surgery in Linz (Austria), in November 2002, during his night shift to a twenty-seven-year-old man suffering from liver failure as a result of hepatitis C and HIV infection against underlying hemophilia and who underwent liver transplantation complicated by severe coagulopathy. The next day, the Head of the Department scolded the doctor with the words: "Never again, or ...!". However, a few days later, after the clinical situation had stabilized, the stent was removed, and a day later the Head of the Department told him: “Congratulations!” [19].

Fig. 9 Jan Danis (1952–2010). Available at: https://slidetodoc.com/stenting-for-acute-variceal-bleeding-an-update-rainer/

Subsequently, a number of authors came to the conclusion that endoscopic hemostasis using a self-expanding nitinol stent is accompanied by fewer side effects and leads to a more reliable control of bleeding than balloon tamponade with a Sengstaken-Blakemore tube. However, the widespread use of self-expanding nitinol stent is currently limited by the lack of well-designed randomized controlled trials needed

to determine its place in the treatment program for esophageal venous variceal bleeding [20, 21].

As time went on, numerous experimental models improved understanding of the portal hypertension pathophysiology. The studies by the teams led by Baveno Jaime Bosch (b. in 1947) (Fig. 10), a Senior Hepatologist-Consultant and Professor of Medicine at the University of Barcelona (Spain), chairman of the Collaboration, and Roberto Groszmann (1939–2021) (Fig. 11), the Head of Digestive Diseases Department at the West Haven Medical Center, Virginia (USA) convincingly showed that increased vascular resistance to portal blood flow was the initial factor responsible for the increase in portal pressure. This resistance appears in the area of the hepatic and portal-collateral circulation and can partially be modified by pharmacological agents. In the last stage, increased portal venous blood flow stimulated by splanchnic vasodilation, contributes to the persistence and exacerbation of portal hypertension. Humoral vasodilators play an important role in splanchnic vasodilation. The latter is associated with hyperkinetic systemic circulation, with a decrease in blood pressure and peripheral resistance and with an increase in cardiac output. Increased plasma volume is observed in all forms of portal hypertension. Plasma volume expansion is explained by the sodium retention in kidneys, which precedes an increase in cardiac output and can be prevented or reversed by sodium restriction and spironolactone. Increased blood volume is another mechanism that contributes to a further increase in portal pressure [22, 23].

Fig. 10. Jaime Bosch (born in 1947). Available at: https://barcelona.academia.edu/JaimeBosch

Fig. 11. Roberto Groszmann (1939-2021). Available at: https://medicine.yale.edu/news-article/roberto-j-groszmann-md-professor-emeritus-of-medicine-dies-at-81/

A better understanding of the pathophysiological mechanisms leading to portal hypertension enabled remarkable progress in the treatment thanks to the implementation of an effective portal antihypertensive therapy.

Gradually, surgery has lost its monopoly on the effective treatment of these patients. Doors have been opened to new alternative therapies. An important step forward was the successful pharmacological therapy to

reduce portal pressure, especially with non-selective β-blockers, which was implemented in Paris (France) by Didier Lebrec (b. in 1945) (Fig. 12) [24].

Fig. 12. Didier Lebrec (born in 1945). Available at: https://www.journal-of-hepatology.eu/article/S0168-8278(13)00335-8/pdf

Guadalupe Garcia-Tsao (Fig. 13), Professor of Medicine at Yale University School of Medicine and the Head of the Department of Digestive Diseases at the Virginia State Health System, Connecticut (USA), paid much attention to studying the usefulness of drugs that reduce portal pressure and their effect on the prevention of poor outcomes in liver cirrhosis..

Fig. 13. Guadalupe Garcia-Tsao. Available at: https://news.ddw.org/news/speaker-spotlight-guadalupe-garcia-tsao-md/

Effective therapy requires a decrease in the venous pressure gradient in the liver to 12 mm Hg or lower, or at least by 20% of the baseline values. Unfortunately, this is only achieved in 1/3–1/2 patients. Combination therapy, including the administration of isosorbide-5-mononitrate and propranolol or nadolol, enhances the decrease in portal pressure and increases the number of patients in whom the hepatic venous pressure gradient decreases by more than 20% of baseline values and below 12 mm Hg. The therapy may be complemented with spironolactone administration.

In the treatment of acute variceal bleeding, pharmacological therapy has the unique advantage of allowing specific therapy to be carried out immediately after arrival at the hospital or even during transport to the hospital by ambulance, since it does not require sophisticated equipment or highly trained medical personnel. Terlipressin act for a longer time is more effective and safer than vasopressin alone or in combination with nitroglycerin. It proved effective and being able to reduce bleeding-associated mortality in double-blind studies showing the

drug to be as effective and safe as emergency sclerotherapy. Terlipressin therapy should be continued for five days to prevent early rebleeding. Somatostatin and octreotide cannot be recommended as the first line treatment.

Medicaton therapy failures should be treated endoscopically. Endoscopic treatment failures require "rescue" with TIPS or bypass surgery. Patients with advanced liver failure should be considered for orthotopic liver transplantation and placed on a waiting list if possible [25–27].

In 1969, at the Oregon Health and Science University in Portland (USA), Josef Rosch (1925–2016) (Fig. 14) in his experiments on dogs and sheep catheterized the portal vein under X-ray guidance, advancing the catheter first through the percutaneous access into the jugular vein, then into the hepatic vein and then, through the hepatic parenchyma, directly into the portal vein.

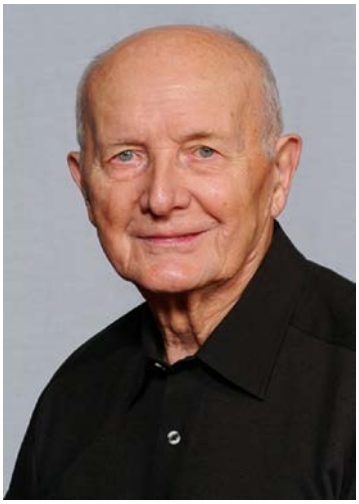

Fig. 14. Josef Rosch (1925-2016). Available at: http://www.crs.cz/cs/hall-of-fame/prof.-josef-roesch.html

So an interventional radiologist, using an endovascular approach through the jugular vein as the site of entry, successfully created an

artificial channel in the liver that established a connection between the afferent portal vein and the efferent hepatic vein [28]. This was followed by technical proposals to strengthen the channel wall in the liver parenchyma using synthetic materials. Under conditions of experimental models of portal hypertension, an artificial channel created by endovascular procedure in the liver ensured the normalization of pressure in the portal vein. However, it was still far from clinical application. The inevitable thrombosis of the shunt required its re-insertion after a short period of time.

For the first time in the clinical setting, a transjugular intrahepatic portosystemic shunt (TIPS) procedure was performed in 1982 by Dr. Ronaldo Colapinto (1931–2010) (Fig. 15) from the University of Toronto (Canada).

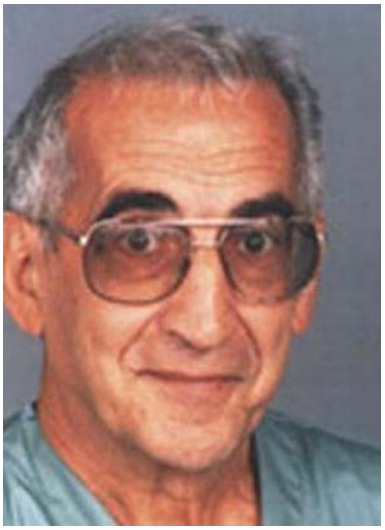

Fig. 15. Ronaldo Colapinto (1931-2010). Available at: https://www.cbc.ca/news/canada/toronto/pioneering-toronto-md-ronald-colapinto-dies-1.1092029

In a patient with cirrhotic esophageal bleeding after channel formation in the liver parenchyma, he performed angioplasty with a 12-

mm balloon for 12 hours [29]. However, the R.F. Colapinto's technique did not become successfully reproducible, because it was not possible to achieve long-term functioning of the portacaval tract artificially created inside the parenchyma of the cirrhotic-process-affected liver by means of the instruments and consumables used in angioplasty of those years. Long-term results were not encouraging and most patients died within a month [3].

A technological breakthrough was required. And it didn't have to wait long. In 1985–86 publications Julio Caesar Palmaz (b. in 1945) (Fig. 16) reported that in an experiment dog model of portal hypertension, he used metal balloon-expandable stents to strengthen the shunt [30, 31]. Even after 48 weeks, the shunts were functioning. Meantime, a histological examination revealed that the stented channel was covered with a thin, tender neointima.

Fig. 16. Julio Caesar Palmaz (born in 1945). Available at: https://www.nae.edu/203087/Dr-Julio-Cesar-Palmaz

In 1989, the first successful TIPS were implemented by M. Rosslea, G. M. Richter, J. C. Palmaz, G. Noeldge et al. at the

University of Freiburg (Germany) [32, 33]. In 2006, J. M. Henderson et al. demonstrated similar results between TIPS and distal splenorenal shunts, even though TIPS required more reoperations and higher costs [34]. Since then, this procedure has been widely accepted as the treatment of choice for portal hypertension that is refractory to medical therapy, replacing the surgical portacaval shunt in this role [35–38].

In our country, an invaluable contribution to the study and development of the TIPS procedure as a form of selective bypass surgery, the shunt being preformed percutaneously, was made by Vladimir Nikolaevich Shipovsky (b. in 1960) (Fig. 17) and Yuri Vladilenovich Horonko (b. in 1958) (Fig. 18), who had the greatest experience in the effective clinical use of TIPS even in patients classified as high surgical risk. First of all, this applies to patients with esophageal-gastric bleeding of cirrhotic origin.

Fig. 17. Vladimir Nikolaevich Shipovsky (born in 1960).
Available at: https://shipovsky.ru

Moreover, they consider this surgical technique to be preferable [39-41].

Fig. 18. Yuriy Vladilenovich Khoronko (born in 1958). Available at: http://rostgmu.ru/образование/факультеты/педиатрический-факультет/кафедра-оперативной-хирургии-и-топог

However, after initial enthusiasm, it had subsequently been shown that although the TIPS procedure involved less surgical trauma, if the shunt was left open, the likelihood of developing encephalopathy remained relatively high. If the shunt is thrombosed, there is a high chance of rebleeding. Thrombosis and TIPS stenosis occur in almost 50% of patients within 2 years. Due to frequent shunt failure, patients require multiple interventions over time. The cost and number of interventions after TIPS are higher than after endoscopic therapy. Therefore, TIPS is recommended as a salvage therapy in patients in whom medical and endoscopic therapy has failed. It is important to define parameters that can identify high-risk patients in whom standard medical and endoscopic treatment has a high chance of failure. This group of patients makes up 10–20% of those who are admitted to the emergency department with variceal bleeding.

In 1996, H. Kanagawa et al. proposed an endovascular operation of balloon-occlusive retrograde transvenous obliteration (BRTO) for the eradication of gastric venous varices in the presence of portal hypertension [42]. In the opinion of Juan Carlos Garcia-Pagan (b. in

1960) (Fig. 19), Associate Professor of the University of Barcelona, a Senior Consultant in Hepatology and Head of the Liver Hemodynamics Department at the Clinical Hospital in Barcelona (Spain), BRTO may be considered as an alternative in the patients not eligible for TIPS. The efficacy of this method was noted in 90% of cases, the recurrence rate of venous varices being 7%. Meanwhile, BRTO is technically feasible to be performed only in the presence of a gastrorenal shunt, that is, a connection between the left renal vein and gastric variceal veins. Such a shunt can be determined in 85% of patients with liver cirrhosis [43].

Fig. 19. Juan Carlos Garcia–Pagan (born in 1960). Available at: https://fundacionfranciscocobos.org/dr-juan-carlos-garcia-pagan-xv-premio-fundacion-francisco-cobos/

On the one hand, BRTO appears to be an easy procedure to successfully control and prevent bleeding from gastric varices. At the same time, BRTO requires prolonged post-procedure monitoring and may have complications associated with balloon rupture and adverse effects from sclerosing agents. Several modified BRTO techniques have been developed, including retrograde transvenous obliteration with various sclerosants (5% ethanolamine oleate with iopamidol, sodium tetradecyl

sulfate foam, polidocanol, and gelatin sponge), retrograde transvenous obliteration with a helix (CARTO) and antegrade transvenous obliteration with balloon occlusion [44]. Currently, there is a lack of objective data to routinely recommend BRTO for the primary prevention of bleeding from gastric varices [45, 46].

Despite the fact that many surgical and non-surgical procedures have been proposed to treat patients with portal hypertension, in the opinion of Layton (Bing) F. Rikkers (b. in 1944) (Fig. 20), Professor Emeritus of the School of Medicine and Public Health at the University of Wisconsin (USA), Editor-in-Chief of Annals of Surgery, none of them has been proven by controlled trials to be superior to others in terms of long-term postoperative survival and has not become ideal for all patients [47, 48].

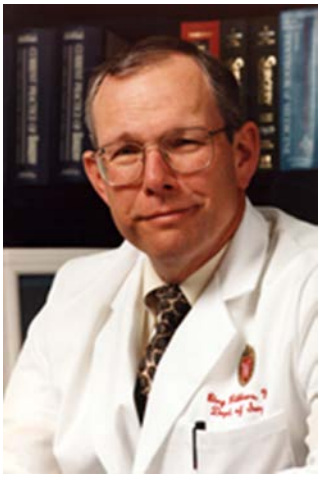

Fig. 20. Layton (Bing) F. Rikkers (born in 1944). Available at: https://www.unmc.edu/surgery/education/lectureships/rikkers.html

According to Vladimir Moiseevich Durleshter (b. in 1959) (Fig. 21), a prerequisite for the treatment of such patients is the use of an interdisciplinary approach involving surgeons, gastroenterologists,

endoscopists, endovascular surgeons, anesthesiologists, and resuscitators. The most acceptable is an individual approach to each patient [49].

Fig. 21. Vladimir Moiseevich Durleshter (born in 1959). Available at: https://m.kkb2-kuban.ru/content/344

In 1983, one of the best reviews of that time was published, which had studied the results of using Eck's fistula and its numerous surgical options in animals and humans, and which is still considered the most authoritative publication since the time of I.P. Pavlov in 1893 [50]. Its authors were Thomas Starzl (1926–2017) (Fig. 22), Professor of Surgery at the University of Pittsburgh Medical School, whose clinical practice took place at the Presbyterian University Hospital, Pittsburgh Children's Hospital and the Oakland Veterans Hospital (USA) and two of his talented collaborators. One of them was Kendrick Arthur Porter (1925–2013) (Fig. 23), the Chairman of the Pathology Department at St Mary's Hospital and the Medical School in London. The other one was Antonio Francavilla (b. in 1927) (Fig. 24), Professor of Biological Chemistry and Head of the Gastroenterology Department at the University of Bari (Italy).

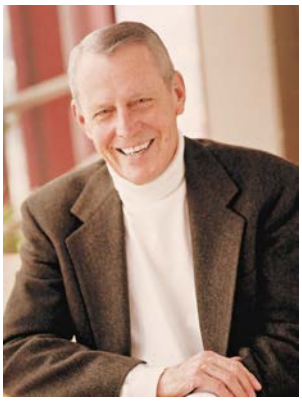

Fig. 22. Thomas Starzl (1926-2017). Available at: https://www.elsevier.es/en-revista-annals-hepatology-16-articulo-in-memoriam-thomas-starzl-m-d--S1665268119304697

Fig. 23. Kendrick Arthur Porter (1925-2013). Available at: https://ukkidney.org/obituary/kendrick-arthur-porter

Fig. 24. Antonio Francavilla (born in 1927). Available at: https://www.sanita.puglia.it/web/debellis/news-in-archivio_det/-/journal_content/56/36092/irccs-la-ricerca-ha-fatto-passi-da-gigante

I.P. Pavlov pointed out the almost complete lack of scientific data resulting from the Eck study, however, noted that the operation would be important because it could open doors to clarify important problems in the pathology, physiology and pharmacology of the liver. No one took advantage of this opportunity with such brilliance and dedication as Thomas Starzl, and in this he had no equal. In all species studied so far, including humans, a portacaval shunt causes similar changes in liver morphology, including hepatocyte atrophy, fatty infiltration, depletion and disorganization of the endoplasmic reticulum being the "cell factory", and less specific damage to other organelles. The Review by T.E. Starzl, K.A. Porter, A. Francavilla presents the scientific rationale for liver transplantation that targets both underlying liver disease and portal hypertension, providing a treatment that simultaneously controls variceal bleeding and restores liver function. Transplantation should be considered for all patients with the end-stage liver disease. Thomas Starzl's initial experience with liver transplantation was less than encouraging. He chose to spend one academic year in the UK with Roy Calne (b. in 1930) (Fig. 25), a Fellow of the Royal Society and Professor of Surgery at the University of Cambridge from 1965 to 1998, whose most studies at that time were related to the improvement of immunosuppression methods aimed at prolonging the life of liver transplant recipients.

Fig. 25. Roy Calne (born in 1930). Available at: https://www.trinhall.cam.ac.uk/contact-us/contact-directory/fellows-and-academics-directory/roy-calne/

A novel immunosuppressive therapy with cyclosporine made liver transplantation a clinical reality [51]. In Pittsburgh, which after Thomas Starzl's arrival became one of the most important surgical centers in the world, he and his group demonstrated a 5-year survival rate in 71% of clinical cases in liver transplant patients who received immunosuppressive therapy with cyclosporine and steroids [52].

In the Russian Federation, as evidenced by the experience of Dr. M.Sh. Khubutiya (b. in 1946) (Fig. 26), the Chief Transplantologist of Moscow, Academician of the Russian Academy of Sciences, liver transplantation has taken its place as the optimal treatment for many patients with portal hypertension, provided that they meet the existing criteria for transplantation [53].

Fig. 26. Mogeli Shalvovich Khubutiya (born in 1946). Available at: https://ria.ru/20170604/1495793530.html

According to Dr. S.V. Gautier (b. in 1947) (Fig. 27), the Chief Transplantologist of Russia, Academician of the Russian Academy of Sciences, there is an urgent need in the Russian Federation for further development of liver transplantation, a radical and highly effective method of treating patients with the portal hypertension syndrome, as there is a respective patient population, and encouraging clinical results have been obtained that differ little from such at the beginning of the operation of foreign transplant programs [54].

Fig. 27. Sergey Vladimirovich Gautier (born in 1947). Available at: https://www.transpl.ru

So, since September 1877, when the experimental dog recipient of the first successful portacaval shunt but forever lost for follow-up

observation, has marked the priority of the surgeon's scalpel, the wheel of history "has completed a full circle" through a series of the latest achievements in science and technology, [55] and again brought to the forefront a surgeon who plays a key role in the management of a patient with portal hypertension.

In this regard, a very important question arises if it is possible in conditions of the current economic development of the state to solve the problem of portal hypertension only by endoscopic ligation or stenting, transjugular intrahepatic portosystemic shunts or liver transplantation. Unfortunately, the answer is no. With the exception of a few limited groups of patients who are in controlled, prospective, and randomized protocols, in which investigators are interested in closely monitoring the results of their procedures, a large proportion of the patient population continues to receive sporadic conservative treatment with high mortality and high rebleeding rates. Every year, hundreds of patients after conservative treatment return to an Emergency Department with new episodes of bleeding and liver failure. It is important to note that if conservative measures fail, some patients die, and many others lose a good liver function and are unlikely to get good results from the operation. That is why considering the problem from this angle requires the surgeon to be both a clinician, and also a strategist and tactician in organizing medical care for patients with portal hypertension of various origins.

In the Republic of Tatarstan, the regional Health Ministry Order "On measures to improve surgical care for patients with chronic diffuse and focal diseases of the liver and portal system complicated by portal hypertension" was issued on March 22, 2019 [56]. For our republic, this Order, without exaggeration, played the same role as the USSR Ministry of Health Order N 728 dated July 13, 1979, “On measures to improve

surgical care for patients with chronic diseases of the liver and portal system complicated by portal hypertension" [57]. In accordance with this Order, the scheme of organizing surgical care for patients with portal hypertension in the Republic of Tatarstan today is as follows. At the local (district and interdistrict) level that includes medical organizations of the 1st and 2nd levels, there are 35 central district hospitals, 16 intermunicipal (interdistrict) centers and city multidisciplinary hospitals designated to support the vital functions of the patient, stabilize his/her condition in the extent of life-saving inpatient surgical care: tube-obturator, vasoactive drugs, azigoportal disconnection surgery. Further, there is the transportation to the republican level facility, to a specialized multidisciplinary surgical center of the 3rd level. High-tech surgical care is provided here using modern diagnostic equipment and performing the full range of surgical interventions: endoscopic ligation; hemostasis by means of self-expanding nitinol stents; transjugular intrahepatic portosystemic shunting; portacaval shunting; liver transplantation. In addition, the federal level should also be highlighted. This implies the leading institutions in Russia for the problem of portal hypertension surgery: the Department of Emergency Surgery and Portal Hypertension of the Academician B.V. Petrovsky Russian Research Center of Surgery (RRCS) at the clinical base of the Moscow City Clinical Hospital named after A.K. Eramishantsev, N.V. Sklifosovsky Research Institute for Emergency Medicine of Moscow Health Department, and Academician V.I.Shumakov Federal Research Center of Transplantology and Artificial Organs of the RF Ministry of Health.

Conclusion

Completing the story about the historical spiral of the portal hypertension surgery development, each turn of this spiral being

associated with some kind of revolutionary event, discovery or achievement of human thought, which significantly influenced the progress that the previous generation could not even imagine, we are aware that in this essay, we managed to recall far from all the brightest personalities, the great thinkers and practitioners in this field of medicine. Honesty in assessing the facts obtained, the courage to abandon old established dogmas, as well as the strength and will to follow personal ideas, despite the fierce resistance of society in general and the professional medical community in particular, lay and lie at the basis of the results they achieved. We bow our heads deeply in memory of the pioneers who have gone from us and salute all active pioneers in this field. The foundation they laid has led today to evidence-based approaches in the treatment of patients with portal hypertension. Having arisen at the very dawn of the human society birth, portal surgery is at the same time eternally young, because it is unthinkable without the use of the latest achievements of human thought, the progress of science and technology. In addition, the rate of the portal surgery development is very high. What yesterday seemed new and was just beginning to be published only in special surgical journals, today becomes routine, everyday work, representing the basis for optimism and hope for future development. As one of the largest representatives of Russian medicine, Maxim Petrovich Konchalovsky, truly stated: “Old signs go down in history, new ones appear, and every day we see that more and more new pages of this tempting book, which is called the clinic, are being opened, and we don’t know who and when will write its last page". Thanks to the efforts of more and more enthusiasts, portal hypertension surgery is constantly being improved, and we will certainly see further progress in the 21st century, in the new millennium.

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