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Liver Regeneration in Surgical Animal Models – A Historical Perspective and Clinical Implications

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Key Words
Animal models · Experimental research · Liver regeneration · Partial hepatectomy · Split liver

Abstract
Methods/Aims: Despite improved preoperative evaluation, surgical techniques and perioperative intensive care, some patients still experience postoperative liver failure in part due to insufficient regeneration. The aim of this review is to give the reader a historical synopsis of the major trends in animal research on liver regeneration from the early experiments in 1877 up to modern investigation. A major focus is placed on the translational value of experimental surgery. ***Methods:*** A systematic review of the English literature published in Medline was undertaken with the search words 'pig, porcine, dog, canine, liver regeneration, experimental'. ***Results:*** The evolution of the various models tentatively explaining the process of liver regeneration is described. ***Conclusions:*** We conclude by emphasizing the importance of large-animal surgical research on liver regeneration as it offers a more integrated, systemic biological understanding of this complex process. Furthermore, in our opinion, a closer collaboration between the hepatologist, liver surgeon/transplant surgeon and the laboratory scientist may advance clinically relevant research in liver regeneration.

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Introduction

Modern liver surgery has seen the development of split-liver grafting [1] and more aggressive, multimodal treatment of primary and secondary liver malignancies, increasing the possibilities for resection [2]. Despite continuous improvement in the surgical technique and perioperative intensive care, some patients still experience deficient regeneration and functional failure in the so-called SFSS occurring after liver transplantation if the graft is of marginal size (graft weight/body weight ratio <0.8%) [3], or if the liver remnant is too small after extend-

Abbreviations: AR = Amphiregulin; C/EBP-β= CCAAT enhancer-binding protein-β; C3a = complement factor 3a; C5a = complement factor 5a; EGF = epidermal growth factor; FGF = fibroblast growth factor; HB-EGF = heparin-binding epidermal growth factor; HGF = hepatocyte growth factor; HSS = hepatic stimulatory substance; IGFBP-1 = insulin-like growth factor binding protein-1; IGF = insulin-like growth factor; IL = interleukin; iNOS = inducible nitric oxide synthase; Met = hepatocyte growth factor receptor; MMP9 = matrix metalloproteinase 9; MT = metallothionein; MyD88 = myeloid differentiation factor 88; OSM = oncostatin M; PCS = portocaval shunt; PHx = partial hepatectomy; PPAR-α = proliferator-activated receptor-α; PVA = portal vein arterialization; SCF = stem cell factor; SFSS = small-for-size syndrome; T_3 = triiodothyronine; TGF = transforming growth factor; TIMP3 = tissue inhibitor of metalloproteinase 3; TNF = tumor necrosis factor; uPA = uroplasminogen activator; VEGF = vascular endothelial growth factor.

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ed hepatectomy (<25% functionally normal liver remaining) [2]. Postresectional liver dysfunction is also a problem with the increasing use of neoadjuvant chemotherapy for colorectal metastasis [4]. The vast amount of research performed on liver regeneration to date has had relatively little practical consequences for the patient with a failing liver except for the development of liver support systems such as the molecular adsorbent recirculating system, bridging the time to transplantation, re-transplantation or as a support during recuperation of the native liver [5]. Contemporary liver surgery is therefore in need of a better understanding of the mechanisms controlling liver regeneration in order to design new treatment strategies to support the functionally deficient and failing organ. At the same time, strategies are needed to enhance its regenerative capacity be it a small-for-size graft or a failing remnant after hepatectomy with or without neoadjuvant chemotherapy. The purpose of this literature review is therefore to summarize previous experimental in vivo research on liver regeneration in animals, beginning with the Eck fistula model in 1877 up to present-day investigations, focusing on how this field has developed as a result of the interplay between clinical challenges and preclinical surgical research (see table 1 for a chronological overview of the studies discussed below). The review is organized according to past and present general themes on liver regeneration and their development over time. For each theme, we aim to highlight residual controversies, formulate new hypotheses and suggest novel experimental models in which they could be tested.

By writing this review we aim to give the reader a historical overview of the major trends in animal research on liver regeneration with emphasis on the importance of in vivo models, the value of translational research, and the necessity of increased collaboration between the basic laboratory scientist and the clinician. In our opinion, these measures are necessary if we are to make any further progress in aiding the patient with a failing liver due to insufficient regeneration.

Sinusoidal Hemodynamics and the Flow Theory

The study of liver regeneration was largely triggered by Eck's seminal paper on complete PCS (Eck fistula) in dogs in 1877 [6] which led to the belief that the liver's homeostasis was not dependent upon portal blood perfusion. However, in 1893 this was contested by Hahn et al. [7] whose dogs did poorly with the Eck fistula, showing signs of liver atrophy, weight loss and encephalopathy. The changes incurred by PCS were for many ensuing years thought to be the result of a lack of sinusoidal distension and/or lack of portal flow through the liver (as opposed to a lack of the substances transported to the liver in the portal blood). The theory of sinusoidal distension was corroborated by Grindlay and Bollman [8] who in 1952 observed that the liver regenerated after a 70% PHx in dogs when constricting the vena cava above the liver, and hence increasing the hepatic venous pressure (in a Budd-Chiari-like manner). The theory of liver volume and functional maintenance by sinusoidal flow per se received much support due to Child's model of portocaval transposition in 1953, where, after a 70% PHx in dogs, the portal vein and vena cava inferior were switched surgically, resulting in the liver remnant receiving only systemic blood from the caudal stump of the vena cava inferior, and all portal blood being diverted to the cranial stump of the vena cava inferior [9]. The observation that the remnant liver (in the portocaval transposition group) regenerated by 50% seemed to support the theory that sinusoidal flow in itself was adequate to initiate and support liver regeneration, irrespective of the quality of the perfusate. Conceptually, the observations in both studies could have been the result of a systemic overflow of growth-stimulating factors from the upper gastrointestinal tract away from the portal circulation and back to the liver via the hepatic artery in Grindlay's experiments, and via the vena cava inferior in Child's experiments, but this possibility is not discussed in either article. Further solid support to the 'flow theory' came from several canine experiments conducted in the 1950s and early 1960s with PVA (after PCS) showing that this maneuver would not only arrest the changes incurred by the Eck fistula, such as 'meat intoxication', weight loss of the animals and liver atrophy [10–12], but also allow liver regeneration to occur after a 42% PHx [13]. However, several of these [11, 12] and other studies [14–16] also reported the development of vasculitis, periportal fibrosis, intima proliferation, lipid infiltration and the development of cirrhosis in long-term (5-year)-arterialized livers [12]. This would indicate the unphysiological nature of PVA. A note of interest at this point is the preceding work of Rous and Larimore [17] in 1920 which illustrated what they coined the phenomenon of 'parenchymal shift'. Upon ligating one of the portal vein branches in the rabbit, they observed ipsilateral atrophy and contralateral hypertrophy of the liver, postulating 'the liver is wholly a portal organ, finding its reason for being in the substances carried to it in the portal blood'. This study had clearly implicated the importance of the humoral effect of splanchnic inflow on liver homeostasis; however, the flow theory prevailed unchallenged until the mid 1960s.

Table 1. Chronological overview of liver regeneration research in animal models

General					Methods							Regeneration model					Varia			
Year	Species	First author	Title	Reference No.	Hepatectomy	Liver transplantation	Splanchnic evisceration	Other manipulations	Vascular rearrangement	PVA	Gene expression	Humoral model	Metabolic model	Flow model	Oxygenation and energy status of the liver	The liver as a source of growth factors	Studies in anatomy	SFSS	Studies reporting hemodynamic data	Growth factor detection
1877	dog	Eck	Concerning ligation of the vena porta	6				x	x											
1920	rabbit	Rous	Relation of the portal blood to liver maintenance	17				x	x			x		x	x					
1939	pig	Brues	Growth inhibition by substances in liver	79				x								x				
1951	rat	Bucher	Regeneration of the liver in parabiotic rats	81	x			x	x			x				x				
1952	dog	Cohn	Some effects upon the liver of complete arterialization of its blood supply	10				x	x	x				x	x					
1952	dog	Grindlay	Regeneration of the liver in the dog after partial hepatectomy – role of the venous circulation	8	x			x	x			x	x	x					x	
1953	dog	Child	Liver regeneration following portocaval transposition in dogs	9	x			x	x					x						
1953	dog	Rather	Some effects upon the liver of complete arterialization of its blood supply	14				x	x	x					x		x		x	
1953	dog	Schilling	Late follow-up on experimental hepatic-portal arteriovenous fistulae	12				x	x	x				x	x			x	x	
1954	dog	Fisher	Effect of increased hepatic blood flow upon liver regeneration	13	x			x	x	x				x	x				x	
1957	dog	McCredie	Total arterialization of the liver	11				x	x	x				x	x				x	
1961	dog	Schwartz	Experimental arterialization of the liver	15				x	x	x				x	x			x		
1963	dog	Sigel	The effect of partial hepatectomy on autotransplanted liver tissue	85	x	x		x	x			x				x				
1963	dog	Zuidema	Segmental portal arterialization of canine liver	16				x	x	x				x				x	x	
1965	dog	Marchioro	Physiologic requirements for auxiliary liver homotransplantation	24	x	x	x	x	x			x								
1965	dog	Marchioro	The specific influence of nonhepatic splanchnic venous blood flow on the liver	19				x	x			x								
1965	dog	Sigel	Tritiated thymidine autoradiography in the regenerating liver of the dog	131	x															
1965	dog	Thomford	Homotransplantation of the canine liver	21	x	x		x	x			x				x				
1965	dog	Tretbar	Homotransplantation of an auxiliary dog liver into the pelvis – effect of portocaval shunt in the prevention of liver atrophy	20		x		x	x			x								
1966	dog	Halgrimson	Auxiliary liver transplantation: effect of host portacaval shunt	22		x		x	x			x								
1967	dog	Marchioro	The effect of partial portacaval transposition on the canine liver	23				x	x	x		x	x	x	x				x	
1967	dog	Mito	Partial heterotopic liver homograft in dogs utilizing portal arterialization	63		x		x	x	x				x	x			x	x	
1967	dog	Sigel	Independence of hyperplastic and hypertrophic responses in liver regeneration	132	x	x		x	x			x				x				
1967	dog	Sigel	Studies of liver lobes autotransplanted outside the abdominal cavity	86		x		x	x	x		x	x	x						

Table 1 (continued)

General					Methods							Regeneration model					Varia			
Year	Species	First author	Title	Reference No.	Hepatectomy	Liver transplantation	Splanchnic evisceration	Other manipulations	Vascular rearrangement	PVA	Gene expression	Humoral model	Metabolic model	Flow model	Oxygenation and energy status of the liver	The liver as a source of growth factors	Studies in anatomy	SFSS	Studies reporting hemodynamic data	Growth factor detection
1971	dog	Price	Characteristics of animals maintained without splanchnic portal organs	25			x	x	x			x								
1972	dog	Price	Glucagon as the portal factor modifying hepatic regeneration	26	x		x		x	x		x								
1973	dog	Starzl	The origin, hormonal nature, and action of hepatotrophic substances in portal venous blood	27				x	x			x								
1974	dog	Starzl	Intraportal insulin protects from the liver injury of portacaval shunt in dogs	28				x	x			x								
1975	dog	Horak	Effect of portacaval shunt and arterialization of the liver on bile acid metabolism	64				x	x	x					x				x	
1975	dog	Starzl	Portal hepatotrophic factors, diabetes mellitus and acute liver atrophy, hypertrophy and regeneration	29	x		x	x	x			x								
1976	dog	Dugay	Regulation of liver regeneration by the pancreas in dogs	133	x		x	x				x								
1976	pig	Gallot	A simplified bloodless procedure for extensive hepatectomy	134	x				x								x			
1976	ape	Putnam	Hepatic encephalopathy and light and electron micrographic changes of the baboon liver after portal division	135				x												
1976	dog	Starzl	Effects of insulin, glucagon and insulin/glucagon infusions on liver morphology and cell division after complete portacaval shunt in dogs	30				x	x			x								
1977	pig	Campdrodon	Intrahepatic vascular division in the pig	136	x												x			
1977	dog	Duguay	Role of the pancreas in regulation of liver regeneration in dogs	31	x		x					x								
1978	dog	Francavilla	Liver regeneration in dogs: morphologic and chemical changes	137	x								x							
1978	dog	Starzl	The effect of splanchnic visceral removal upon canine liver regeneration	34			x			x		x								
1978	dog	Starzl	The effect upon the liver of evisceration with or without hormone replacement	33	x		x					x								
1979	dog	Starzl	Growth-stimulating factor in regenerating canine liver	87				x	x							x				
1980	pig	Kahn	Thymidine kinase: an inexpensive index of liver regeneration in a large animal model	138	x															
1980	dog	Starzl	Further studies on hepatic stimulatory substance (SS) after partial hepatectomy	88	x		x		x							x				
1980	dog	Terblanche	Stimulation of hepatic regeneration after partial hepatectomy by infusion of a cytosol extract from regenerating dog liver	89	x			x								x				
1981	pig	Van Hoorn-Hickman	Is there a regeneration stimulator substance in the effluent from perfused partially hepatectomized livers?	90	x				x							x				
1982	pig	Kahn	The stimulatory effect of a partially hepatectomized auxiliary graft upon the host liver	91	x	x		x	x							x				

Table 1 (continued)

General					Methods							Regeneration model					Varia			
Year	Species	First author	Title	Reference No.	Hepatectomy	Liver transplantation	Splanchnic evisceration	Other manipulations	Vascular rearrangement	PVA	Gene expression	Humoral model	Metabolic model	Flow model	Oxygenation and energy status of the liver	The liver as a source of growth factors	Studies in anatomy	SFSS	Studies reporting hemodynamic data	Growth factor detection
1984	pig	Kahn	Liver blood flow after partial hepatectomy in the pig	139	x														x	
1985	pig	Nordlinger	High-yield preparation of porcine hepatocytes for long survival after transplantation in the spleen	140		x														
1987	dog	Francavilla	Extraction and partial purification of a hepatic stimulatory substance in rats, mice, and dogs	141	x							x				x				x
1987	dog	Kam	Evidence that host size determines liver size: studies in dogs receiving orthotopic liver transplants	142		x							x							
1988	pig	Kahn	A porcine model for the study of liver regeneration	143	x															
1988	pig	Kahn	Partial hepatectomy and liver regeneration in pigs. The response to different resection sizes	144	x															
1988	pig	Kahn	Hepatic stimulator substance in extracts from regenerating porcine liver	145	x											x				x
1991	dog	Francavilla	Screening for candidate hepatic growth factors by selective portal infusion after canine Eck's fistula	35				x	x			x								x
1991	dog	Nonami	Effect of hyperdynamic circulatory support on hepatic hemodynamics, oxygen supply and demand after massive hepatectomy	70	x			x							x				x	
1995	dog	Ku	Evidence that portal vein decompression improves survival of canine quarter orthotopic liver transplantation	52	x			x	x					x				x	x	
1995	dog	Ueno	Effect of prior portosystemic shunt on early hemodynamics and sinusoids following 84% hepatectomy in dogs	57	x				x									x		
1995	pig	Yanaga	Partial hepatic grafting: porcine study on critical volume reduction	146	x	x												x		
1997	pig	Chow	Serial ultrasound-guided percutaneous liver biopsy in a partial hepatectomy porcine model: a new technique in the study of liver regeneration	147	x															
1997	dog	Ogata	Short-term effect of portal vein arterialization on hepatic protein synthesis and endotoxemia after extended hepatectomy in dogs	148	x				x	x				x				x	x	
1997	rat	Sato	Acute portal hypertension reflecting shear stress as a trigger of liver regeneration following partial hepatectomy	40	x									x					x	
1998	cat	Macedo	Shear-induced modulation of vasoconstriction in the hepatic artery and portal vein by nitric oxide	43				x	x					x					x	
1998	rat	Wang	Evidence of nitric oxide, a flow-dependent factor, being a trigger of liver regeneration in rats	44	x									x					x	
1998	rat	Yoshioka	Hepatic venous hemoglobin oxygen saturation predicts regenerative status of remnant liver after partial hepatectomy in rats	73	x										x					

Table 1 (continued)

General					Methods							Regeneration model					Varia			
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1999	pig	Sun	Liver regeneration after partial hepatectomy is non-uniform: flow-cytometric bromodeoxyuridine incorporation and cell cycle studies in a porcine model	149	x											x	x			
1999	dog	Yabe	Portal blood flow and liver regeneration in auxiliary partial orthotopic liver transplantation in a canine model	150	x	x			x			x				x				
1999	rat	Niiya	Immediate increase of portal pressure, reflecting sinusoidal shear stress, induced liver regeneration after partial hepatectomy	41	x				x					x					x	
2000	pig	Calise	Intrasplenic hepatocyte transplantation in the pig: new technical aspects	151	x							x				x				
2000	pig	Lai	Changes in prostaglandin and nitric oxide levels in the hyperdynamic circulation following liver resection	152	x														x	
2000	rat	Shimizu	Beneficial effects of arterialization of the portal vein on extended hepatectomy	74	x										x					
2001	dog	Pouyet	Hemodynamic tolerance and rapid hypertrophy of a hepatic graft corresponding to less than 30% of the ideal mass in pigs	53		x		x	x			x		x				x	x	
2001	rat	Schoen	Shear stress-induced nitric oxide release triggers the regeneration cascade	45	x									x					x	
2002	pig	Alvira	Influence of cyclosporine on graft regeneration and function after liver transplantation: trial in pigs	153		x														
2002	pig	Smyrniotis	Hemodynamic interaction between portal vein and hepatic artery flow in small-for-size split transplantation	78		x								x	x			x	x	
2002	rat	Schoen	Nitric oxide potentiates C-Fos mRNA expression after 2/3 partial hepatectomy	46	x									x					x	
2002	rat	Fan	Effects of portal vein arterialization on liver regeneration after partial hepatectomy in the rat	75	x			x	x	x					x					
2003	pig	Asakura	Portal vein pressure is the key for successful liver transplantation of an extremely small graft in the pig model	50		x			x					x				x		
2003	pig	Court	Segmental nature of the porcine liver and its potential as a model for experimental partial hepatectomy	154													x			
2003	pig	Ishiguro	Auxiliary partial orthotopic liver transplantation for fulminant hepatitis: regeneration of the diseased native liver in pig model	155		x														
2003	pig	Mahlati	The regenerative response in intact young livers grafted into different sized recipient pigs	156		x							x							
2003	pig	Ott	Portal vein arterialisation as a technical option in liver transplantation: impact on function, regeneration, and morphology of the liver following hemihepatectomy in pigs	65	x				x	x				x	x			x		

Table 1 (continued)

General					Methods							Regeneration model					Varia			
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2003	pig	Smyrniotis	Effect of mesocaval shunt on survival of small-for-size liver grafts: experimental study in pigs	54		x		x	x					x				x	x	
2004	pig	Court	Subtotal hepatectomy: a porcine model for the study of liver regeneration	157	x															
2004	pig	Kelly	Porcine partial liver transplantation: a novel model of the "small-for-size" liver graft	51		x								x				x		
2005	pig	Ladurner	Extended liver resection and hepatic ischemia in pigs: a new, potentially reversible model to induce acute liver failure and study artificial liver support systems	158	x				x											
2005	pig	Wang	Excessive portal flow causes graft failure in extremely small-for-size liver transplantation in pigs	55		x			x						x			x		
2006	rat	Nardo	Portal vein arterialization for the treatment of post resection acute liver failure in the rat	76	x			x	x	x					x					
2007	pig	Knubben	A new surgical model for hepatectomy in pigs	159	x				x								x			
2007	pig	Lida	Improvement of morphological changes after 70% hepatectomy with portocaval shunt: preclinical study in porcine model	56	x				x					x				x		
2007	pig	Piecuch	Liver regeneration following portal blood arterialization and splenectomy in acute hepatic failure	160						x					x					
2007	pig	Pouyet	Liver regeneration and hemodynamics in pigs with mesocaval shunt	161	x				x			x		x						
2007	pig	Wege	Regeneration in pig livers by compensatory hyperplasia induces high levels of telomerase activity	162	x															
2008	pig	Kano	Differentially expressed genes in a porcine adult hepatic stem-like cell line and their expression in developing and regenerating liver	163	x						x									
2008	pig	Mortensen	Regenerative response in the pig liver remnant varies with the degree of resection and rise in portal pressure	47	x						x		x	x					x	
2008	pig	Xia	Extended hepatectomy with segments I and VII as resection remnant: a simple model for small-for-size injuries in pigs	164	x												x	x		
2009	pig	Ladurner	Cellular liver regeneration after extended hepatic resection in pigs	49	x				x			x	x	x						
2009	pig	Liska	Interleukin-6 augments activation of liver regeneration in porcine model of partial portal vein ligation	165					x			x				x				
2010	pig	Mortensen	Increased sinusoidal flow is not the primary stimulus to liver regeneration	48				x	x	x	x	x	x	x					x	

Table 2. Tabular overview of known priming factors, genuinely hepatotrophic factors, implicated hepatotrophic factors and inhibitory factors

Factor	Priming	Genuinely trophic	Implicated	Inhibitory	Reference
TNF	x				98
IL-6	x				99
HGF		x			100
TGF-α		x			101
EGF		x			102
AR		x			103
HB-EGF		x			104
SCF		x			105
OSM		x			106
Insulin		x			29
Bile acids			x		107
Serotonin			x		108
VEGF			x		109
IGF-II			x		35
T_3			x		35
Glucagon			x		26
Estrogens			x		110
Noradrenaline			x		38
Follistatin			x		111
TGF-β				x	112
Activin				x	113

The Evolution of the 'Humoral Theory'

With the advent of auxiliary liver grafting in the 1960s unveiling the phenomenon of graft atrophy due to the portal steal effect came the realization that there must be certain substances delivered to the liver in the portal blood only, upon which the organ is dependent to regenerate and/or maintain its volume and function [18]. One could no longer regard liver homeostasis as a result of mechanical portal flow stimuli (which was hypothesized by Rous and Larimore [17] 40 years earlier). A period of intense investigation followed from 1965 to 1978 with a large body of experiments revealing the importance of the hormonal and nutritional effect of portal blood on liver regeneration, in particular insulin (table 2). This period commenced with canine models of split portocaval transposition (one portal branch perfused with blood from the vena cava inferior and the other portal branch perfused with portal blood, with similar flow rates and oxygen tension). This eliminated the possible confounding effect that graft rejection could have had in causing graft atrophy in previous auxiliary transplantation experiments. After 3 months of split portocaval transposition in dogs, Marchioro et al. [19] observed hypertrophy with glycogen deposition, increased DNA synthesis and mitosis on the side receiving splanchnic blood and atrophy on the side receiving systemic blood. The importance of portal blood supply to the liver's homeostasis in auxiliary grafting was consequently corroborated the same year (1965) by Tretbar et al. [20], Thomford et al. [21] and Halgrimson et al. [22]. Marchioro et al. [23] also substituted the blood flow in one of the portal vein branches over 3 months, observing that increasing the flow and oxygen supply to one side of the liver could not compensate for the qualitative loss of the portal blood stimulus.

Given that the trophic substances seemed to be found in the portal blood, subsequent investigations were designed to disclose their origin. Separating the portal inflow coming from the upper gastrointestinal tract (distal stomach, duodenum, pancreas and spleen) from that originating from the small intestine (model of splanchnic flow division), Marchioro et al. [24] transplanted auxiliary liver grafts supplying them with portal blood from the small intestine only, while the native liver received pancreaticogastroduodenosplenic blood. This resulted in atrophy, centrilobular necrosis, cytoplasmic fat deposits in hepatocytes, hemosiderin deposits in Kupffer cells and collapse of the reticulin framework in the grafts [24]. Further research in the 1970s utilized various canine models of splanchnic evisceration: Price et al. [25, 26] eviscerated dogs, simultaneously performing portocaval transposition (maintaining liver perfusion with systemic blood), with or without glucagon infusion and suggested that glucagon was a main factor as it could reverse the many effects of portal blood deprivation. This was challenged by Starzl et al. [27] a year later in experiments of splanchnic flow division with diversion of the pancreaticogastroduodenosplenic venous blood to one half of the liver and blood from the small intestine to the other half resulting in atrophy of liver parenchyma not receiving pancreaticogastroduodenosplenic venous blood, postulating that the substance in question was insulin. This theory was later corroborated by the same investigator upon constructing an Eck fistula and infusing insulin into one of the portal vein branches, which limited the atrophy (on the side receiving insulin) caused by PCS [28] and further fortified by observing liver atrophy and lack of regeneration after PHx in alloxan-induced diabetes mellitus in dogs [29]. However, contrary to the findings of Starzl et al. [30], Duguay and Orloff [31] did find some additive effect of glucagon infusion in addition to insulin in 1976.

At this stage, it became apparent that the liver regeneration observed in Child's model of PHx and portocaval transposition, once thought to be the result of flow stimulus, was in fact the result of redirecting the portal stimulants via the PCS to the systemic circulation and back to the liver via the vena cava inferior [32]. Further experiments in dogs with various degrees of splanchnic evisceration and PHx followed by portal infusion of insulin and/or glucagon confirmed the importance of insulin in the process of liver regeneration but also demonstrated that this hormone could not compensate for total evisceration [33]. This hormonal effect was also demonstrated in the liver after splanchnic evisceration and PCS and intraportal insulin infusion, preventing atrophy and glycogen depletion and promoting DNA synthesis [34].

With the importance of insulin for liver maintenance and regeneration firmly established, research evolved to screen for other potential hepatotrophic substances in the portal blood. Francavilla et al. [35] utilized a canine Eck fistula model in 1991, infusing T_3, glucagon, prolactin, angiotensin II, vasopressin, norepinephrine, estradiol, IGF-II, HSS, TGF-α, HGF (also termed hepatopoietin-A), EGF, TGF-β, tamoxifen, IL-1, IL-2 and insulin into one of the detached portal vein branches above the shunt [35]. Insulin and partly T_3, IGF-II, HSS, TGF-α and HGF inhibited liver atrophy. The remaining substances were inert. Interestingly, TGF-β increased atrophy, but this effect was reversed upon concomitant insulin infusion. This is an important study because it illustrates the importance of performing in vivo studies when studying a complex and integrated process such as liver regeneration: several of the above substances were found to enhance hepatocyte replication in in vitro studies (EGF [36], angiotensin II [37] and norepinephrine [38]) but they were not active when placed in context in a living, biological system, as was done in the above study. Certainly, cell culture models have their advantage in that one may study signaling pathways in individual cell lines without the confounding effects of different cell types, but the cross-talk between the extracellular matrix and different cell types in the liver parenchyma known to be particularly important to liver regeneration is missed [39]. This leaves us with the classic scientific paradox of the investigator changing the things he aims to observe by his act of intervention when utilizing the more 'mechanistic' model of cell culture. In contradistinction to this, animal models provide a more integrated and realistic means to study the highly coordinated process of liver regeneration.

Quality versus Quantity – The Conflict between the Flow and Humoral Theories Approaches an End?

Despite the numerous surgical models with splanchnic vascular manipulation and liver transplantation over a period of approximately 100 years implying the dominant role of humoral regulative mechanisms initiating liver regeneration and maintaining liver homeostasis, new studies appeared suggesting that increased sinusoidal flow after PHx could play a role after all. In the late 1990s, Sato et al. [40] and Niiya et al. [41] suggested that the acute portal hypertension and increased shear stress over the sinusoidal endothelial surface caused by PHx (and increased flow per gram remaining liver) triggered the regeneration cascade. In the same period, increased endothelial shear stress was found to modulate the endothelial production of nitric oxide and influence the hepatic vascular bed [42–44]. Later, liver regeneration after PHx in rats was shown to be inhibited by the administration of the NO antagonist N^G-nitro-L-arginine methyl ester, and restored by the NO donor 3-morpholinosydnonimine-1 [45, 46]. This potential renaissance of the flow theory was challenged by Mortensen et al. [47] in a porcine model of PHx and gene expression analysis. By increasing the degree of liver resection (and consequently the rise in portal pressure and flow per gram remaining liver tissue) they observed a switch of the genetic response in the liver remnant from one of primarily cell cycle propagation (after 62% PHx) to that of modulation of the intracellular redox status and the caspase cascade (after 75% PHx) [47]. The different genetic response was proposed to be either due to the differences in sinusoidal pressure/shear stress and flow per gram remaining tissue, or due to differences in the amount of portal hepatotrophic substances delivered to the remnant. This was further investigated by constructing an aortoportal shunt from the aorta to the left portal vein, selectively increasing the flow to segments II, III and IV to the same flow levels as that seen after a 75% PHx (2.89 ml/g/min). The investigators observed that these segments remained unchanged over 3 weeks, whilst the right side of the liver, receiving only portal blood in the same period, hypertrophied. The augmented flow seemed to inactivate the hyperperfused segments, as was reflected by the general down-regulation of transcriptional activity (according to microarray analysis). This suggested once more that increased flow in itself is not an adequate stimulus to trigger either hypertrophy or hyperplasia of the liver – the flow must be of splanchnic origin [48]. At the same time, the importance of the remnant perfusate quality (vs.

quantity) was further illustrated by Ladurner et al. [49] who performed a 75% PHx in pigs assigning one group to receive a side-to-side portosystemic H shunt decompressing the portal system. As expected, the portal vein flow (to the liver remnant) in the H-shunt group was significantly lower than in animals without the shunt. However, the livers in both groups showed no differences in regenerative response, again providing evidence in support of the dominant stimulatory role of portal blood constituents.

To conclude, the flow theory seems again less credible although the optimal amount of portal and sinusoidal flow in the liver remnant seems to be undetermined. However, what is established is the damage caused by too much sinusoidal flow, as observed in the clinical scenarios of what has been termed SFSS [3]. Could it be that this syndrome is not only the result of the well-recognized sinusoidal congestion and endothelial damage, but also due to the lack of liver regeneration? If so, this would indirectly be an argument for the role of the flow theory. The observation of the fact that a graft weight/body weight ratio <0.8% predisposes to SFSS has resulted in the assumption that portal hyperperfusion is the main culprit as the flow per gram liver tissue through the liver sinusoids increases to a harmful level. Evidence that this is the case is seen in preclinical large-animal models with portal vein decompression by portosystemic shunting in transplantation of small-for-size grafts [50–55] and in combined models of hepatectomy with marginal liver remnants and portosystemic shunting [56, 57]. Portal vein decompression, a normalization of the portal vein pressure and portal flow improves liver regeneration. This has been confirmed in clinical (human) studies [58–61]. As a decrease in portal inflow results in a reciprocal increase in the hepatic artery flow due to the hepatic arterial buffer response [62], one could speculate that one of the reasons for the improved graft function and regeneration with portosystemic shunting is the increased oxygen tension in the regenerating liver, which brings us to the next topic.

The Importance of the Oxygen/Energy Status in the Liver

In a canine Eck fistula model in 1952, Cohn and Herrod [10] observed that arterialization of the portal vein stump over 4 months prevented liver atrophy. The oxygen tension in the hepatic veins was similar to control groups, indicating a pronounced oxygen extraction by the liver deprived of its portal blood supply. Consequent long-term canine experiments performed the next 10 years in animals with Eck fistula and portal vein stump arterialization showed that this altered hepatic vascularity was compatible with life, although many reported the development of vascular damage and liver fibrosis progressing to cirrhosis [11, 12, 14–16]. However, in 1954, Fisher et al. [13] did report superior liver regeneration after a 42% PHx in a dog model with Eck fistula and arterialization of the portal vein stump (controls regenerated to 80% of original volume vs. 103% in the arterialized group) and hypothesized that the increased oxygen delivery (and preserved flow) contributed to this difference. Furthermore, in 1967 Mito et al. [63] observed growth of a partial heterotopic homograft arterialized with an aortoportal shunt (grading the pressure in the shunt to 25–35 mm Hg by a Teflon cuff) over a period of 16 days. Notably, this occurred despite the fact that the native liver received all the portal flow. In 1975, Horak et al. [64] also noted similar protective effects of PVA in Eck fistula dogs over a period of 10 weeks (also grading the arterial shunt flow with flow probes to equal flow in the portal vein before establishment of the Eck fistula) and, recently, Ott el al. [65] observed increased regeneration of the porcine liver remnant after PHx upon PVA compared to pigs with portal perfusion of the liver remnant. Not all investigators have reported beneficial effects of PVA though: in a study by Marchioro et al. [23], the arterialized side of the liver atrophied after 60 days in a canine model of split portocaval transposition and portal vein branch arterialization. This, however, occurred in conjunction with undisturbed portal flow to the contralateral side of the liver which hypertrophied, in effect, taking over the liver function (not unlike the 'parenchymal shift' described by Rous and Larimore 47 years earlier [17]).

In the clinical setting, PVA has been found useful in counteracting the portoprival state of the liver and hepatic encephalopathy in cirrhotic patients with Eck fistula [66, 67], but later experience with PVA of liver grafts has varied from being problematic due to histological changes in microsteatosis and fibrosis [68] to unproblematic in other series with good long-term liver function [69].

How can we explain the apparent beneficial short-term effects of PVA on regeneration and liver homeostasis and what is relevant to research on liver regeneration? As obvious as it may seem, rodent models of PHx from the 1970s and canine models from the 1990s have shown that the capacity of the liver remnant to regenerate after PHx is dependent upon an increased supply of energy

[70–72]. After PHx in rats, Yoshioka et al. [73] showed that oxygen supply to the liver increases by increased hepatic artery flow. Simultaneously, the hepatic oxygen extraction rate increases, while the total energy load decreases along with increased DNA synthesis. Arterialization of the liver remnant leads to improved survival in rats after extended hepatectomy [74–76], and this has also been shown to be beneficial in humans after extended hepatectomy [77]. While investigating the mechanisms behind SFSS, Smyrniotis et al. [78] studied the hemodynamic changes in differently sized liver grafts in pigs and disclosed that while the portal pressure and flow per gram liver increased inversely with graft size, hepatic artery flow decreased. However, the hepatic arterial buffer response was preserved, even showing an increased response with decreasing graft size. One could therefore hypothesize that a graded PVA could prove beneficial for the function and regeneration of the marginal liver remnant and the small-for-size liver graft, as arterialization potentially leads to an optimal oxidative status and energy charge in the hepatocytes. Accordingly, a surgical model of extended hepatectomy with arterialization of the functionally small and deficient remnant with observations of energy charge and histological signs of regeneration could cast light on this aspect and potentially be used as a bridge to complete regeneration in patients with small-for-size grafts. To avoid the deleterious effects of long-term arterialization in the patient, the end-to-side shunt should be embolized upon completed liver regeneration or normalization of liver function.

The Liver as a Source of Growth Factors in Liver Regeneration

The preceding sections have focused on how liver homeostasis and regeneration is influenced by the amount, pressure and the composition of its blood supply and drainage, but the liver itself is also a source of growth factors and cytokines which play a vital role in regeneration. In 1939, Brues et al. [79] found that a liver extract from adult and embryonic porcine liver would inhibit growth of cultured fibroblasts, with the process being reversible, suggesting that the liver was a source of growth inhibition. However, in 1952, Glinos and Gey [80] found the serum of PHx rats to exert a growth-promoting action on fibroblasts in tissue culture. Around the same time, Bucher et al. [81] and Wenneker and Sussman [82] reported an increased number of mitoses in the non-hepatectomized partner in parabiotic rats with cross circulation indicating the presence of growth-stimulating factors in the effluent from the liver remnant [81, 82]. This hypothesis was corroborated in in vivo rodent models by several investigators who observed increased liver cell mitosis in intact animals injected with serum from hepatectomized counterparts [83, 84]. To circumvent the changes in portal hemodynamics caused by PHx, Sigel et al. [85] conducted canine experiments in the early 1960s with autotransplanting of small liver grafts to the jejunal mesentery, later randomizing the animals to a 70% PHx of the native liver. In contrast to control groups, the autografts in the animals with 70% PHx did not undergo atrophy, indicating again a growth stimulus from the resected liver to the autografts via the systemic circulation [85]. Similarly, in another experiment, autografts transplanted to the neck did not undergo atrophy, tentatively stimulated by the native liver manipulated with an Eck fistula (in contrast to animals without an Eck fistula) [86]. Thomford et al. [21] showed similar results in 1965 in dogs with heterotopic allografts, where the grafts did not suffer from atrophy when the native liver, receiving all the portal blood, was resected, again indicating a growth-stimulating effect from the liver effluent after PHx. Fourteen years later, Starzl et al. [87] extracted cytosol from hepatectomized canine livers (48 and 72 h after PHx) injecting it into the portal vein stump of Eck fistula dogs and observed a proliferative response. A year later, it was observed that the growth-stimulating factor in the cytosol extract from regenerating canine livers (termed HSS) was organ specific in that it did not stimulate any glomerular proliferative activity when injected into the renal artery. Additionally, HSS was not found in liver extracts from animals that underwent splanchnic evisceration synchronously with PHx, indicating that its synthesis in the liver probably was a result of splanchnic 'collaboration' [88]. Investigating how factors in the recipient liver influenced the action of HSS, Terblanche et al. [89] injected regenerative liver extract into the portal vein perfusing normal canine livers without any response. However, an augmented proliferative response was seen upon injecting the extract into the portal vein of the liver remnants 48 and 72 h after PHx. Further investigations of possible growth-stimulatory substances in the liver effluent from PHx pigs were performed by van Hoorn-Hickman et al. [90] in 1981 by cross circulation with recipient animals or exchange perfusion. Increased thymidine kinase activity and mitotic indices in biopsies from PCS (recipient) pigs corroborated Starzl's previous observations in dogs. Kahn et al. [91] also showed in 1982 that a stimulatory substance was transferred from a transplanted PHx liver

to the host liver (which had PCS), stimulating a proliferative response in the latter (as judged by increased thymidine kinase activity and mitotic indices). The authors discussed whether this phenomenon could be clinically useful in aiding liver regeneration in the host liver in patients with liver failure treated by auxiliary liver grafting, leading to the question of whether the development of an acute or acute-upon-chronic liver failure in a large-animal model is useful to test the effect of injecting serum extracts of liver hepatotrophic substances from resected livers on the regeneration of damaged liver. Is it possible that infusion of a concentrate of the patients' own serum in the portal vein may assist in the regeneration of the remnant liver after an extensive liver resection and could a small-for-size graft procured from living donor split-liver grafting profit or in some way be supported by the stimulus that the serum of the donor could offer?

What Has Happened the Last 2 Decades and Has It Helped Our Patients?

During the last 20 years, the focus of research on liver regeneration after PHx has turned from examining extrinsic hepatic factors, such as portal and hepatic arterial blood flow and its content, to the intrinsic consequences these changes have in the extracellular matrix, the intracellular signal transduction mechanisms and genetic response in the liver. Studies in various cell culture models, stem cell transplantation, microarray analysis in rodent and porcine models, the impact of the immune system, blood platelets and serotonin, the complement system, cytokines and the interaction between the many different cell types now known to regulate the regenerative process have all unquestionably added much knowledge to the research on liver regeneration. However, at the same time, these studies have made the picture complex and seemingly increasingly intangible when it comes to the clinical application of the knowledge gained.

Although this review comprises traditional surgical animal models, novel genetic engineering with rodent knockout models warrants mention because this area of research will most likely become increasingly dominant in future investigations of liver regeneration (table 3). This technique is unquestionably very powerful, in a deterministic sense, and has illuminated the roles of several important genes and gene products concerned with the priming of hepatocytes (IL-6, TNF, C3a, C5a, MyD88 and TIMP3), extracellular matrix remodeling (uPA, MT and MMP9), intracellular signal transduction (C/EBP-β, IGFBP-1, HB-EGF, OSM, TGF-α, Met and caveolin-1), lipid metabolism (PPAR-α) and termination of liver regeneration (TGF-β). The challenge, on a larger scale, however, lies in linking all the bits of information together.

Extensive reviews of the vast amount of more contemporary published literature on the molecular control of liver regeneration in the past 20–30 years have been written by authorities on liver research and require mention here. In 2004, Taub [92] outlined the 'cytokine' and 'growth-factor' pathways eventually leading to the activation of downstream intracellular signaling substances promoting cell cycle entry and mitosis, and the (relatively few number of) molecules arresting liver growth, maintaining a constant liver/body mass. The review concludes that what remains unclear is how the size of the liver is determined, 'how the known molecular pathways necessary for liver regeneration are altered in human disease', and that 'greater insight will be required to develop improved pharmacological therapeutics and surgical approaches'. There is no mention of any clinical application of the knowledge gained so far [92]. In 2006, Fausto et al. [93] reviewed research in liver regeneration and also described the 'cytokine' and 'growth-factor' pathways and their interaction and, additionally, the influence of metabolic stimuli in regeneration. They concluded that the study of liver regeneration affords a unique model to study signal transduction mechanisms and cell cycle events and emphasized the importance of understanding the process of liver regeneration for the appropriate management of acute liver failure and liver cirrhosis. They added that what is needed is a more 'rigorous effort to apply the knowledge gained in experimental work to solve clinical problems'. However, the review does not mention if and how all this scientific work has resulted in a single therapeutic procedure [93]. In his published Rous-Whipple Award Lecture from 2010, Michalapoulos [39] summarized the control of liver regeneration by the so-called 'complete mitogens' that are mitogenic in hepatocyte cell cultures (HGF and receptor c-MET and ligands of the EGF, TGF-α, HB-EGF and AR), and by 'auxiliary mitogens', the ablation of which delay the regeneration process (amongst others, norepinephrine, TNF, IL-6, VEGF, bile acids, serotonin, complement proteins, leptin, FGF-1, FGF-2 and insulin). A redundancy exists in all these different pathways as there seems to be a considerable overlap between the many signaling cascades – blockage of one route is compensated by another, leading to completion of liver regeneration. In this comprehensive review, the author concludes that 'liver failure, essentially a fail-

Table 3. Chronological summary of transgenic models of liver regeneration

Year	Gene product	Study title and brief description of the study	Reference
1994	TGF-α	'Overexpression of transforming growth factor-alpha causes liver enlargement and increased hepatocyte proliferation in transgenic mice'. TGF-α stimulates hepatocyte DNA replication.	114
1996	IL-6	'Liver failure and defective hepatocyte regeneration in interleukin-6-deficient mice'. The role of IL-6 in priming quiescent hepatocytes in the G0 phase is illustrated.	99
1997	TNF	'Initiation of liver growth by tumor necrosis factor: deficient liver regeneration in mice lacking type I tumor necrosis factor receptor'. The role of TNF in priming quiescent hepatocytes in the G0 phase is determined.	115
1998	iNOS	'Impaired liver regeneration in inducible nitric oxide synthase-deficient mice'. The protective role of nitric oxide against cytokine injury during regeneration is reported.	116
1998	C/EBP-β	'CCAAT enhancer-binding protein beta is required for normal hepatocyte proliferation in mice after partial hepatectomy'. C/EBP-β is a transcription factor activating several genes important in the acute-phase response and early stages of liver regeneration.	117
1998	uPA	'Liver regeneration is transiently impaired in urokinase-deficient mice'. uPA is important in initial phases of regeneration as it activates dormant HGF in liver remnant matrix immediately after resection.	118
2002	PPAR-α	'Delayed liver regeneration in peroxisome proliferator-activated receptor-alpha-null mice'. The importance of the regulation of lipid turnover during liver regeneration is illustrated.	119
2003	C3a/C5a	'The proinflammatory mediators C3a and C5a are essential for liver regeneration'. Complement factors are implicated in early phases of regeneration as knockout mice for C3a and C5a have impaired production of TNF and IL-6 after resection.	120
2003	IGFBP-1	'Impaired hepatocyte DNA synthetic response posthepatectomy in insulin-like growth factor binding protein 1-deficient mice with defects in C/EBP beta and mitogen-activated protein kinase/extracellular signal-regulated kinase regulation'.	121
2004	TIMP3	'Abnormal TNF activity in Timp3(–/–) mice leads to chronic hepatic inflammation and failure of liver regeneration'. In a liver regeneration model that requires TNF signaling, Timp3(–/–) mice succumbed to liver failure. These data indicate that TIMP3 is a crucial innate negative regulator of TNF.	122
2004	Met	'Met provides essential signals for liver regeneration'. This study demonstrates that the HGF/scatter factor/Met signaling system is essential for cell cycle entry after partial hepatectomy.	123
2004	OSM	'Hepatocyte proliferation and tissue remodeling is impaired after liver injury in oncostatin M receptor knockout mice'. OSM signaling is required for hepatocyte proliferation and tissue remodeling during liver regeneration. OSM is also a key mediator of IL-6 in liver regeneration.	106
2004	TGF-β	'Intact signaling by transforming growth factor beta is not required for termination of liver regeneration in mice'. TGF-β inhibits regeneration in early phases of regeneration but is not solely responsible for the termination of liver regeneration.	124
2005	HB-EGF	'Heparin-binding epidermal growth factor-like growth factor links hepatocyte priming with cell cycle progression during liver regeneration'. DNA replication after partial hepatectomy is delayed in HB-EGF knockout mice.	125
2005	MT	'Impaired hepatic regeneration in metallothionein-I/II knockout mice'. The importance of matrix remodeling during liver regeneration is discussed.	126
2005	MyD88	'Contribution of Toll-like receptor/myeloid differentiation factor 88 signaling to murine liver regeneration'. Bacterial endotoxin (lipopolysaccharide) induced production of TNF (e.g. TNF-α) is deficient in MyD88 null mice (lipopolysaccharide is also a primer for hepatocytes in the G0 phase).	127
2006	MMP9	'Matrix metalloproteinase-9 is an important factor in hepatic regeneration after partial hepatectomy in mice'. The importance of matrix remodeling during regeneration is illustrated.	128
2006	Caveolin-1	'Caveolin-1 is essential for liver regeneration'. Caveolin-1 plays a crucial role in the mechanisms that coordinate lipid metabolism with the proliferative response occurring in the liver after cellular injury.	129
2007	Caveolin-1	'Dispensability and dynamics of caveolin-1 during liver regeneration and in isolated hepatic cells'. Caveolin is important but not essential for regeneration.	130

ure of regeneration, should be subject to mechanistic analysis based on knowledge already gained on regeneration, and perhaps therapeutic interventions may be designed with impact on human liver disease' [39]. Hence it seems clear that the authors are aware of the gap between basic laboratory investigation and clinical appliance in this field.

The Benefits of 133 Years of Surgical Research on Liver Regeneration

How then has research on liver regeneration in the past 133 years benefited the patient with liver cirrhosis, acute liver failure or liver metastasis? The recognition of the importance of portal blood to liver homeostasis and regeneration was obviously crucial to the pioneers of liver transplantation as they observed how the auxiliary graft would undergo atrophy without portal blood constituent stimulus [18]. The earlier canine and porcine PVA experiments [10–14, 63–65] also illustrated to the transplantation surgeon that the auxiliary graft could be perfused by PVA as an option to leave the hilus of the native liver untouched and also in cases of portal vein thrombosis [94–97]. Could PVA of the small-for-size graft be an option in the future to avoid the small-for-size syndrome?

Furthermore, as part of the emerging multimodal three-stage treatment of colorectal metastases [2], surgeons may now embolize the portal vein before performing large resections in order to stimulate liver hyperplasia in the remnant to be. By this, one may avoid postoperative liver failure, acknowledging that diverting portal flow away from one side to the other results in the 'parenchymal shift' described by Rous and Larimore [17] in 1920.

Conclusion

The surgical principles and practice of preoperative portal vein embolization to induce hyperplasia of the remnant liver after PHx, and portal vein decompression by portosystemic shunting to reduce sinusoidal congestion in the case of SFSS after liver transplantation are well established. Apart from these, there are no novel patient therapies available to aid and augment the process of liver regeneration after extended liver resections, toxic liver insults or in the cirrhotic patient. This is in spite of all the modern technological advances and the knowledge gained on the microscopic and molecular aspects of liver regeneration in the past 20–30 years. We suggest that it is time to turn back to the systemic large-animal surgical research on liver regeneration as it offers a more integrated, systemic biological understanding of this complex process, and that a more clinically relevant progression could possibly be made with a closer collaboration between the hepatologist, liver surgeon/transplant surgeon and the laboratory scientist.

Disclosure Statement

The authors have no conflict of interest.

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