Evaluation of a Humoral Factor in Liver Regeneration Utilizing Liver Transplants

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SUMMARY

Information has been obtained concerning the extracellular control of liver regeneration by transplanting, with blood vessel anastomoses, auxiliary livers into isologous rats. Partial or whole livers, vascularized one of three ways, were inserted into hosts with whole or partially hepatectomized livers in which there was either a normal blood supply or an absence of portal flow. Bile ducts of transplants were either cannulated or ligated. Hepatic parenchymal cell activity was determined by number of mitoses and incorporation of $^{32}$P into DNA.

Findings obtained from a variety of host and transplant combinations indicate the following. (a) They failed to confirm a factor, as more conventionally described by others, in hepatic regeneration. A partial (30%) liver transplant failed to initiate a parenchymal cell response in whole host livers and, similarly, partial hepatectomy of the latter resulted in no stimulation of such cells in whole-liver transplants. An explanation for the difference in results is presented which suggests that there is a portal blood factor (PBF) which is capable of stimulating hepatic cells and that its effectiveness is inversely related to the number of liver cells present. (b) This PBF was neither destroyed nor inhibited in systemic blood, since livers in portacaval-shunted, partially hepatectomized, nontransplanted animals responded similarly to such livers in nonshunted animals. (c) The diversion of portal blood through a whole-liver transplant prior to its entry into the systemic circulation prevented such a response in the liver remnant of the host as well as in the transplant. (d) Diversion of portal blood through a partial liver transplant resulted in a response in the transplant similar to that which occurred in the remnant of a partially hepatectomized, nontransplanted animal, despite the presence of an additional whole liver (host), which failed to demonstrate stimulation. (e) When a partial liver was transplanted into a hepatectomized host and the transplant received portal blood, it responded as would a similar nontransplanted liver remnant, whereas the host liver remnant response was considerably diminished, indicating utilization of the factor by the transplant so that little was available for stimulation of the host liver. Such findings are difficult to relate to reduction of inhibitor by partial hepatectomy as a factor in regeneration. They more readily suggest that a disturbance of the "normal" relationship between the quantity of PBF available and the number of hepatic cells present results in the regenerative response. With proliferation of liver cells and restoration of the "equilibrium," regeneration ceases. Studies relative to the nature, site of origin, mechanism of action, and regulation of concentration of PBF are in progress.

INTRODUCTION

Previous studies by us (8, 10) have failed to support the concept that a specific humoral factor is present in the serum or plasma of hepatectomized animals which, when injected into normal animals, influences hepatic parenchymal cell activity. Nor was evidence obtained that hepatectomy in one member of a parabiotic pair affected liver cells of the other member in that regard. These findings were in keeping with those of a number of other investigators who, using similar methods, likewise failed to support the role of a humoral factor in the control of liver regeneration (14, 19, 21, 24, 27) but differed from those who promulgated such a concept (1, 3, 5, 13, 18, 31, 33). As a consequence of the diversity of findings, the importance of such a factor in hepatic restitution has remained uncertain.

Recently, however, interest in hepatic regeneration has been renewed by evidence obtained from differing experimental models which tend to affirm a humoral mechanism. Sigel et al. (30), utilizing small autologous "pedicle transplants" of liver, observed a marked increase in DNA synthesis in both the transplant and the remnant following partial removal of the main liver. Leong et al. (23) and Virolainen (32) demonstrated similar results with partial hepatic autografts in rats. By utilizing extracorporeal cross-circulation techniques, Moolten and Bucher (26) have likewise observed stimulation of an intact liver following partial resection of the liver of the other member of the pair.

Much of the difficulty and inconsistency in demonstrating a humoral factor may be related to the formidable nature of establishing an experimental model where the blood flow to livers will be relatively consistent, the effects of bile duct obstruction will not be a factor, and the liver serving as the target for detection of a blood-borne factor will consist of uniform numbers of parenchymal cells. Unfortunately, some of the model systems utilized to obtain the above information are difficult to assess with respect to one or more of these criteria.

When it became possible in our laboratory to transplant, with uniform success, auxiliary livers by means of blood vessel anastomoses in isologous rats, it seemed that such a
preparation could provide definitive information concerning the existence and role of a humoral factor in liver regeneration. From studies with a number of host and transplant combinations, data have been obtained that contribute to an understanding of the extracellular control of the process.

MATERIALS AND METHODS

Female Lewis rats (isologous strain) weighing 300 g were used as donors and recipients of livers and as sham-transplanted controls. Auxiliary, heterotopic hepatic transplants were performed with either the whole donor liver or a 30% segment. When the latter was used, a 70% hepatectomy was done prior to removal of the liver for transplantation. The technique for partial hepatectomy was that described by Higgins and Anderson (17).

Transplants were vascularized by 1 of 3 ways. In type I, the entire host portal blood supply was diverted into the transplant by an end-to-side anastomosis of host and transplant portal veins (Fig. 1), and the hepatic artery of the transplant was ligated. The cephalad portion of the donor vena cava was joined to the host cava by an end-to-side anastomosis. Host livers, having been deprived of portal blood, derived their blood supply from their hepatic artery.

The blood supply of type II transplants was entirely arterial via their hepatic artery, the portal vein having been ligated (Fig. 2). In the removal of donor livers for this technique of transplantation, the hepatic artery was excised and attached to a segment of aorta, the distal end of which was ligated. The proximal lumen of the aortic segment was used for construction of an end-to-side anastomosis to the recipient aorta. The donor and host vena cava were united as in type I transplants. In this model, the blood supply of host livers was unaltered.

The third type of transplant (III) was joined to the host by anastomosing (end-to-side) the portal vein of the transplant to the host vena cava caudal to the renal veins. An arteriovenous fistula was created between the host aorta and host caval segment to the portacaval anastomosis. With partial ligation of the host caval cephalad to the portacaval junction, host aortic blood was diverted via the fistula and vena cava into the donor portal system (Fig. 3). Thus, the entire blood supply of the transplant was arterial via its own portal vein. Transplant efferent blood was conveyed to the host via a vena caval connection similar to that in the other models. The blood supply to host livers was undisturbed.

Following mobilization and just prior to removal, all donor livers were perfused via their portal veins and hepatic arteries with cold Ringer's solution containing penicillin, streptomycin, and heparin. Approximately 10 ml of solution were injected via each vessel when whole livers were used, and 5 ml were injected when 30% portions were transplanted. After removal, livers were placed in cold Ringer's solution (2°) during preparation of the host (approximately 10 min). Common bile ducts of transplants were either cannulated with PE-50 polyethylene tubing which was delivered exteriorly through a stab wound in the skin or were ligated as close to the liver as possible. All transplants were anchored to the host by fixing the ligature used to ligate the caudal portion of donor vena cava to the lateral abdominal wall of the host. A detailed description of the microvascular techniques developed over the years in this laboratory and utilized in this study has been presented elsewhere (9).

Utilizing the type I vascularization, 8 groups of animals were evaluated. In 4 animals bile ducts of transplants were cannulated, and in 4 animals they were ligated. Under each circumstance, (a) whole livers were transplanted to hosts with intact livers (W³ to W); (b) partial-liver transplants were inserted into hosts with intact livers (PH to W); (c) whole livers were transplanted into partially hepatectomized hosts (W to PH); and (d) portions of liver were transplanted into partially hepatectomized hosts (PH to PH). With type II vascularization, 3 groups of animals with transplant bile ducts cannulated were studied (W to W, PH to W, and W to PH) and 4 groups with transplant bile ducts ligated (W to W, PH to W, W to PH, and PH to PH) were evaluated. When transplants were vascularized by arterialization of their portal circulation (type III), one group with duct ligation (PH to W) and one with duct cannulation (PH to W) were evaluated.

All animals were sacrificed by decapitation between 2:00 and 4:00 p.m. at the termination of each experiment. Pieces of liver were immediately removed, fixed in 10% neutral formalin, sectioned at 5 µ, and stained with hematoxylin and eosin. With a magnification of X 970, at least 100 oil immersion fields were examined for mitoses. The number of parenchymal cells per oil immersion field was determined by cell count of representative fields, and the number of mitotic figures per 1 X 10² parenchymal cells was calculated and designated as the mitotic index. A cell was counted in mitosis only when its nucleus was in late prophase or when there were definite chromosomal figures indicative of metaphase, anaphase, or telophase. Care was taken to avoid inclusion of bile duct epithelial cells or littoral cells in the counting since, following bile duct ligation, mitotic figures were frequently observed in such cells.

The uptake of ³²P as DNA phosphorus (DNA-³²P) was determined in all control and transplanted animals. ³²P diluted with 0.9% NaCl solution so that 0.2 mCi/g of body weight was contained in 0.2 to 0.3 ml was injected i.p. 20 hr posttransplant or post-sham transplant and 28 hr prior to sacrifice of all animals. Livers were immediately removed, cut into thin slices, blotted free of blood, and frozen on Dry Ice. Samples were stored at —15° until analysis which was usually within 24 hr. DNA was separated by the method of Daooust and Hooper (6). Following ashing, samples were diluted with water, and an aliquot was taken for total phosphorus determination. ³²P uptake was expressed as cpm/ µg DNA-P.

RESULTS

Nontransplanted Controls (Table 1). Livers from sham-operated rats with a normal hepatic blood supply served

³The abbreviations used are: W, whole livers or intact hosts; PH, partial hepatectomized livers or partially hepatectomized hosts; PBF, portal blood factor.
as controls for both host and transplanted livers with a portal
blood flow. Those from portacaval-shunted animals were
controls for either transplanted or host livers which had no
portal blood supply or for transplants that received arterial
blood via their portal veins. Such an alteration of hepatic
vasculature had no significant effect on either DNA-\(^{32}P\) or the
number of mitoses in whole livers of animals with normal bile
ducts. Ligation of bile ducts resulted in an increase in those
parameters in whole livers with either type of blood supply.

Following partial hepatectomy, liver mitoses were increased
to the same degree in all animals regardless of alteration of
blood supply and/or bile duct ligation. \(^{32}P\) uptake was
greatest in animals with a normal portal circulation and no
biliary obstruction (401 ± 158 cpm/\(\mu\)g DNA-P). Shunting of
portal blood resulted in a decrease in \(^{32}P\) incorporation, but
the uptake (135 ± 42 cpm/\(\mu\)g DNA-P) was greater than that by
whole livers with a similar blood supply (9 ± 3 cpm/\(\mu\)g
DNA-P). Ligation or cannulation of bile ducts of partially
hepatectomized rats with a normal portal circulation resulted
in a \(^{32}P\) uptake which was no greater than that observed in
whole livers of nonshunted animals. Portacaval-shunted
animals subjected to partial hepatectomy and bile duct ligation
failed to survive.

**Transplants with Portal Circulation (Charts 1 and 2).**
Numbers of mitoses and uptake of \(^{32}P\) were similar in both
transplants and host livers when the host portal blood was
diverted to the transplant, regardless of whether the bile duct
was ligated or cannulated. Such values differed little from
those occurring in sham-transplanted controls.

Transplantation of portions of liver (with bile ducts
cannulated or ligated) into hosts with intact livers resulted in
markedly increased numbers of mitosis in transplants. The

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**Table 1**

**DNA-\(^{32}P\) and mitoses in livers of nontransplanted control rats**

<table>
<thead>
<tr>
<th>Livers</th>
<th>Portal circulation</th>
<th>Bile duct</th>
<th>No. of rats</th>
<th>DNA-(^{32}P) (cpm/(\mu)g DNA-P)</th>
<th>No. of mitoses/10^6 cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole</td>
<td>Present</td>
<td>Normal</td>
<td>6</td>
<td>3 ± 2</td>
<td>8 ± 13</td>
</tr>
<tr>
<td></td>
<td>Present</td>
<td>Ligated</td>
<td>6</td>
<td>34 ± 7</td>
<td>81 ± 54</td>
</tr>
<tr>
<td></td>
<td>Absent</td>
<td>Normal</td>
<td>6</td>
<td>9 ± 3</td>
<td>8 ± 16</td>
</tr>
<tr>
<td></td>
<td>Absent</td>
<td>Ligated</td>
<td>6</td>
<td>56 ± 30</td>
<td>92 ± 79</td>
</tr>
<tr>
<td>Partially hepatectomized</td>
<td>Present</td>
<td>Normal</td>
<td>7</td>
<td>401 ± 158</td>
<td>1537 ± 1175</td>
</tr>
<tr>
<td></td>
<td>Present</td>
<td>Ligated</td>
<td>11</td>
<td>46 ± 28</td>
<td>1045 ± 431</td>
</tr>
<tr>
<td></td>
<td>Present</td>
<td>Cannulated</td>
<td>5</td>
<td>34 ± 7</td>
<td>1638 ± 1151</td>
</tr>
<tr>
<td></td>
<td>Absent</td>
<td>Normal</td>
<td>7</td>
<td>135 ± 42</td>
<td>1573 ± 522</td>
</tr>
<tr>
<td></td>
<td>Absent</td>
<td>Ligated</td>
<td>30</td>
<td>No survivors</td>
<td></td>
</tr>
</tbody>
</table>

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**Chart 1.** Mitoses and DNA-\(^{32}P\) of host and transplanted livers 48 hr after transplant. Transplants with portal circulation and bile ducts cannulated.
Chart 2. Mitoses and DNA-\(^{32}\)P of host and transplanted livers 48 hr after transplant. Transplants with portal circulation and bile ducts ligated.

Chart 3. Mitoses and DNA-\(^{32}\)P of host and transplanted livers 48 hr after transplant. Transplants with no portal circulation and bile ducts cannulated.
observed augmentation was comparable to that observed in livers of sham-transplanted, partially hepatectomized rats. Likewise, DNA-\(^{32}\)P was increased, more so in duct-ligated transplants. Host livers failed to demonstrate a mitotic response to the transplants, and the amount of DNA-\(^{32}\)P in such livers also failed to exhibit a significant increase.

When whole livers were transplanted into partially hepatectomized hosts, only those transplants in which bile ducts were ligated demonstrated some mitotic increase. Such a stimulation of mitoses was observed in 3 of 6 animals. Results from the group as a whole (241 ± 385 mitoses) were not significantly different (\(p = 0.4\)) from sham-transplanted controls (81 ± 54 mitoses). When compared with the mitotic response of whole livers transplanted to hosts with intact livers, the difference likewise failed to achieve significance (\(p > 0.2\)). Of marked interest was the observation that partially hepatectomized host livers in such transplanted animals demonstrated relatively little mitotic response or uptake of \(^{32}\)P. Values for these parameters, in both bile duct-cannulated and ligated animals, were significantly less than in appropriate sham-transplanted control livers, i.e., partially hepatectomized livers in portacaval-shunted animals.

When portions of livers, with bile ducts either cannulated or ligated, were transplanted into partially hepatectomized hosts, the mitotic response and \(^{32}\)P uptake in transplants were similar to that observed in livers of sham-transplanted hepatectomized control animals or in partial-liver transplants inserted into hosts with intact livers. Mitoses and DNA-\(^{32}\)P of partially hepatectomized host livers were significantly less than in appropriate controls.

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**Chart 4. Mitoses and DNA-\(^{32}\)P of host and transplanted livers 48 hr after transplant. Transplants with no portal circulation and bile ducts ligated.**
Duct-ligated transplants showed no increase in ³²P uptake, and the mitotic index (52 ± 27) was only slightly greater than that in appropriate control livers.

Following insertion of partial liver transplants with bile ducts ligated into hepatectomized hosts, a mitotic response similar to that observed in all hepatectomized animals receiving portal blood was observed in host livers. ³²P incorporation was not commensurately increased. Neither mitoses nor DNA-³²P of transplants was remarkably elevated.

Arterialization of Portal Blood Supply of Transplant (Chart 5). Thirty %portions of livers were transplanted so that they were vascularized via their portal veins. In contrast to the group receiving host portal blood via those veins, the blood was arterial (coming from the host aorta). The blood supply of host livers was intact. When bile ducts of transplants were cannulated, mitotic stimulation of either transplant or host livers failed to occur. ³²P was slightly increased in the transplant (70 ± 49 cpm/µg) as well as the host liver (37 ± 7 cpm/µg). With bile duct ligation, an increase in mitotic index occurred in the transplant (325 ± 175) which was not as great as that observed in similar transplants vascularized with portal blood, regardless of whether the bile duct was ligated or not. No such increase was observed in host livers. Likewise, no increase of DNA-³²P was observed in either transplant or host livers.

DISCUSSION

Interpretation of findings from these studies in conjunction with other available information contributes to an understanding of the extracellular regulation of liver regeneration. Data seem to indicate that there is a PBF which is capable of stimulating proliferation of hepatic parenchymal cells. In the presence of intact liver(s), however, this agent is not effective, either because of its destruction by the liver or, more probably, because its concentration per number of liver cells is inadequate to produce a response (Chart 6A). Following reduction of liver by partial hepatectomy, the hepatic remnant is capable of responding to this stimulus (Chart 6B). Findings indicate that it is not mandatory that portal blood (and the PBF) go directly to the hepatectomized liver for this response to occur (Chart 6, C and D). That livers of portacaval-shunted, partially hepatectomized, nontransplanted animals demonstrated a reaction equivalent to that of such livers in nonsunted animals substantiates this conclusion. Such a finding confirms our original observations in this regard first reported in 1962 (10) and seems to eliminate the possibility that PBF is destroyed or inhibited in systemic blood. Moreover, its concentration, while most probably reduced in the systemic circulation from that in portal blood, remains adequate to produce an effect.

When, however, such portal blood was diverted through a whole-liver transplant prior to its reaching the systemic circulation (Chart 6, E and F), the liver remnant of a partially hepatectomized host as well as the whole-liver transplant failed to demonstrate stimulation. When it was diverted through a partial liver transplant (Chart 6G), the transplant responded in similar (or even greater) fashion to a partially hepatectomized liver remnant in a nontransplanted animal despite the presence of an additional whole liver (that of the host) which failed to demonstrate any stimulation. Support for this interpretation was provided by the finding that results were similar either when portal blood first traversed a transplant and the host liver served as the target for detection of a blood-borne factor or when portal blood traversed the host liver first and the
transplant became the target. Such findings seem related to observations (16) that there is a preferential localization of DNA synthesis and mitosis in regenerating liver in the part of the lobule first exposed to inflowing blood. While normally this is in the perportal area, it has been shown (29) that when flow of blood was reversed so that livers were perfused via their hepatic veins, hepatocytes which were centrally located became stimulated. Moolten and Bucher (26), commenting on those patterns, felt that they “are consistent with physiologically significant changes in the concentration of a humoral agent during a single passage of blood through a hepatic sinusoid.” Such a consideration seems compatible with our findings. For, as previously noted, while a partially hepatectomized liver even in the absence of portal blood flowing to it should demonstrate a regenerative response, when a partial liver was transplanted into a hepatectomized host so that one or the other was the recipient of portal blood, the liver segment receiving the portal flow (A) responded as would a nontransplanted, partially hepatectomized liver in a normal animal, whereas the other (B) demonstrated considerably less parenchymal cell activity. It would seem that the A liver was the recipient of a PBF which was utilized so that little was available for stimulation of the B liver fragment (Chart 6H). Since there was some response in B livers on occasion, it would seem that all of the factor was not utilized by the A liver, but some did reach the general circulation to go to the second liver. The possibility of a delayed response in the second liver has been considered and warrants evaluation. Thus, it is likely that while the greatest concentration of factor is in portal blood in partially hepatectomized, nontransplanted animals, that factor which has traversed the liver remnant initially becomes reavailable to it via its arterial flow. The relation of the quantity of factor in the systemic circulation to the number of hepatic cells in the target may account, at least in part, for the difference reported relative to the finding of a humoral factor in liver regeneration. In those studies in which parenchymal cell activity was observed in heterotopically placed autografts of liver following partial resection of the nongrafted liver, the locus of liver tissue which served as the target, i.e., the graft, consisted of relatively few hepatic cells (23, 30, 32). Consequently, the PBF that traversed the resected liver to gain access to the general circulation may have been of adequate concentration to effect a response on those few cells. Failure in these studies to observe such a response could have been due to the fact that a whole liver served as the target. As a result, the concentration of PBF in the general circulation relative to the number of cells in the target may have been inadequate to be effective.

Our findings in general, and particularly those obtained from partially hepatectomized hosts with segmental liver transplants, tend to minimize the role of an inhibitor in the control of regeneration. While it is difficult with partially hepatectomized, nontransplanted animals to refute the possibility that the onset of regeneration is related to a reduction of inhibitor following partial resection, the recognition of a response in one resected liver but not in the other is hard to relate to such a phenomenon.

Results following bile duct ligation of transplanted livers were similar in both host and transplant to those observed when bile ducts of the latter were cannulated. Data from sham-transplanted normal animals suggested that bile duct ligation resulted in stimulation of hepatic parenchymal cell activity. Such findings are in keeping with those of Andrus et al. (2), who noted similar liver cell proliferation and attributed this to “histologically inapparent injury to liver cells.” As a consequence of injury or destruction of parenchymal cells by bile duct ligation or other mechanisms, the number of viable or functional cells would be reduced which, in keeping with the above hypothesis, would result in a relative increase of available PBF to the remaining cells initiating regeneration. This concept likewise relates to information which has demonstrated that the magnitude of the regenerative response is directly related to the extent of the partial hepatectomy (4, 25). With proliferation of liver cells and restoration of the “normal” relationship between the quantity of PBF available and the number of hepatic cells present, parenchymal cell stimulation and the regenerative process should cease, as indeed it does.

The great variation of findings observed by all investigators following partial hepatectomy is worthy of consideration. In any series of experiments, the deviation of mitosis or DNA synthesis is extensive. This may be the result of nonuniformity in production of PBF rather than of a variation in response by
the liver. The same reason may explain the differences reported (3, 5, 8, 27, 33) relative to the response observed in nonoperated partners when the second rat in parabiotic union is partially hepatectomized. The amount of factor gaining access to the conjoined general circulation of such animals after traversing the partially resected liver may depend upon its quantitative production. Such variability, together with a similar nonuniformity of production in the nonhepatectomized member, could account for differences in the amount of factor available to nonhepatectomized livers with the consequence of dissimilar results.

It has been adequately demonstrated by these findings as well as those of others (20, 22) that, at least in the rat, liver regeneration is not impaired by absence of the hepatic artery. This information minimizes the role of arterial blood supply in this process.

The conclusion from this study that there is a PBF which is capable of stimulating hepatic parenchymal cell replication might seem to be in conflict with other findings previously reported from this laboratory (7, 10—12). Interpretations of those observations tended to minimize the importance of portal blood per se for the maintenance of hepatic integrity and also failed to confirm the presence of a humoral factor responsible for liver regeneration. A reassessment of the findings in light of present results seems warranted. The findings together with those now presented, more sharply emphasize, as has Sigel (28), the need to delineate between liver regeneration which is related to cell division (e.g., mitoses of DNA synthesis) and the maintenance of liver mass (organ weight) without cell proliferation. The present findings indicate that portal blood contains a factor which is necessary for the initiation of the regenerative process, but it is not necessary for portal blood per se to enter the liver directly for this to be accomplished. There is no disadvantage to the host in this regard if portal blood is deviated away from the liver, providing there is no other target (e.g., a liver transplant) that will compete for the factor so as to reduce its effective level. For prevention of liver atrophy, it would seem that blood, but not necessarily visceral, in the hepatic portal system is necessary. Such nonsplanchnic blood, while preventing atrophy, does not influence regeneration as was evidenced by findings in studies following arterIALIZATION of portal veins of partial-liver transplants. Despite the enhanced flow through the portal veins, the partially resected livers showed only a slight response. Thus, while portal flow is necessary to prevent atrophy and portal blood to institute regeneration, the greater the portal flow is the greater is the possibility that more factor will be recycled through the liver with its consequent effect on regeneration. In our earlier study of regeneration in arterIALIZED livers (12), although portal blood was deviated away from such livers, the PBF was still available for their regeneration. Moreover, because of the replacement of portal blood with systemic arterial flow via the hepatic portal channels, not only was the PBF more readily delivered to livers but liver atrophy was also prevented. It would appear that for maintenance of hepatic integrity, both in terms of cell number and of cell size, availability of PBF and of portal flow (not necessarily portal blood) are both essential.

In another study by us (8), results led to the conclusion that there was no evidence to support the concept that a specific humoral factor existed in serum or plasma of hepatectomized animals which influenced hepatic regeneration. While such agents had a significant effect (albeit erratic) when injected into normal rats, serum and plasma from nonhepatectomized animals likewise did so. Others had also observed a similar response to normal serum (15). Consequently, the findings were considered by us to be nonspecific. Reassessment of results suggests that they may have been significant since normal as well as partially hepatectomized animals may have harbored PBF (perhaps quantitatively different) in their systemic circulations, thus accounting for the similar response. In retrospect, the utilization in such studies of serum obtained from systemic blood, as practically all investigators have done, was ill-advised. Portal blood would have been more appropriate. Indeed, it has been noted (1) that posthepatectomy serum had a profound stimulation of liver mitoses when it was prepared from hepatic vein blood, a finding in keeping with this suggestion.

Results of the present studies and reconsideration of our past efforts indicate that a factor in portal blood is responsible for the initiation of liver regeneration. Elucidation of its origin, its mechanism of action, and regulation of its concentration is the subject of investigation in this laboratory.

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REFERENCES

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Fig. 1. Type I transplant. Transplant blood supply from host portal vein. Host liver blood supply from its hepatic artery. a, host liver; b, transplant; c, host portal vein; d, transplant portal vein; e, host vena cava; f, transplant vena cava; g, bile duct (cannulated); h, host aorta; i, transplant aortic segment; j, host hepatic artery attached to i; k, arteriovenous fistula; l, vena cava ligature.

Fig. 2. Type II transplant. Transplant blood supply arterial via its hepatic artery. Host liver blood supply normal. For labels, see Fig. 1.

Fig. 3. Type III transplant. Transplant blood supply arterial via arteriovenous fistula and its portal vein. Host liver blood supply normal. For labels, see Fig. 1.
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