

163

163

AUXILIARY
HOMOTRANSPLANTATION OF
THE CANINE LIVER WITH THE
USE OF A "REVERSE" WELCH
TECHNIQUE

PIERRE M. DALOZE, M.D.
CLAUDE HUGUET, M.D.
KEN A. PORTER, M.D., D.Sc.
THOMAS E. STARZL, Ph.D., M.D.
Denver, Colo.

From the Department of Surgery, University of
Colorado School of Medicine and Veterans
Administration Hospital

Reprinted from
SURGERY
St. Louis

Vol. 64, No. 5, Pages 934-939, November, 1968

(Copyright © 1968 by The C. V. Mosby Company)
(Printed in the U. S. A.)

Auxiliary homotransplantation of the canine liver with the use of a "reverse" Welch technique

PIERRE M. DALOZE, M.D.*
CLAUDE HUGUET, M.D.
KEN A. PORTER, M.D., D.Sc.
THOMAS E. STARZL, Ph.D., M.D.
DENVER, COLO.

From the Department of Surgery, University of Colorado School of Medicine and Veterans Administration Hospital

During recent years, it has been established that auxiliary liver homografts which are placed in ectopic locations can undergo involution by other means than rejection. The prototype of this operation was described by Welch^{1,3} and Goodrich and associates.³ They placed the extra liver in the right paravertebral gutter. The hepatic arterial supply was derived from the aorta or iliac artery. Venous inflow was reconstituted by anastomosing the distal iliac vein or inferior vena cava to the homograft portal vein. It has been shown that the total blood flow to such Welch homografts is equal to that in the dog's own undisturbed liver.² Nevertheless, even though the transplanted organs are protected from rejection by host immunosuppression, they atrophy¹⁰ in a way not seen in orthotopic homografts that are normally vascularized in the liver fossa.

Previous studies from our laboratory^{7, 8} have provided a simple physiological explanation for the atrophy, and one which has been confirmed and extended by other investigators.^{5, 9, 11} When two livers or separate liver fragments coexist, they appear to compete for metabolites. The nutritional substrate or substrates are apparently highly extractable by the liver and are present in

the highest concentrations in nonhepatic splanchnic blood. Thus, if all other conditions including the volume of blood flow are equal, a piece of liver which is perfused by the intestinal venous effluent has an advantage over a companion hepatic fragment which has had its portal flow replaced from systemic venous sources; the latter unfavored liver tissue undergoes rapid atrophy and deglycogenation.⁷ Factors other than the quantity and quality of the blood supply can influence the outcome of such an experiment. For example, the competitive ability can be reduced by obstructing the biliary drainage¹² and presumably anything else which causes liver injury would have this disabling effect.

In experiments with auxiliary homotransplantation, there is by definition an inherent inequality of the two organs since the homograft is under immunologic attack and the animal's own liver is not. This was well illustrated by Halgrimson and co-workers,⁵ who demonstrated that, if only an arterial supply were provided to each of the two organs, the homograft invariably underwent selective atrophy. As shown by Marchioro and co-workers,⁵ Halgrimson and co-workers,⁵ and others,^{6, 11} the graft atrophy could be reduced by giving the auxiliary liver a disproportionately great blood supply, especially if this included a portal inflow from the nonhepatic splanchnic bed.⁸

In the present study, a new modification of auxiliary transplantation was designed in order to further test the interrelationship

This work was supported by United States Public Health Service Grants AM-06344, HE-07735, AM-07772, AI-04152, FR-00051, FR-00069, AM-12148, and AI-08898.

Received for publication Feb. 9, 1968.

*Fellow of the McLaughlin Foundation, Toronto.

between host and graft livers in immuno-suppressed dogs. The results indicate that even diversion of all splanchnic venous flow through the homograft cannot prevent its atrophy if the recipient liver receives a quantitatively similar blood flow from non-splanchnic sources. These findings may be important in assessing the feasibility of auxiliary transplantation for the treatment of diseases such as congenital biliary atresia in which a considerable functional reserve may still be present in the diseased host liver.

METHODS

Of the 24 experiments performed, only the 11 brought to completion will be considered further. The auxiliary transplantations were

between unrelated mongrel dogs. The recipients weighed 13.2 to 19 kilograms and the donors were selected for an approximate size match. Homografts were weighed at the time of operation and inserted as shown in Fig. 1. The important features of the operation included the facts that the blood leaving the homograft did not pass through the portal system of the recipient's own liver, that instead the host portal inflow was derived entirely from systemic venous blood which in turn bypassed the auxiliary liver, and that the splanchnic return from the host intestines all passed through the homograft. During the time when the suprarenal inferior vena cava was transected, the animals were heparinized and the venous pool decom-

M.D.*
D.
D.Sc.
Ph.D., M.D.

ry, University of
and Veterans

is in nonhepatic
of all other condi-
of blood flow are
ich is perfused by
nt has an advan-
hepatic fragment
low replaced from
e latter unfavor-
d atrophy and de-
er than the quan-
ood supply can in-
ch an experiment.
tive ability can be
biliary drainage¹²
else which causes
is disabling effect.
xiliary homotrans-
nition an inherent
ns since the homo-
ic attack and the
t. This was well
and co-workers.⁷
f only an arterial
each of the two
riably underwent
wn by Marchioro
on and co-workers.⁹
trophly could be re-
siliary liver a dis-
d supply, especially
flow from the non-

new modification
on was designed in
e interrelationship

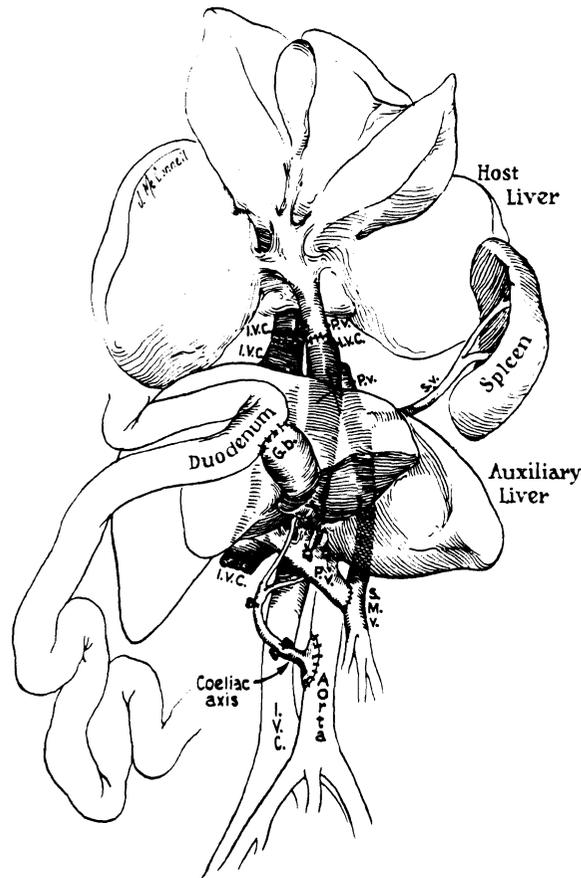


Fig. 1. Technique used for transplanting auxiliary livers. Note that the host liver is revascularized in the same way as with portacaval transposition. The ectopically placed homograft receives nonhepatic splanchnic blood. The features of the blood supply to the respective organs are thus the opposite of those in the classical Welch preparation.

pressed with an external plastic femorojugular bypass. Postoperative immunosuppression was with heterologous antilymphocyte globulin (ALG), azathioprine, and prednisone as previously described.¹ Antibiotics were given.

The animals were followed with frequent hematologic and biweekly liver function studies. After one and three weeks, they were anesthetized with pentobarbital and phen-cyclidine hydrochloride and re-examined surgically. Biopsy specimens were obtained from the livers, venograms were obtained with catheters inserted into the femoral vein and mesenteric venous branches, and venous pressures were measured with the use of the estimated level of the right atrium as a baseline. In four dogs, catheters were then brought externally at the time of the three-week study for blood flow measurement a day later in the awake state with the Xe¹³³ technique as described elsewhere^{2, 4}; the femoral and mesenteric catheters were used to inject into the autologous liver and the homograft respectively. The same procedures were repeated at six weeks in dogs that lived this long.

When the animal died or was put to death, the patency of anastomoses was verified. Final tissues were taken for pathologic examination. Both the host liver and the homograft were dissected free of extraneous tissue and weighed.

RESULTS

In eight recipients, all the vascular anastomoses remained patent. Hereafter, these dogs are classified as belonging to Group I. The other three animals developed thrombosis at the cavoportal anastomosis through which the portal flow to the autologous liver was dependent. The host organ thus eventually had only an arterial supply; the latter dogs constituted Group II. The dogs of both groups lost weight (0.5 to 5.5 kilograms) and had early marked and later chronic low-grade elevations in serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), and alkaline phosphatase. They did not become jaundiced or develop ascites. Anemia was common. There were no overt differences in the clinical behavior of members of Groups I and II.

Table I. *Auxiliary liver transplantation*

No.	Survival (days)	Rejection	Homograft weight (Gm.)		Host liver weight		Blood flow at 3 wk. (ml./min./100 Gm. tissue)	
			At operation	At death	Estimated*	At death	Homograft	Host liver
<i>Group I. All anastomoses patent</i>								
1	56†	Mild	379	208	316	294	226	199
2	22	None	367	295	260	250	—	—
3	45†	Mod.	336	263	395	413	198	204
4	40	Severe	212	204	371	494	303	245
5	39†	Severe	522	94‡	395	399	—	—
6	38	Mild	323	230	367	360	247	276
7	20	Mild	345	325	328	365	—	—
8	23	None	304	310	328	330	—	—
Mean	35.6		324‡	262‡	340‡	358‡	244	231
<i>Group II. Cavoportal anastomoses clotted</i>								
1	17	Severe	230	130	371	389	—	—
2	12	None	274	310	350	320	—	—
3	74†	Severe	344	220	328	310	—	—
Mean	34.3		283	220	350	340	—	—

*Estimated as 2.8 percent of body weight.

†These animals were put to death. The others died of pneumonitis (3), extrapulmonary sepsis (3), or intussusception (2).

‡Dog 5 excluded from average because of divided splanchnic drainage.

or was put to
moses was veri-
for pathologic
liver and the
e of extraneous

vascular anas-
hereafter, these
ng to Group I.
loped thrombo-
omosis through
autologous liver
gan thus even-
pply: the latter
he dogs of both
(5.5 kilograms)
later chronic
rum glutamic
(GOT), serum
e (SGPT), and
lid not become
s. Anemia was
vert differences
f members of

Flow at 3 wk. (min./100 Gm. tissue)	Host liver
199	—
204	—
245	—
276	—
—	—
—	—
231	—
—	—
—	—
—	—
—	—

intussusception (2).

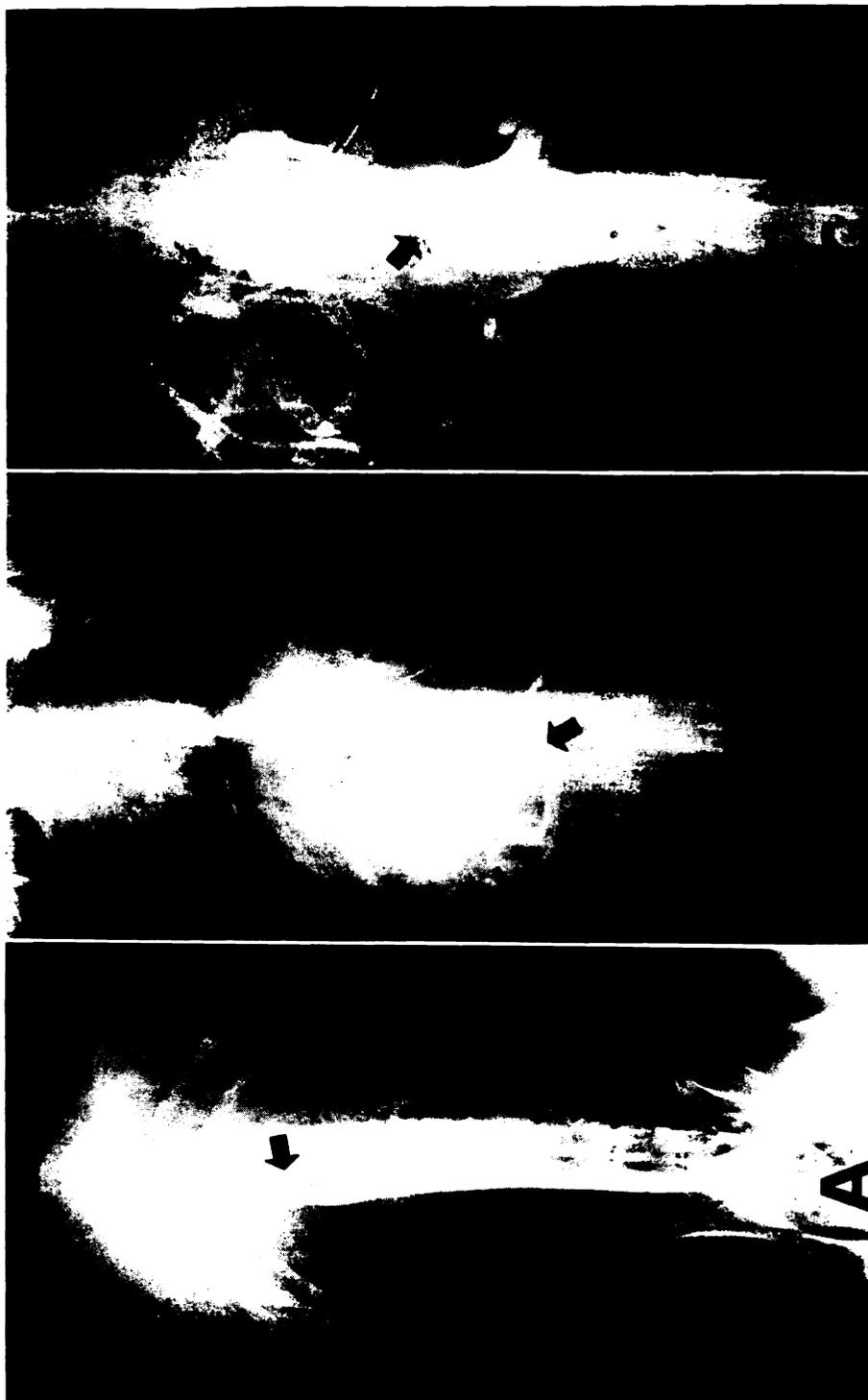


Fig. 2. Angiographic studies of the host and auxiliary livers. The upper arrows in *A* and *B* indicate the sites of the venous anastomoses. In *C* this is shown by the lower arrow, and the upper one points to a branch of the left gastric vein. *A*, Dye injected into the inferior vena cava passes through the host portal vein into the autologous liver. *B*, Dye injected into a splenic venous tributary passes into the homograft. *C*, Dog 5. In this animal a large branch entered the host portal vein above the site of its ligation. Thus, splanchnic blood flow was shared by both livers. The homograft underwent profound atrophy, its weight declining from 524 to 94 grams in a 39 day period.

Group I. In 7 of the 8 dogs, the angiograms showed passage of vena caval flow into the recipient liver (Fig. 2, *A*), and apparently complete drainage of the splanchnic bed through the homograft (Fig. 2, *B*). The central pressures in the respective venous systems were 8.8 ± 3.6 (S.D.) and 13.8 ± 2.0 (S.D.) cm. H₂O. Dog 5 had a tributary entering the portal vein above the site of ligation. In this case, the dye injected in the nonhepatic splanchnic system appeared in both livers (Fig. 2, *C*). There were four experiments in which technically satisfactory blood flow measurements were obtained at 3 weeks. The values were approximately the same for the homograft and host livers (Table I).

The homograft weights at operation and at death from 20 to 56 days later are given in Table I. There was a significant weight loss in 4 of the 7 auxiliary livers which received undivided splanchnic flow. In contrast, there was no evidence of atrophy in the autologous organs; the anticipated weights of the host livers, computed as 2.8 per cent of the total body weight,⁷ conformed well to those actually measured after death (Table I).

Since the pathologic findings in the homografts and host livers were generally similar to those previously reported after auxiliary transplantation,^{5, 8} these will not be described again. However, the findings from study of the biopsy specimens and postmortem tissues of the homografts were reviewed and an over-all evaluation given of the degree of early plus late rejection (the grading is summarized in Table I).

Group II. Comparable data on survival, liver weights, and pathologic gradings are summarized in Table I. The findings are subject to the reservation that the times when cavoportal occlusion occurred were not known.

DISCUSSION

The procedure used for these experiments might be considered a "reverse" Welch operation. In Welch's preparation, the au-

tologous liver had a normal blood supply while the homograft was vascularized in the same way as with a portacaval transposition. In contrast, the host liver in our animals was subjected to the transposition and portal flow was directed through the homograft.

With this change, extreme homograft atrophy was avoided. In three of the seven animals in which all the splanchnic flow seemed by angiography to pass to the homograft, there was little or no weight loss of the transplant; in the other four the degree of atrophy was moderate, compared to that seen in Welch-type auxiliary livers.¹⁰ The improvement was evidently not due to an imbalance in the volume of blood flow to the dual organs. It has been shown that the blood flow to the two livers after Welch's procedure is equivalent²; the same finding pertained in the present study. Instead, the partial protection of the homografts was probably the result of perfusing it with splanchnic venous blood according to the concept developed by Marchioro and associates,⁷ and confirmed by Price and associates.⁹ The incompleteness of the homograft protection in contrast to that previously described by Marchioro and associates⁵ was explicable by the fact that there was a more normal total volume of flow to the host liver than in Marchioro's original experiments.

The fact that some homograft atrophy commonly occurred despite its perfusion with splanchnic venous blood adds a further precautionary note about the wisdom of auxiliary hepatic transplantation to patients whose own livers possess significant residual function. In a competitive environment, primary exposure to splanchnic blood flow is a physiologic advantage but one which may not be sufficient if the homograft is subjected to the injury of severe but potentially reversible rejection. Under the latter circumstance, the only hope for long-term transplant function may be if the new organ is unopposed, as is the case with orthotopic homotransplantation.

normal blood supply was vascularized in a portacaval transposition of the host liver in our study directed through the

extreme homograft atrophy. In three of the seven dogs the splanchnic flow was able to pass to the homograft or no weight loss of the other four the degree of atrophy, compared to that of auxiliary livers.¹⁰ The atrophy is probably not due to an absolute decrease of blood flow to the homograft as has been shown that the blood flow to the livers after Welch's technique is the same finding in our present study. Instead, the atrophy of the homografts was probably due to the lack of perfusing it with blood according to the technique described by Marchioro and associated by Price and associates⁵ and the stenosis of the homograft. In contrast to that previously reported by Price and associates⁵ it was found that there was a more adequate blood flow to the host liver after Welch's original experi-

ence. The homograft atrophy despite its perfusion with blood adds a further precaution to the wisdom of auxiliary liver transplantation to patients whose liver has a significant residual function in a hostile environment. In patients whose primary blood flow is a physiologic one which may not be adequate if the homograft is subjected to a potentially reversible atrophy. Under either circumstance, the homograft transplant function is not unopposed, as is the case in orthotopic homotransplanta-

SUMMARY

Auxiliary liver homografts were revascularized in the lower abdomen of dogs with an arterial blood supply from the aorta and with a portal venous supply that was derived from the host splanchnic bed. The animals' own livers were deprived of splanchnic flow but this was replaced with systemic venous blood. Total hepatic blood flow in the co-existing livers was approximately equal. Under these conditions the homograft atrophy often seen after auxiliary transplantation was reduced but not prevented. The findings have been discussed as they relate to the mechanism of homograft atrophy and to the applicability of such techniques for the treatment of human disease.

REFERENCES

1. Brettschneider, L., Daloz, P. M., Huguet, C., Porter, K. A., Groth, C. G., Kashiwagi, N., Hutchison, D. E., and Starzl, T. E.: The use of combined preservation techniques for extended storage of orthotopic liver homografts, *Surg. Gynec. & Obst.* 126: 263, 1968.
2. Daloz, P. M., Huguet, C., Groth, C. G., and Stoll, F.: Blood flow in auxiliary canine liver homografts. In press.
3. Goodrich, E. O., Welch, H. F., Nelson, J. A., Beecher, T. A., and Welch, C. S.: Homotransplantation of the canine liver, *SURGERY* 39: 244, 1956.
4. Groth, C. G., Porter, K. A., Otte, J. B., Daloz, P. M., Marchioro, T. L., Brettschneider, L., and Starzl, T. E.: Studies of blood flow and ultrastructural changes in rejecting and nonrejecting canine orthotopic liver homografts, *SURGERY* 63: 658, 1968.
5. Halgrimson, C. G., Marchioro, T. L., Faris, T. D., Porter, K. A., Peters, G. N., and Starzl, T. E.: Auxiliary liver transplantation: Effect of host portacaval shunt, *Arch. Surg.* 93: 107, 1966.
6. Lee, S., and Edginton, T. S.: Liver transplantation in the rat, *S. Forum* 17: 220, 1966.
7. Marchioro, T. L., Porter, K. A., Brown, B. I., Otte, J. B., and Starzl, T. E.: The effect of partial portacaval transposition on the canine liver, *SURGERY* 61: 723, 1967.
8. Marchioro, T. L., Porter, K. A., Dickinson, T. C., Faris, T. D., and Starzl, T. E.: Physiologic requirements for auxiliary liver homotransplantation, *Surg. Gynec. & Obst.* 121: 17, 1965.
9. Price, J. B., Voorhees, A. B., Jr., and Britton, R. C.: The role of portal blood in regeneration and function of completely revascularized hepatic autografts, *SURGERY* 62: 195, 1967.
10. Starzl, T. E., Marchioro, T. L., Rowlands, D. T., Kirkpatrick, C. H., Wilson, W. E. C., Rifkind, D., and Waddell, W. R.: Immunosuppression after experimental and clinical homotransplantation of the liver, *Ann. Surg.* 160: 411, 1964.
11. Tretbar, L. L., Beven, E. G., and Hermann, R. E.: The effects of portacaval shunt and portal flow occlusion on canine auxiliary liver homotransplants, *SURGERY* 61: 733, 1967.
12. Van der Heyde, N. H., Schalm, L., and Vink, M.: The role of functional competition in auxiliary liver transplantation, *Transplantation* 5: 78, 1967.
13. Welch, C. S.: A note on the transplantation of the whole liver in dogs, *Transplant. Bull.* 2: 54, 1955.