leads to T cell unresponsiveness (Fig. 4a). In the situation where the DST is irradiated before administration, however, donor cells simply fail to survive for long enough for these abortive encounters to occur (Bushell A, et al., unpublished data), and as a result relatively undiminished T cell responses are directed toward the graft after transplantation (Fig. 4b). Thus, acute rejection in the "YTA/single-dose irradiated DST" protocol is explained not by a failure to establish microchimerism but by a reduction in antigen persistence. The success of the "YTA/multiple-dose irradiated DST" protocol supports the hypothesis that short-term antigen persistence is the dominant factor in the development of unresponsiveness following donor-specific transfusion under anti-CD4 antibody cover. Our data do not rule out the possibility that once the graft is in place the maintenance of tolerance may involve peripheral microchimerism, especially since it has been shown that donor dendritic cells migrate rapidly from the cardiac allograft to the spleen (*25*). However, other experiments carried out in this laboratory using the mouse heart model indicate that microchimerism does not play a direct role in the maintenance of tolerance and demonstrate clearly that continued unresponsiveness is dependent on the presence of the graft itself (*26*). Significantly, other studies have also identified antigen persistence as a critical factor in the development and maintenance of unresponsiveness both to MHC (*27, 28*) and non-MHC antigens (*29, 30*).

The results of the present study indicate that the short-term persistence of donor antigen rather than the development of microchimerism is the critical factor in the induction of operational tolerance in this transplant model. Further studies in experimental models and the clinical setting are required to determine whether these observations apply to all aspects of solid-organ transplantation.

Note added in proof. C3H/He controls pretreated with YTA 3.1.2 on days −28 and −27 plus 1 ml of irradiated B10 blood on day −27 rejected their B.10 hearts with an MST of 39 days.

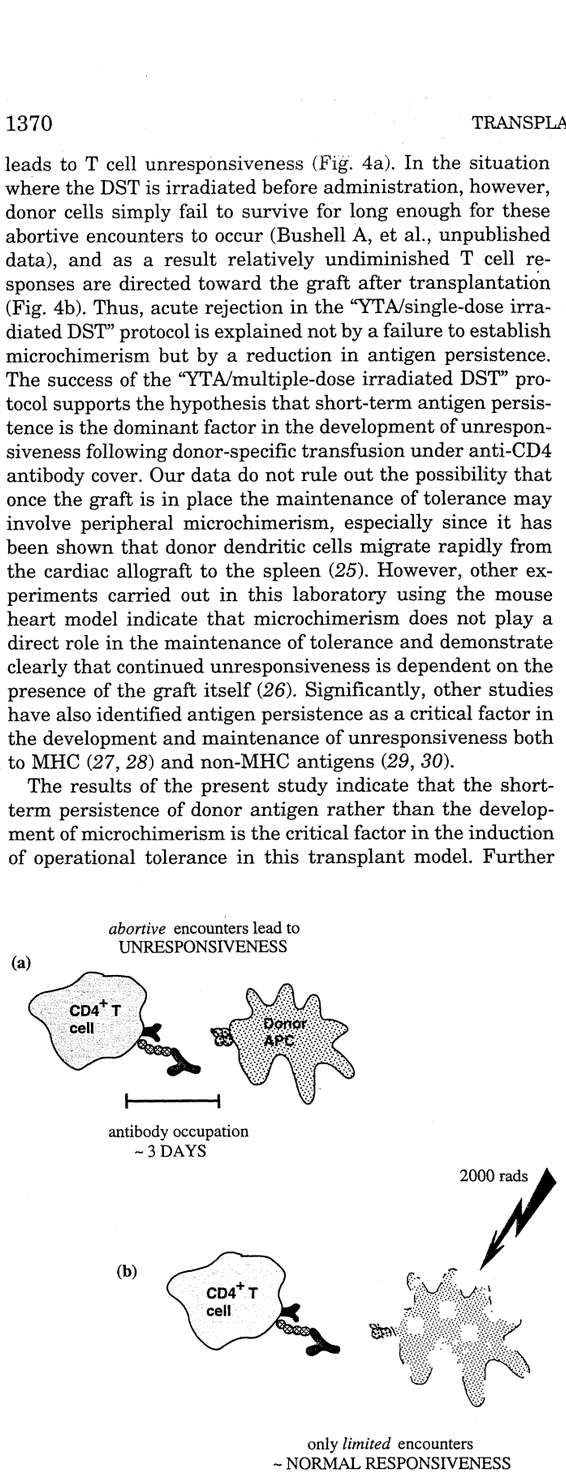

FIGURE 4. Induction of unresponsiveness by donor-specific transfusion under anti-CD4 antibody cover. Abortive interactions between donor antigen-presenting cells and recipient $CD4^+$ T cells during a brief period of CD4 occupation result in T cell unresponsiveness and lead to graft prolongation. Irradiated cells are unable to persist for long enough in vivo for these abortive interactions to occur, and T cell responses are thus relatively unaffected.

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SPLIT LIVER TRANSPLANTATION IN EUROPE—1988 to 1993[1]

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The shortage of liver grafts results in the fact that 8% of potential recipients die before receiving a graft. Liver graft division has therefore been proposed to maximize the current available liver graft pool. However, the question of benefit or additional risk for the recipient that this technique might carry remains unanswered. The European Split Liver Registry was opened in March 1993 and reviewed retrospectively the clinical experience obtained at nine European centers regarding the use of split liver transplants, during the five year period from March 1988 to March 1993. From 50 donor livers, 100 grafts were prepared: 2 grafts were discarded and the other 98 were transplanted in 53 children (2 times in 3 children) and 42 adults (2/42 in heterotopic position). Sixty-three grafts were implanted in an urgent recipient (half of whom had acute hepatic failure). Portal vein thrombosis, hepatic artery thrombosis, biliary complications, and retransplantation rates were 4%, 11.5%, 18.7%, and 18.7%, respectively. Most of these complications were unrelated to the technique itself. Actual 6-month graft survivals of elective and urgent orthotopic transplants were 80% and 61.3% in children, and 72.2% and 55.6% in adults; actual 6-month patient survival rates for similar groupings were 88.9% and 61.1%, and 80% and 67.7%, respectively. Similar rates are reported after conventional transplants in Europe. It is concluded that split liver transplantation is an efficient transplant technique that benefits both urgent patients who otherwise could have died before getting a graft in time and elective patients.

Since the shortage of liver donors was the main obstacle to expansion of liver programs, the concept of "one liver for two" was introduced clinically in 1988 (*1–4*). Several centers developed this technique (*3–7*) and satisfactory results were reported after 1990 (*7, 8*). It did not, however, receive major impetus, probably because of scepticism about the maximizing effect on donor organ availability, or because of fear that the technique might be detrimental to one of the two recipients (*9, 10*).

The first European Workshop on Split Liver Transplantation was organized in Brussels on March 19, 1993. The clinical data were retrospectively obtained from the European

[1] The European Split Liver Registry was established in March 1993 to collect data concerning donor liver splitting procedures and split liver graft transplantations from the collaborating centers in Europe.

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Transplant Centers performing split liver transplantation. The participating centers agreed to start the European Split Liver Registry (ESLR). A review of this largest collected experience with split liver transplantation is presented as the first ESLR* report.

MATERIALS AND METHODS

Between March 1988 and March 1993, 100 split liver grafts were prepared from 50 donor livers in 9 European transplantation centers. All centers reported their full clinical experience to the ESLR. The data analyzed were collected retrospectively with questionnaires. Data were provided on a voluntary basis by the different teams, who received the Registry standard forms to report anatomical and technical details about the split procedure and the grafts. Separate forms had to be completed to report postoperative complications and graft outcome.

At the time of the study, it appeared that a formal pretransplant informed consent had not been requested by the teams. This issue was not further addressed in this retrospective analysis which focused mainly on results.

The following items were recorded: the age and weight of donors and recipients, the indications for liver replacement, the ABO match, the total ischemic time, and the recipient's pretransplant clinical condition classified as elective (recipient waiting at home), or urgent (intensive-care or hospital-bound); within the urgent group, highly urgent recipients (defined as patients with acute liver failure) were analyzed as a particular subgroup. When analyzing postoperative technical complications, graft anatomy, types and sites of vascular and biliary anastomoses, and the eventual use of homografts for vascular reconstruction were taken into account. Since it was the minimal follow-up period for all grafts, 6-month actual survival rates were calculated according to each type of graft or age group (teenagers above the age of 15 were classified in the adult group). The results of heterotopic transplants were analyzed separately.

Categorical and numerical variables were compared by chi-square and Wilcoxon rank sum test, respectively. Values are expressed as mean±SD.

In order to compare the results of this series with survival after conventional liver transplants, data were obtained from the European Liver Transplantation Registry (Castaing D, personal communication). This Registry collected data concerning 12518 orthotopic liver transplantations performed in a contemporaneous group (1988–1993) that included 21% of highly urgent patients. These results were analyzed according to age group (<3 y, 3 to 15 y, or adults), pretransplant condition (elective or urgent), and type of graft (full- or reduced-size liver).

* ELTR, European liver transplant registry; ESLR, European split liver registry; OLT, orthotopic liver transplantation.

RESULTS

Out of 50 donor livers, 100 split liver grafts were prepared; 2 of them had to be discarded secondarily, because of death of the recipient before implantation in one case and for logistical reasons in the other. Nine grafts (3 left and 6 right parts) were shipped to another center after preparation. The annual number of split liver transplantations performed showed a clear increase, from 4 in 1988 to 20 in 1992. General data concerning donors and recipients are shown in Table 1.

In 24 cases, the transplant teams decided to perform a liver graft division in order to transplant 2 urgent patients simultaneously; in 20 cases, splitting replaced a reducing procedure and benefited 19 adults and 1 child who came to receive the right part of the liver (including 3 adults with liver tumor and 6 others clinically deteriorating). In 1 case, an oversized graft implanted in a small-weight adult had to be reduced, and the left part was used to transplant an urgent patient. Experienced teams divided 5 livers for elective recipients only (all survivors).

Technical data. Two left grafts were implanted heterotopically in 2 adults. Orthotopic transplantation was performed in 39 adults (1 left graft and 38 right grafts), and in 54 children (46 left parts and 11 right parts: 3 children received 2 left split liver grafts).

Twenty donors had vascular anatomical variations, which did not preclude liver splitting but required appropriate reconstruction in 13 cases. They consisted in accessory right hepatic artery (n=2), left hepatic artery (n=5), or both (n=1), and/or trifurcation of the portal trunk (n=2), and/or trifurcation of the common bile duct (n=14), and/or a long common trunk for left and median hepatic veins (n=15).

Dividing the vascular tract, the coeliac axis was usually kept with the left graft (n=43). The common bile duct was retained with the right part 37 times and resected in 8 other cases. The portal trunk was kept more often with the right graft (n=31). The left medial segment (segment 4) was resected in half the cases.

Eurocollins or HTK preservation solution was used in 2 cases. All others were preserved with Wisconsin solution, and ischemic time was 872±261 min for right parts and 767±267 min for left parts. Nineteen transplants had a very long ischemic time (>18 h), including 3 with primary nonfunction.

Complications and graft outcome. Portal vein thrombosis occurred in 4 grafts supplied with the portal trunk. It was caused by factors unrelated to the splitting technique. Three left graft recipients weighed less than 15 kg. One of them had a primary hypercoagulative state, and in another one thrombosis occurred secondarily to low blood flow related to multiple organ failure. One adult with a right graft developed portal vein thrombosis after duodenal ulcer perforation.

All grafts except 3 were provided with a single first-order artery ready for anastomosis. Thirty-two vascular grafts were used (9 saphenous grafts, 23 arterial homografts); 19 of them were interposed to reach the recipient aorta. Hepatic artery thrombosis (n=11/96: 11.5%) did not occur significantly more frequently after homograft interposition (n=4/32: 12.5%). The hepatic artery thrombosis rate was not influenced by the retention (or not) of the coeliac axis with the graft (n=5/49 and 6/49, respectively), or by the type of graft (left part: n=5, and right part: n=6). In 3 adults, thrombosis occurred early (7.7%); in another one it was diagnosed during terminal failure of a graft in which arterial flow was normal previously.

Overall, one or more predisposing factors for arterial thrombosis were found in all except one: recipient weight <20 kg (n=5), ischemia >15 hr (n=6), ABO mismatch (n=3), hypercoagulable state (n=1), postoperative injection of vasopressin (n=1), late occurrence during acute rejection (n=1), or multiple organ failure (n=1). Overall, vascular thrombosis (2 portal vein, 4 arterial, and 1 combined thromboses) led directly to the loss of 7 grafts; 3 other thromboses (1 portal vein and 2 arterial) were diagnosed in grafts lost through the patient's death. Four grafts with hepatic artery thrombosis were functioning 428 to 1023 days after transplantation. Overall patient survival after vascular thrombosis was 53.8%.

Twenty biliary tract complications occurred in 7 right (14.3%) and 11 left grafts (23.4%), consisting of 10 anastomotic strictures, 7 anastomotic leaks, and 3 intrahepatic strictures. Biliary complications were not correlated with a longer ischemic time in this series. None of these biliary complications led directly to graft loss; 3 grafts were replaced for other reasons, and the follow-up of the 15 others was 292 to 1190 days (median 653 d). All patients are currently alive.

Cut surface biliary leaks occurred in 5 patients, and were caused by anastomotic stricture in 2 others (4 right and 3 left grafts). Two grafts were lost through unrelated death of the patient; the remaining grafts were functioning at 1-year follow-up.

Causes of graft loss and patient survival (Table 2). Twenty split grafts were lost through causes related to the graft, 4 being lost more than 6 months after transplantation. Of these 20 cases, 2 recipients died due to graft complication and 18 grafts needed to be replaced. Retransplantation was successful in 8 of them (44%). In 21 other cases, the graft was lost through death of the patient: all deaths were unrelated to the technique itself. Six recipients died from neurological problems: cerebral hemorrhage (n=1), postoperative brain death (n=4: 3 patients had pretransplant acute liver failure), or encephalitis occurring 6 months after transplant (n=1). Sepsis and multiple organ failure were the cause of 11 deaths, and occurred preferentially in the urgent patient group (n=8, of whom 5 had acute liver failure). One patient died of intraabdominal hemorrhage that was not related to the graft.

Overall, the actual 6-month survival rates after elective or urgent orthotopic split liver transplantation were 75.6% and 57.1% (P=0.072) for grafts, and 84.8% and 63.3% (P=0.029) for patients, respectively (Table 3). Elective right graft transplantation was performed in 18 adults and 1 child. All elective left graft recipients were children, including 8 patients with biliary atresia. The lowest survival rates were observed in the subgroup of highly urgent recipients, which represented 36% of children and 29% of adults. Half the graft losses due to death of the patient following septic or cerebral problems (n=9/18) were encountered in the highly urgent group.

Two patients received a graft in the heterotopic position; one had accelerated terminal liver failure and died due to multiple organ failure on day 3. The second patient needed a transplantation because of deteriorating clinical condition; the graft was lost due to primary nonfunction, and the patient successfully received a second graft.

TABLE 1. Donor to recipient match, recipient pretransplant clinical condition, and indications for liver replacement

	Right split liver grafts (n=49)	Left split liver grafts (n=49)	
Donor/recipient match			
Weight ratio (range)	1.5±0.8 (0.5–5.5)	4.8±2.3 (1–10.7)	
ABO-identical (n)	42	41	
Compatible (n)	6	6	P=0.8
Incompatible (n)	1	2	
Recipient pretransplant condition (n)			
Urgent[a]	30	34	
Elective	19	15	P=0.4
Indications			
Fulminant hepatitis	6	7	
Posthepatitic cirrhosis	11	1	
Cholestatic cirrhosis[b]	11	22	P=0.006
Others[6]	16	10	
Retransplantation	5	9	

[a] Urgent = hospital or ICU-bound. In both groups, 16 recipients were in highly urgent condition (acute liver failure and vital medical support).

[b] Respectively, for right and left graft: biliary atresia patients accounted for 3 and 16 cases. Other indications were: liver tumor (n=7 and 1), metabolic disease (n=2 and 8), and various cirrhoses (n=6 and 1).

TABLE 2. Causes of graft loss related to graft or recipient death after orthotopic split liver graft transplantation

	Right grafts (F-up [days])	Left grafts (F-up [days])
Graft loss related to the graft (n)	10	10
Primary nonfunction	3 (1, 1, 9)	1 (4)
Vascular thrombosis	4 (7, 7, 82, 107)	3 (98, 1, 42)
Uncontrolled rejection	2 (10, 12)	1 (17)
Chronic rejection	1 (85)	3 (223, 241, 450)
Budd-Chiari syndrome	–	1 (17)
Hepatitis	–	1 (222)
Graft loss related to patient death (n)	10	11
Recurrent disease[a]	2 (375, 833)	1 (130)
Cerebral problems[b]	1	5*
Sepsis ± multiple organ failure	6	5
Hemorrhage[c]	1	–

[a] Recurrence was neoplasic (n=2) or viral (n=1).

[b] All except one* (death on day 179) occurred during the first postoperative week.

[c] Hemorrhage was unrelated to the hepatic graft.

TABLE 3. Six-month survival of orthotopically transplanted grafts according to recipient pretransplant status, type of graft, and recipient age group

Pretransplant clinical condition		Elective	Urgent	Highly urgent[a]	Total
Left split liver grafts[b]					
Graft survival	n=47	11/14 (79%)	19/33 (58%)	(10/16)	30/47
Patient survival[c]	n=44	11/14 (79%)	18/30 (60%)	(9/15)	29/44
Right split liver grafts[b]					
Graft survival	n=49	14/19 (74%)	17/30 (57%)	(5/16)	31/49
Patient survival	n=49	17/19 (90%)	20/30 (67%)	(7/16)	37/49

[a] Patients with acute liver failure necessitating vital support; considered as a particular subgroup of urgent cases.
[b] Left split liver grafts were transplanted in 1 adult and 43 children, and right split liver grafts in 38 adults and 11 children.
[c] Three children were transplanted twice using a left split liver graft; the clinical status group depended on the first transplant status.

Results of conventional liver transplantations. The actual 6-month survival rates of conventional orthotopic liver transplants performed in Europe during the same period are detailed in Table 4. These transplants consisted of both full- and reduced-size liver grafts implanted in children, and only full-size liver grafts in the adult group. Comparison with the rates obtained after split liver transplantations in this series did not shown any significant differences, either for the graft (P=0.1 to 0.8) or patient survival (P=0.4 to 0.9), or for retransplantation rates (P=0.1 to 0.9) (Table 4).

DISCUSSION

In Europe, split liver transplantation has been developed in centers having extensive experience in liver graft reduction technique. In addition to transplanting a reduced left lobe into a pediatric recipient, the use of the right lobe to transplant another patient was considered more a logical evolution than a real innovation, as remarked by Lantos (*11*). Therefore, teams informed their recipients about the various techniques they used without requesting formal informed consent. However, during open discussion at the first Symposium on split liver transplantation (March 1993, Brussels), it was proposed that, in future, the question of informed consent should be addressed by each institution for itself, according to its own experience.

Overall, initial results of split liver transplantation were disappointing, but this is probably because this innovative technique was being most frequently applied in its early days in high risk and in highly urgent patients (*2*, *3*, *5*), for whom a poor prognosis is currently reported (*12–14*). A learning phase probably contributed to a higher rate of complications and graft loss. With increasing experience, better results have been reported (*7*, *8*). Initial results with split liver transplants seem to mirror those obtained with reduced or living related donor grafts (which are obviously split liver grafts as well): complications have decreased with experience and results are currently as good as those after full-size liver grafting, provided the urgency code is taken into account (*8*, *15–20*).

Portal vein thrombosis occurred mostly in small children (n=3/4), in whom it is not unfrequently observed (0.8–7.7%) (*18*, *19*, *21*). The incidence of arterial occlusion in adults was 7.7% (excluding premortem thrombosis) and 12.5% in children. In recently reported series, the rates range from 0 to 6% in adults (*22–25*) and from 3.2% to 16.7% in children (2.8–11.4% for reduced-size liver grafts) (*8*, *18–21*, *23–26*). Vascular complications were thus in the upper range of what is currently reported; it must, however, be taken into account that they were often caused by factors unrelated to the technique itself. Since of 15 vascular thromboses, 10 occurred in a split liver graft procured with the main trunk, they do not seem to be directly caused by the use of second-order vessels after division.

In published series, biliary complications range from 12.6% to 19.5% in adults (*25*, *27*, *28*), and from 5% to 22% in children (5% to 13.2% for reduced-size liver grafts) (*8*, *18*, *19*, *26*, *28*). In this small series, half the biliary complications consisted of anastomotic strictures, for which the reported incidence is 4–5% in adult cases (*28*, *29*) and around 9% in pediatric series (*28–30*). Anastomosing small bile ducts obviously increases the risk of anastomotic problems; technical refinements seem to be necessary in this area.

Ischemic time was particularly long in this series, and primary nonfunction was linked to excessive ischemia in 3 cases. Our 5% rate is, however, similar to that reported by others (*8*, *18*, *19*, *21*, *23*).

Overall left and right graft survival rates were similar, clearly showing that both liver halves provided a graft of equal quality. Most of the grafts and patients were lost through causes unrelated to the technique itself. Overall graft and patient survival rates after vascular and/or biliary complications were 24/32 (75%) and 25/31 (80.6%), respectively; medical or surgical treatment was thus effective in complicated graft salvage.

Comparison of survival rates with those of the European Liver Transplant Registry did not show significant differences. In elective adult patients receiving a split graft, the retransplantation rate was 22.2% compared with 10.3% in ELTR,* and patient survival was also higher (88.9% versus 80.3%): thus patients benefited from more efficacious retransplantation strategy. On the other hand, in the case of elective children receiving a split liver transplant, graft loss and retransplantation rates were lower.

It is a fact that there is an absolute shortage of liver donor organs (*31*). Prolongation of the waiting period is often associated with clinical deterioration, higher risk at transplantation, increased posttransplant morbidity and mortality, and finally with a higher cost (*12*, *14*). Analysis of the dynamics of the waiting lists of both Eurotransplant[3] and United Network for Organ Sharing[4] during the 4-year period 1990–1993, shows that the minimal pretransplant death rate remains ≥7.9% while the registration rate has increased by ≥50%. In United States, median waiting time increased from 45±1.6 days to 142±4.5 days. Since liver division has the potential to create two allografts where formerly there was but one, it can quickly maximize the current available donor pool, and benefit patients who otherwise would die before getting a graft in time or would deteriorate clinically during their long waiting period. In this series, liver division was planned in half the cases in order to carry out a simultaneous transplantation for 2 urgent recipients. In the others, division replaced reduction: the part formerly discarded was retained and usually benefited an urgent patient who otherwise would have waited longer.

According to the "Equipoise" principle (*9*), a new technique that can achieve at least a similar overall (pre- and post-transplant) survival rate becomes ethically acceptable. One can also anticipate that developing split liver transplantation on a large scale would have a significant effect on liver graft availability, and probably on the overall mortality since a shortage of liver allografts is likely to persist.

TABLE 4. European Liver Transplant Registry (ELTR) and European Split Liver Registry (ESLR): six-month graft and patient survivals after orthototopic liver transplantation (OLT), according to first or retransplantation, recipient pretransplant status, and age group[a]

		Pre-OLT* status	Grafts			Patients	
			n	Survival (%)	Re-OLT (%)	n	Alive (%)
ELTR Adults[b]	First OLT	Elective	7219	75,3	10,3	6888	80,3
		Urgent	2197	53,4	12,2	1928	63,7
	Re-OLT	Urgent	698	42,9	9,1		
Children[b]	First OLT	Elective	1223	74,7	18,2	1001	83,5
		Urgent	575	53,4	16,2	482	66,6
	Re-OLT	Urgent	215	43,7	14		
ESLR Adults	First OLT	Elective	18	72	22	18	89
		Urgent	18	56	11	18	61
	Re-OLT	Urgent	3	0	33		
Children	First OLT	Elective	15	80	7	15	80
		Urgent	31	61	16	31	68
	Re-OLT	Urgent	11	64	9		

[a] Comparison of survival and retransplantation rates (similar groups, ELTR versus ESLR) did not show any significant differences.
[b] Whole liver graft in adults, and whole liver or reduced-size liver graft in children.

[3] SOURCE: Annual Eurotransplant Liver meeting, September 22, 1994, Leiden, the Netherlands.
[4] SOURCE: UNOS data as of June 1, 1994. Data request number: 092894–2.

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ARTICLES

XENOTRANSPLANTATION OF PORCINE AND BOVINE ISLETS WITHOUT IMMUNOSUPPRESSION USING UNCOATED ALGINATE MICROSPHERES[1]

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Uncoated spherical hydrogel microspheres (calcium alginate, nominal M_r exclusion of >600 kD) 800–900 μm in diameter were employed to prevent immune rejection of discordant islet xenografts isolated from pigs and cows. The islets were immobilized in the microspheres and injected into the peritoneum of 14 non-immunosuppressed streptozotocin (STZ)-induced diabetic C57BL/6J mice. Four recipients received islet grafts from bovine calves, and 10 received islet grafts from pigs. In the control group of 15 diabetic mice implanted with nonencapsulated islets, 6 received i.p. porcine islets and 5 received i.p. bovine islets, whereas the remaining 4 received porcine islets under the kidney capsule. Plasma glucose concentrations in recipients of the alginate-encapsulated islets promptly dropped from a preimplantation value of 498±47 (mean ± SEM) to 142±6 (bovine) and 178±7 mg/dl (porcine) during the first wk. All the animals sustained these levels for at least 1 mo. Two mice implanted with bovine islets subsequently reverted to diabetes (plasma glucose >250 mg/dl) at 43 days postimplantation. The remaining grafts maintained function for >10 wk. In contrast, nonencapsulated islets failed to function, or sustained euglycemia for <4 days. Mice receiving encapsulated islets showed a 23–38% gain in body weight during the first mo after implantation, compared with <1% ($P<0.002$) and 32% ($P=0.84$) for the untreated diabetic (n=6) and normal control (n=6) groups. Immunohistochemical staining of long-term grafts (>10 wk) revealed viable islets, with well-granulated α, β, and δ cells; the external surfaces of the microreactors were free of fibrotic overgrowth and exhibited only occasional host cell adherence. Uptake studies with IgG and thyroglobulin (M_r of 669 kD) suggest that the microreactors were permeable to molecules with a molecular weight of up to >600 kD (including the various proteins of the complement system, M_r of 24–570 kD). Spheres implanted in the peritoneum after only 1 wk stained positive for both IgG and for the C3 component of complement. These findings suggest that prolonged survival of discordant xenografts of porcine and bovine islets in the STZ diabetic mouse model can be achieved with uncoated alginate microspheres that are permeable to IgG and complement. The question of whether similar results can be achieved with uncoated alginate microspheres in higher animals remains to be fully determined.[1]

A number of immunoisolation systems are on the verge of successful clinical trials (*1*, *2*). These include microcapsules (*3–6*), diffusion chambers (*7–9*), and devices anastomosed to the vascular system as arteriovenous shunts (*10*, *11*). In all of these systems, the transplanted tissue is isolated from the immune system of the host by a selectively permeable artificial membrane. Low-molecular-weight substances such as nutrients, electrolytes, oxygen, bioactive secretory products, and cellular waste products can diffuse across the membrane while immunoglobulins and other immune effector mechanisms are excluded (*12*, *13*). However, problems such as fragility, limited surface area, and—in the case of vascular approaches—the surgery required for implantation or shunt connection limit the usefulness of these devices (*1*, *14*, *15*). Moreover, the placement of synthetic materials in the peritoneum can lead to an interstitial acute and/or chronic inflammatory reaction and development of granulation tissue (*16*), intestinal adhesions (*17*), and abscess formation (*18*). Furthermore, it is uncertain whether these implants will require localization and removal. Surgical excision could also be necessary if the implants become fibroencapsulated. Consequently, we have investigated the use of uncoated hydrogel spheres (calcium alginate, nominal M_r exclusion of >600 kD) that are biocompatible, and that in the long-term are resorbed and excreted in the urine (Skjåk-Bræk G, unpublished observations). This report describes studies of porcine and bovine islet xenografts encapsulated within these hydrogel microspheres (microreactors) and injected into nonimmunosuppressed streptozotocin-induced diabetic mice.

MATERIALS AND METHODS

Animals. Adult male C57BL/6J mice (Jackson Laboratory, Bar Harbor, ME) weighing 20–25 g were used. Animals were fed ad libitum with a standard pelleted diet (Agway, No. 3000 RHM-Prolab) and allowed free access to water. Diabetes was induced by a single

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