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Opportunities and Costs of Clinical Research

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Orthotopic hepatic transplantation offers selected patients a surgical cure of their otherwise hopelessly advanced liver disease. It also presents the medical-scientific community with an almost limitless list of new questions to be asked, unique materials to be studied, and an opportunity to extend the current understanding of liver disease and its complications. Presented below is a list of five major areas of research that orthotopic liver transplantation has made possible, the list certainly is not all-inclusive. These topics have been selected as examples of the investigative areas in liver disease that should benefit dramatically as a consequence of the increasing performance of the procedure and the involvement of more and new investigative groups in transplant programs. They are: (1) preservation of the liver; (2) hepatic regeneration; (3) the pathogenesis of various unusual metabolic liver diseases; (4) the immune mechanisms involved in rejection as well as in various primary hepatic diseases; and (5) the problem of hepatic encephalopathy, its pathogenesis, consequences, and reversibility. Each of these major areas of investigative interest to hepatologists and hepatic surgeons will be discussed individually.

HEPATIC PRESERVATION

The present technique of hepatic removal from the donor and method of cold storage of the organ in an iced solution of fluid resembling intracellular fluid is well known and widely used. The method has certain advantages: its relative simplicity and its comparability to that used for other organs also being harvested for transplantation from the same donor. However, this technique severely limits the number of donor organs available to a potential recipient because of the limited ex vivo life-span of the donor organ. This is probably no greater than 12 to 14 hours maximally, and ideally should be no longer than 6 to 8 hours for optimum early graft survival. Ideally, for maximal donor use and better organ recipient matching, possibly with tissue typing, donor organs should be able to survive for periods of 24 to 36 hours with good postimplantation function. Such a time frame would allow donor organs from anywhere in the world to be harvested and used either where the need for an organ is most critical or where the donor organ is best suited for a given recipient.

HEPATIC REGENERATION

Despite the current best technique of organ harvesting and rapid engraftment, some degree of ischemic injury occurs in each organ grafted. Such injury requires hepatic graft regeneration for its resolution and subsequent maximal function in the recipient.

In some cases, the donor organ is larger than anticipated and thus may have to be reduced in size surgically for successful engraftment. As a consequence of such reductional surgery, the donor organ experiences an additional injury that necessitates an additional regenerative response, following successful engraftment in the recipient, for maximal postimplantation function. Less often, but also fairly common, is the circumstance of a donor organ that is too small for a given recipient. Under such circumstances, an intact, small organ is not of sufficient size to return the recipient to a state of maximal or ideal hepatic function. In such cases,

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the donor organ can be seen to increase rapidly in size, presumably as a consequence of hepatic regeneration, until the donor organ more closely matches the required hepatic mass of the recipient for putative ideal function.[9,10]

In addition, it should be remembered that the rejection process is continual. Thus, maximal hepatic function in a successfully engrafted organ requires the continual replacement of hepatocytes and cholangiolar cells destroyed by the immune system as well as those lost by simple attrition over time.

The liver graft responds to each of these putative injuries, at least in part, by the process of hepatic regeneration. Thus, a better understanding of the process of regeneration is crucial to any further improvements in the results of clinical hepatic transplantation. Importantly, it must be recognized that the signals and factors that regulate the regenerative responses of the engrafted liver to each of these putative injuries may be quite different. Specifically, hepatic transplantation has shown that the issue of hepatic regeneration is considerably more complex than the current simple models, all of which involve the idea of recruitment of new hepatocytes,[9,10] and suggests that the only important clinical problem requiring hepatic regeneration is that of massive hepatic necrosis. Thus, new models of hepatic regeneration will have to be formulated and developed to answer specific questions related to issues of liver transplantation. Such models will have to address the more specific signals for and controls of the regenerative process. They may also provide important additional information so that the entire process of hepatic regeneration can be better understood and possibly even manipulated specifically, as may be required by a given clinical situation.[11]

RECOGNITION, PATHOGENESIS, AND CORRECTION OF METABOLIC AND OTHER UNUSUAL LIVER DISEASE

The development of a liver transplant center that offers a therapeutic option to patients with otherwise untreatable liver disease serves as a focus for the referral of such cases. As a consequence of such referrals, clinicians in transplant centers see many more cases of "obscure" liver disease than do clinicians at major medical referral centers, including centers of hepatic expertise not having a transplant program.[11] As a direct result of such intensified clinical experience with liver disease, clinical signs of and unusual presentations of the less common metabolic liver diseases become recognized. Moreover, better methods of caring for such patients until transplantation is required can be developed and validated by clinical trials. In addition, epidemiologic studies become possible to evaluate clues to pathogenesis as well as to examine factors that modulate the clinical expression and/or rate of progression of such diseases. An easy example is that of alpha$_1$-antitrypsin disease. Why do some individuals with this disease develop liver disease and others develop pulmonary disease? Why do some individuals with alpha$_1$-antitrypsin deficiency develop clincially evident liver disease as children and others only as adults? Another example is the problem of biliary atresia and the various biliary hypoplasia syndromes. Are these many diseases or simply variable expressions of a single disease? Are they environmentally determined? Certainly, many other interesting questions can be generated and will be addressed in the future.

Already, new insights into the specific defects of Wilson's disease, alpha$_1$-antitrypsin deficiency, tyrosinemia, and other such diseases are being made or are being pursued by investigators located at transplant centers.[12] With the availability of the entire resected diseased liver, the problem of insufficient amount of tissue sample, such as is frequently required for sophisticated biochemical and genetic engineering studies, should no longer exist. Furthermore, the identification of individual metabolic liver diseases in biochemical terms as well as the genetic site of the defect in terms of its chromosomal location, nucleic acid base pair alterations, and gene product abnormality should be resolvable. The answers to such questions may provide alternative therapies to transplantation, such as correct (normal) gene product replacement or the development of alternative medical therapies based on a better understanding of the specific disease process involved.

IMMUNOLOGIC DISEASES AND THE IMMUNE RESPONSE

Certainly as a direct consequence of hepatic transplantation, new data concerning the immunologic characteristics of the liver will be obtained. Specifically, the cellular sites of the liver that elicit an immune response will be identified and characterized. New technologies will be developed to limit or modify the immunologic reactivity of these hepatic tissues and the body's way of reacting to them. Already, the histopathology of early and late rejection has been characterized using the light

microscope and standard staining methods.[8,13-15] Data concerning the specific phenotypic characteristics of the lymphoid cells found in areas of and adjacent to the rejection process are also forthcoming. Eventually, these cells will be isolated, cloned, and characterized functionally as well as phenotypically.

Recently, it has been shown that bile ductular cells express HLA antigens, and it has been suggested that this is the reason that the bile ductules appear to be selectively destroyed as a consequence of the immune response associated with rejection.[13] This finding of bile ductular expression of HLA antigens has been demonstrated also in primary biliary cirrhosis and graft versus host disease, two disease processes that are characterized also by the presence of bile ductular destruction. This fact probably provides the reason for the histopathologic similarity between primary biliary cirrhosis, rejection, and graft versus host disease. Whether individuals with primary sclerosing cholangitis will also express HLA antigens in the areas of their liver, which are being destroyed by a mixed inflammatory infiltrate, needs yet to be determined. Data concerning the nature of the cellular infiltrates present in late liver disease due to primary sclerosing cholangitis are already available. Whether similar findings will be evident in early disease remains to be determined.

Certainly, a question that will need to be answered is, if chronic active hepatitis is the consequence of an immune response directed at the liver, why does it differ so markedly from the histologic appearance of rejection? It appears certain from the available data that the recognition sites for the immune response in each must be different, being the hepatocyte in the case of chronic active hepatitis and predominantly bile ductular cells in rejection. Similarly, what are the immunologic signals that exist between immunologically responsive cells that help to explain the differences between the two conditions? Moreover, if cyclosporine and prednisone can either prevent or markedly reduce the process of rejection, why are they so inconsistent or poor in their ability to modulate the immune response that results in chronic active hepatitis? These questions are but a few of the many that will be asked and answered in the next several years as we follow patients with transplants and care for those awaiting transplantation.

Hepatic Encephalopathy

Hepatic encephalopathy has been a problem of keen interest to physicians, particularly hepatologists, since the very dawn of medicine. We have been taught that the central nervous system cannot repair itself once injured. We have been taught also that there are histologic findings that are characteristic of chronic portal-systemic encephalopathy (PSE). Certainly, the condition of patients demonstration PSE tends to wax and wane, as does the course of their liver disease, and particularly the extrahepatic parameters that modulate the residual hepatic function present in patients with PSE. Can the central nervous system in such patients, following transplantation and the return of normal hepatic function, repair itself and return to normal or can it only return to some baseline of "disease" that allows the patient to be quite functional but nonetheless quantitatively abnormal? Preliminary data obtained 1 year after liver transplantation suggest that the brain does, in fact, improve, but that it has not entirely returned to normal, at least at the 1-year follow-up point.[16] Will it ever? If so how long will it take? If not, what residual defects will remain? What will be their significance? How should we follow and monitor such patients? Are there special precautions we should suggest to patients who are successfully transplanted, but yet continue to express evidence of PSE?

Interestingly, preliminary data suggest that the specific pathophysiologic nature of the liver disease affects the type of neuropsychologic defects identifiable in patients with PSE.[17,18] This suggests that the reason for the transplant (the primary liver disease) may determine the rate and degee of neuropsychologic improvement expected to occur in a given patient after successful transplantation. Moreover, it suggests that the specific underlying pathophysiologic basis for PSE may differ in each etiologic case. Thus, specific, rather than (or at least, in addition to) generic, modalities, such as lactulose, a low protein diet, and neomycin, may be indicated for patients awaiting transplantation and manifesting evidence of PSE. These and many other important questions concerning PSE will be answered in the next decade, at least in part as a consequence of the ability to transplant patients successfully, thereby correcting their liver disease and simply following them and collecting data in a prospective manner.

Who Pays for Liver Transplantation and the Knowledge that Accrues from It?

The answer to this question is multifactorial and varies as to what specifically is intended by either the question or the answer.[19] For example, the patient pays, his insurance carrier pays, the National Institute of Health (NIH) pays, and the

physician (surgeon/hepatologist) pays. Moreover, individual benefactors, foundations, pharmaceutical companies, and many others have paid and continue to pay for such knowledge.

The patient pays by experiencing first hand the complications, problems, and difficulties associated with his or her liver disease. Moreover, only the patient undergoes the rigors of the preoperative evaluation, the fear of having or not having the operation, the operation itself, the postoperative recovery period, the fear of the actual experience of a rejection episode, and a life after successful transplantation complicated by the need to take and pay for costly immunosuppressive agents, worry about opportunistic infections and the unknown possibility of recurrent or even new liver disease. Thus, the patient continues to be an experimental model, thereby repaying the debt owed former transplant patients and pointing the way toward a better method of transplantation and rejection prevention and control for transplant recipients of the future.

The insurance company pays by assuming the cost of the transplant procedure and its evaluation for one of its insured. It has accepted such responsibility by accepting premiums from the insured and has done so expecting to make a profit by amortizing the costs of the procedure over the cost of the insurance provided a much larger subscriber population, most of whom are not expected to require the procedure. It should be noted, however, that insurance carriers only pay for required services and procedures. They do not and have not paid directly for any research that has been or continues to be accomplished using their subscribers.

The various insurance companies and programs that have paid for a liver transplant in Pittsburgh are shown in Table 1. This is not an all-inclusive listing of companies that may have paid for or are willing to pay for liver transplantation. It is only a listing of those who have paid for one of their subscribers to have a transplant or a specific institution to date.

The NIH have paid and continue to pay by supporting grants and contracts directed toward issues related to liver transplantation. Tables 2 and 3 document the agencies within the NIH that have

TABLE 1. Insurance Providers that Have Paid for a Liver Transplant in Pittsburgh

Commercial Insurance Companies	*Blue Cross Plans*	*State Governments (Medicaid)*	*Federal Government*
Aetna Life	Capitol (Harrisburg, PA)	Kentucky	Armed Services
Allstate	Central Ohio (Columbus)	Massachusetts	Champus
American Postal Workers	Connecticut	Missouri	Veterans Administration
Bankers Life	Delaware	New Jersey	
Continental Life	Georgia	New Mexico	
Connecticut General	Greater New York	New York	
Educators Mutual	Greater Philadelphia	Pennsylvania	
Equitable Life	Idaho	Ohio	
Fireman's Fund	Illinois	South Dakota	
Firestone Tire & Rubber	Indiana		
John Hancock Life	Lehigh Valley (Allentown)		
Liberty Mutual	Louisiana		
Lincoln National	Massachusetts		
Metropolitan Life	Michigan		
Mutual Benefit Life	Mississippi		
Motorola	Montana		
National Association of Letter Carriers	New Hampshire		
New England Life	New Jersey		
New York Life	North Dakota		
Pilot Life	Northeastern Ohio		
Prudential Life	(Cleveland)		
Time Insurance	Northern California		
Travelers Life	(Oakland)		
Sheet Metal Welfare Fund	Oklahoma		
	Rhode Island		
	Rochester, New York		
	South Carolina		
	Tennessee		
	Texas		
	Vermont		
	Western Pennsylvania		
	(Pittsburgh)		

TABLE 2. Funds Expended by NIH by Institute* for Liver Transplantation Research and Development

Year	*NIADDK*	*NCI*	*DRR*	*NHLBI*	*NIAID*	*Total*
1972	406,883	42,942	74,707	63,004	237,495	825,031
1973	263,794	184,151	33,021	151,324	236,353	868,643
1974	246,975	192,859	31,809	168,501	0	640,144
1975	152,629	208,959	100,007	87,671	82,961	632,227
1976	242,249	166,926	115,342	17,440	89,054	631,011
1977	288,629	26,805	145,861	0	312,980	774,275
1978	280,069	182,144	129,794	0	109,782	701,789
1979	197,631	156,672	138,303	0	120,111	612,717
1980	265,060	43,583	132,189	0	0	440,832
1981	252,055	189,562	111,364	0	0	552,981
1982	318,313	143,743	73,204	0	0	535,260
1983	525,761	215,098	27,330	0	140,916	909,135
1984	954,417	181,884	45,378	0	161,762	180,959
1985	1,211,923	231,571	50,941	0	180,959	1,675,394
Total						11,142,888

*NIADDK: National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases; NCI: National Cancer Institute; DRR: Division Research Resources; NHLBI: National Heart, Lung, and Blood Institute; NIAID: National Institute of Allergy and Infectious Diseases.

supported liver transplant-directed research (Table 2) and the types of awards funded (Table 3) on an annual basis from 1972 through most of 1985. This listing of governmental support is not complete, in that only, the NIH data were available for review. The Alcohol, Drug Abuse, and Mental Health Administration (ADAMHA) and other agencies may have funded, at least in part, research related to transplantation, but no data about such support were available for our review. Moreover, the listings in Tables 2 and 3 are minimum figures chosen from a listing of the titles of the awards for each of the years cited. Had a research project title not included a reference to transplantation of the liver, it would not have been considered for inclusion in either of the tables.

TABLE 3. Types of Grant Awards Expended by NIH for Liver Transplantation Research and Development

Year	*Regular Grant*	*Program Project*	*CRC**	*Contract*	*Total*
1972	5	9	7	0	21
1973	4	14	6	0	24
1974	3	9	4	0	16
1975	3	9	4	0	16
1976	3	11	4	0	18
1977	5	9	7	0	21
1978	5	9	3	0	17
1979	5	6	2	0	13
1980	4	3	3	0	10
1981	4	2	4	0	10
1982	3	2	0	0	5
1983	6	0	3	0	9
1984	8	1	4	0	13
1985	9	1	4	0	14
Total					207

*CRC: Clinical Research Centers.

In addition, the physicians and scientists involved in the broad area of liver transplantation have paid by spending hours in the care of patients, collecting and reporting data on patients and animals, and by taking the risks associated with the use of a novel form of treatment before it has become accepted generally by the medical establishment. Much of this effort has been without financial reward, performed after other obligations have been fulfilled, and at times against the will of peers and superiors.

Private industry has paid also in the form of subsidies of drugs, such as cyclosporine, and other biologic materials, such as antilymphocyte and antithymocyte globulins, used in preliminary trials by patients and physicians involved in hepatic transplantation. Besides providing such potentially useful experimental agents, many companies have either paid for or have developed assay systems for monitoring drug levels, biologic agent effectiveness, and the accumulation of data concerning both beneficial and adverse effects of the agents in which they have a vested interest.

In addition to each of these individuals or groups, others, such as individual philanthropists, group philanthropies, various foundations and regional and national foundations having an interest in transplantation, liver disease, and health in general, have provided both funds and support for liver transplantation research and development and its clinical application.

Who Benefits from Liver Transplantation?

This question, like the preceding one, is quite complex and the answer varies depending on the sophistication of the questioner, the responder, or both.[19] A strong case can be made for liver transplantation benefiting each of the following individuals or groups: the patient, his or her family, patients of the future and their families, individuals with liver disease (including those not expected to require a transplant), clinical and basic researchers interested in such issues as the liver in general, transplantation, rejection, and hepatic regeneration in particular, and the broad area of hepatic pathophysiology. Certainly physicians and surgeons caring for patients with liver disease now and in the future have and will continue to benefit from the experience accrued as a result of the clinical application of liver transplantation. Society also benefits by the return of a formerly critically ill, incapacitated consumer of health care and related benefits to a life that includes a return to gainful employment and the payment of health care premiums rather than the continued consumption of health care benefits. Society also benefits from the application of lessons learned from hepatic transplantation, so that generations of people with liver disease in the future need not endure what patients with liver disease in the past have done.

The benefits of a liver transplantation program extend to, and are appreciated by, all of the patients cared for by physicians and institutions involved in the care of patients with liver disease, not just those institutions in which there is a clinical hepatic transplantation program. Liver transplantation centers benefit by becoming recognized as referral centers for patients with liver diseases, including many with unusual or rare hepatic diseases. As a consequence, opportunities for the training of health professionals interested in liver disease become available in such centers. Moreover, by concentrating patients with rare or unusual diseases at a few such specialized centers, useful clinical and research observations can be made and confirmed by physicians and scientists working at such specialized centers. Finally, by acting as a focus for physicians and scientists interested in issues such as transplantation, liver disease, and the many fields that intercept with these two broad areas, the insights and efforts of the few investigators at such centers can be examined, reexamined, amplified, and then made available to society at large for use by individuals outside the center. Clearly, the benefits are legion.

COMMENT

It is hoped the preceding discussion has helped to put in focus for physicians, surgeons, medical investigators, governmental as well as public and private funding agencies, and most importantly, the lay public, the many advantages associated with liver transplantation. The investment by each designated group has been and continues to be great. Nonetheless, the dividends to be gained by each and for society are clearly worth the investment and more.

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