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THEMES OF LIVER TRANSPLANTATION

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ABSTRACT

Liver transplantation was the product of 5 interlocking themes. These began in 1958-59 with canine studies of then theoretical hepatotrophic molecules in portal venous blood (Theme I) and with the contemporaneous parallel development of liver and multivisceral transplant models (Theme II). Further Theme I investigations showed that insulin was the principal, although not the only, portal hepatotrophic factor. In addition to resolving long-standing controversies about the pathophysiology of portacaval shunt, the hepatotrophic studies blazed new trails in the regulation of liver size, function, and regeneration. They also targeted inborn metabolic errors (e.g. familial hyperlipoproteinemia) whose palliation by portal diversion presaged definitive correction with liver replacement. Clinical use of the Theme II transplant models depended on multiple drug immunosuppression (Theme III, Immunology), guided by an empirical algorithm of pattern recognition and therapeutic response. Successful liver replacement was first accomplished in 1967 with azathioprine, prednisone, and ALG. With this regimen, the world's longest surviving liver recipient is now 40 years postoperative. Incremental improvements in survival outcome occurred (Theme IV) when azathioprine was replaced by cyclosporine (1979) which was replaced in turn by tacrolimus (1989). However, the biologic meaning of alloengraftment remained enigmatic until multilineage donor leukocyte microchimerism was discovered in 1992 in long surviving organ recipients. Seminal mechanisms were then identified (clonal exhaustion-deletion and immune ignorance) that linked organ engraftment and the acquired tolerance of bone marrow transplantation and eventually clarified the relationship of transplantation immunology to the immunology of infections, neoplasms, and autoimmune disorders. With this insight, better strategies of immunosuppression have evolved. As liver and other kinds of organ transplantation became accepted as healthcare standards, the ethical, legal, equity, and the other humanism issues of Theme V have been resolved less conclusively than the medical-scientific problems of Themes I-IV.

The purpose of this contribution to the Master's Perspective Series is to describe in detail the provenance of liver replacement. In the absence until now of such an account, liver transplantation often has been characterized as a natural extension of renal transplantation. In reality, liver and kidney transplantation were co-developed with the liver as the flagship organ, or alternatively the engine, for much of the time. In the process, the rising tide of organ transplantation altered the practice of hepatology, nephrology, and other organ-defined medical specialties, enriched multiple areas of basic and clinical science, and had pervasive ripple effects in law, public policy, ethics, and religion.

At first, liver transplantation was a fantasy. Transformation of the idea into a reality required the essentially *de novo* development between 1957 and 1962 of 5 separate but interconnected themes: (I) metabolic interactions between intra-abdominal organs (hepatotrophic physiology), (II) the liver and multivisceral transplant models including donor organ procurement and preservation, (III) the immune system and its control without or with therapeutic immunosuppression, (IV) transplantation outcomes, and (V) humanism-associated issues (social, ethical, legal, public policy).

The 5 themes can be used to categorize all of the liver transplant milestones of the last half century (1-71) as has been done by thematic color-coding and by numbers in Table 1. To help connect this history with the present and future, John Fung was recruited as a collaborating author, fresh from his 5-year tenure as Chief Editor of *Hepatology's* sister journal, *Liver Transplantation*.

MY LIVERLESS EARLY LIFE

I was born in 1926 in the small town of LeMars, Iowa, and remained there uneventfully until joining the United States Navy directly from high school in 1944 (72). After the war's end, I remained "in training" for 14 consecutive years, beginning at Westminster College (Fulton, Missouri), and continuing in chronologic order at the university medical centers of Northwestern, UCLA, Johns Hopkins, Miami, and again Northwestern. Tangible results from this period included PhD and MD diplomas (Northwestern, 1952), board certificates in general and thoracic surgery, and a dozen publications of which the first 5 were in neuroscience.

The Neuroscience Venture

My research on the brain stem circuitry of cats (and eventually monkeys) was started at Northwestern at the age of 23 years under the neurophysiology pioneer, Horace W. Magoun and finished at UCLA after Magoun's recruitment there as one of the new school's founding chairpersons. Each of the 5 resulting publications (73-77) generated 100 to 300 citations, and a figure from one (75) was immortalized as the logo of the UCLA Brain Institute. However, the Ph.D.

thesis from this research and completion of the Northwestern M.D. requirements marked the end of my neurophysiology career at the age of 26 years.

The science environment that existed 60 years ago at both Northwestern and UCLA was described in my long letter of response in 1991 to a request by a UCLA Brain Institute archivist (see Supplementary Appendix #1). As described in that letter, Magoun's influence cut deeply. He had no interest in, and very little tolerance for, research that did not have a clear mega-purpose. In our project, the global objective was to delineate with electrophysiologic technology the neural pathways serving the most fundamental elements of brain function: sleep versus wakefulness, cognition, and memory.

A Side Trip to Cardiac Physiology

The Supplementary Appendix #1 also contains a 1951 letter (discovered 4 decades later) from Magoun to Alfred Blalock, Chairman of Surgery at the Johns Hopkins Hospital, that undoubtedly contributed to my acceptance for surgical training at that great institution (1952-56). After completing the first year in Baltimore, I put aside all clinical work for 18 months to develop a model of complete heart block in dogs, a complication being caused in patients by efforts to close atrial or ventricular septal defects.

With the technology adapted from my neurophysiology experience, I showed that low voltage bipolar stimulation at any place on the ventricle was safe and efficient treatment for the bradycardia of heart block. The cardiac pacemaking was promptly instituted clinically at Hopkins and elsewhere. Although the articles describing the experimental work (78-80) also were frequently cited, my involvement in the subject of heart block now reached a dead end.

However, the youthful excursions were not wasted. What survived from my exposure to Magoun, and was evident in the heart block research, was the view that all biologic functions were products of a hierarchy of interacting systems and subsystems over which there were controls at multiple levels (i.e. regulatory brain equivalents). In this context, it was more important to learn how a given function was governed than to endlessly pursue details. The "big picture" approach (systems biology) would, in fact, be applied to liver transplantation, the third subject to which I directed concentrated attention.

THE SUCCESSION OF THEMES

Anatomically-influenced physiologic interactions between organs (Theme I)

While still at Johns Hopkins, I assisted Dr. Blalock perform a splenorenal shunt in a cirrhotic patient with insulin-dependent diabetes mellitus who then became insulin-free. The possibility that the portal diversion was responsible for

the metabolic change seemed consistent with a then current hypothesis that excessive degradation of endogenous insulin during its primary passage to the liver via the portal vein was the cause of some forms of diabetes (81). Testing elements of this hypothesis was not possible until after I moved to the new medical school of the University of Miami to complete my general surgery residency (1956-58).

In Miami, I produced a colony of alloxan diabetic dogs, established the animals' steady state insulin needs, and modified the liver's blood supply with portacaval shunt (Eck's fistula) or other alterations of the portal venous system (82,83). The objective of surgically ameliorating diabetes evaporated when the portal diversion procedures increased instead of decreasing the insulin requirements (83). In addition, the hepatic atrophy and systemic morbidity caused by portacaval shunt in normal dogs (84,85) appeared to be exaggerated in our diabetic animals.

Development of liver transplant models (Theme II)

A connection of these studies to liver transplantation was made when C. Stuart Welch of Albany, New York, visited Miami in 1957 to give a lecture on the treatment of portal hypertension. During his talk, Welch made casual reference to a canine operation that he had reported in 1955 (1) and more extensively a year later (86). In these articles, the term "liver transplantation" was used for the first time in the scientific literature. The Welch operation consisted of revascularization of an auxiliary liver allograft in the recipient's right paravertebral gutter with provision of portal venous inflow from the inferior vena cava (Figure 1).

Recognizing that failure to provide the extra liver with a normal portal venous supply could handicap the allograft in the same way as the native livers were damaged in my non-transplant portal diversion models, I began the development of versatile transplant procedures to study the special qualities of splanchnic venous blood in dogs. One of the models was a method of total recipient hepatectomy, the unique feature of which was preservation of the retrohepatic inferior vena cava (2) as in the first stage of today's piggy-back human liver transplantation. For liver allograft implantation, it was technically easier to simply remove this portion of the recipient vena cava and replace it with the comparable segment of the donor liver's vena cava into which all of the hepatic veins empty (3).

Operative survival with the complete canine replacement operation (Figure 2) was not accomplished until a few days after I moved to Northwestern in June, 1958, for a final 12 months of cardiovascular surgical training that was expected to culminate in an academic practice in thoracic surgery. Instead, 2 steps were taken during the summer of 1958 that ensured pursuit of the liver research for at least 5 years beyond completion of the thoracic residency. The first step was the submission of a 4 page NIH grant focused on metabolic studies in which liver

replacement was one of the experimental models. The second step was my nomination by Northwestern for a John and Mary Markle Scholarship. Here, the emphasis was radically different.

Markle Scholar candidates were expected to identify an open-ended career objective. Ignoring advice to develop a "more realistic" project in the emerging field of open heart surgery, I proposed the life goal of clinical liver transplantation. In the autumn of 1958, I learned that the NIH grant would be fully funded for 5 years, and shortly thereafter that I had been selected as a Markle Scholar. The first phase of the canine liver project was nearly completed by the time I finished the thoracic residency and the dual revenue streams began on 1 July 1959. In addition, a second operation had been perfected in which the liver was transplanted as part of an allograft that contained all of the other intra-abdominal viscera (Figure 3) (6,7).

The magnitude of the Markle proposal should have been intimidating, but it did not seem so at the time. The slate of liver transplantation was nearly blank in 1958, but what had to be done was transparent: make the operation biologically sound, make it practical, and find a way to prevent allograft rejection. I was not the only person to think that way. Although I did not learn of it until a year later, Francis D. (Franny) Moore had begun independent efforts to replace the dog liver during the summer of 1958 at the Peter Bent Brigham Hospital in Boston (4,5) that continued until the mid-1960s (87,88).

Moore's transplant interests were not confined to the liver. This can be perceived most clearly by reading his book, *Give and Take* (89) and his autobiography *A Miracle and a Privilege* (90) written 4 decades later. Epitomizing his ubiquitous presence, Moore presided as chief of surgery at the Brigham over the clinical renal transplant trials of Murray and Merrill that yielded the world's first example in any species of $\geq$ one year survival of an organ allograft (91). In this case, the kidney from a fraternal twin was transplanted to his irradiated brother on January 24, 1959, and functioned for the next 20 years without maintenance immunosuppression (Table 2).

From my point of view, this faint signal that the genetic/immunologic barrier to organ alloengraftment might be surmountable made the liver transplant objective less distant. It seemed almost providential that the 5-year Markle Scholarship and NIH funding (1959-64) for my liver project began a few months after the fraternal twin transplantation. The 5 years was equally split between Northwestern where I was elevated to a junior faculty position on 1 July 1959, and the University of Colorado where I was appointed Associate Professor of Surgery and Chief Surgeon at the Denver VA Hospital from November 1961.

The Immune System and Its Control (Theme III)

Until 1958-60 the only organ allograft whose unmodified rejection had been thoroughly studied was the kidney. Rejection to death of our canine liver

recipients usually occurred in 5 to 10 days (3). However, in rare outlyers in which the biochemical indices of rejection improved spontaneously, the liver allograft's dominant histopathologic findings by 3 weeks were those of repair and regeneration (92). These were the first recorded exceptions to the existing dogma (based on skin graft research) that rejection, once started, was inexorable.

In the multivisceral grafts (Figure 3), the pathology was subtly different. Rejection of the various organs if they were part of the multivisceral graft was less severe than when the organs were transplanted alone. Moreover, there was overt evidence in recipient tissues of a graft versus host (GVH) reaction, but without a skin rash or other manifestations of graft versus host disease (GVHD) (7). The double immune reaction (host versus graft [HVG] and graft versus host) exposed by those experiments was shown a third of a century later to be a feature of alloengraftment and acquired tolerance no matter what the transplanted organ (see later).

Both my liver-alone and multivisceral transplant models were generally viewed as technical exercises of little if any scientific interest. One reason was the prevailing view that was concisely expressed in 1961 by the 1960 Nobel Laureate, F.M. Burnet in a New England Journal of Medicine review entitled, *The New Approach to Immunology*. The discouraging passage read: ". . . Much thought has been given to ways by which tissues or organs not genetically and antigenically identical with the recipient might be made to survive and function in the alien environment. On the whole, the present outlook is highly unfavorable to success" (93).

I was poorly equipped to rebut this kind of opinion. My attempts in Chicago to use radiation therapy for canine liver transplantation in 1959-60 failed miserably (94). During this bleak time, however, it was reported in a closely-spaced succession of articles that 6 mercaptopurine and/or its analogue, azathioprine, were immunosuppressive in non-transplant (95,96), rabbit skin graft (97,98), and canine kidney transplant models (99,100). The most extensive kidney transplant experiments were done by the 30 year old English surgeon, Roy Calne (101) who began his studies at the Royal Free Hospital in London in 1959 while still a registrar (resident). The work was continued in Boston with Joseph Murray after July 1960 (102).

In 1961, Calne visited our laboratory in Chicago and described his results. Shortly thereafter, I moved to Colorado, after making the decision to develop a human kidney transplant program there with drug immunosuppression as a forerunner for the liver objective. This would be a bold step since the renal center at the Brigham was the only one in America at the time with an active clinical transplant arm. After demonstrating in parallel canine kidney and liver transplant studies of azathioprine that advances with either organ would be applicable to the other, we concentrated our immunosuppression research on the

simpler kidney model. Our most promising results were obtained by giving daily doses of azathioprine monotherapy before as well as after kidney transplantation, adding postoperative prednisone only when overt rejection developed.

By the time the incremental drug protocol was taken to the clinic in the autumn of 1962, 6 renal allograft recipients treated primarily or exclusively with the total body irradiation protocol of Murray's fraternal twin case (see earlier) had either passed or would soon reach the one year survival milestone, including 2 French patients to whom the donors were not genetically related (Table 2) (91,103-105). In addition, Murray had transplanted a deceased donor allograft in Boston on April 5, 1962, under azathioprine-based immunosuppression (106,107). The kidney was destined to function for 17 months and become the world's first to survive $\geq$ 1 year with a radiation-free (drugs-only) protocol. Enthusiasm generated by this last case was tempered, however, by the fact that the recipient was the only one of the first 10 in the Boston azathioprine series to survive longer than 6 months (details annotated in Ref 108).

Some members of our Denver team concluded from this sobering news that our accrual of more renal transplant cases would be a futile and embarrassing undertaking. My counter argument was that our laboratory-based treatment strategy differed in many ways from the one used in the Boston protocol, including a role of prednisone equal in importance to that of azathioprine. The differences proved to be crucial. First in dogs, and then in human kidney recipients, the graded use of azathioprine and prednisone exposed the 2 features of the alloimmune response that provided the basis for the transplantation of all kinds of organs.

The 2 phenomena were capsulized in the title of a 1963 report of the first-ever series of successful kidney allotransplantations: "*The reversal of rejection in human renal homografts with subsequent development of homograft tolerance*" (8). The principal evidence that the allografts (then called homografts) had somehow induced variable donor specific tolerance was that the reversal of rejection frequently was succeeded by a time-related reduction, or in some cases elimination, of the need for maintenance immunosuppression. In fact, 8 recipients in the 1962-64 Colorado series of 64 still bear the world's longest functioning renal allografts, 45 or more years later (109). Six of the 8 have been off all immunosuppression medications for 12 to 46 years.

Transplantation Outcomes With the Forerunner Kidney (Theme IV)

The > 70% one year patient and renal graft survival in our seminal Colorado series (110,111) exceeded my own expectations, and was not considered to be credible until David Hume in Richmond and others added their confirmatory experience. The world-wide reaction was remarkable. In the spring of 1963, there had been only 3 clinically active renal transplant centers in North America (Boston, Denver, and by now Richmond) and scarcely more in Europe.

One year later, 50 new renal programs in the United States alone were either fully functional or were gearing up.

In reflecting back a dozen years later on the kidney transplant revolution of 1962-64, I began my founding lecture for the American Society of Transplant Surgeons (ASTS) with the comments that: "*From time to time, a news story appears about the birth of a husky, full-term baby, much to the amazement of the chagrined mother who had not realized that she was pregnant. Mother surgery seemed to have been thus caught by surprise when clinical transplantation burst upon the scene in the early 1960s*" (112).

Issues of humanism (Theme V)

Liver transplantation was swept up in the 1962-64 kidney momentum. However, there were many reasons to be cautious, not the least of which were social, ethical, and legal concerns. Throughout 1962, I discussed these issues personally with key non-university persons: the Colorado Governor (John Love), our United State Senator (Gordon Allot), the Denver Coroner, the Chief Justice of the Colorado Supreme Court, and clerical leaders. All ultimately expressed support. Resistance within the University was dealt with by the legendary medical school dean, Robert J. Glaser, and the University Chairman of Surgery, William R. Waddell.

Unprecedented technical challenges were expected. The liver replacement operation, which was difficult even under the optimal circumstances of the animal laboratory, predictably would be harder in recipients with portal hypertension and other pathophysiologic and anatomic changes of chronic liver disease. In the absence of artificial organ support, failure of the hepatic graft to promptly function would be tantamount to death. Finally, how could immediately life-supporting deceased donor livers be obtained in an era in which death was defined as the cessation of heart beat and respiration?

These questions and issues mandated consideration of the less draconian auxiliary hepatic transplant operation of Welch that might allow recipient survival, even if the graft failed. This option was undermined when the rapid atrophy of auxiliary livers that previously had been ascribed to rejection in unmodified dogs (86,113), was shown to be equally severe in animals in which rejection was prevented with azathioprine (11). The die was cast for the liver replacement (orthotopic) option.

THE FIRST HUMAN LIVER TRANSPLANTATIONS

Liver replacement was carried out in 7 deceased donor liver recipients between March 1963 and January 1964: 5 in Denver (cases 1-4 and 6), Boston (case 5 by Moore's team) and Paris (case 7) (Table 3) (10,11,88,114). All 7 patients died, 2 during the operation and the other 5 after 6.5 to 23 days. Neither primary non-function nor uncontrolled rejection of the grafts were lethal factors in any of the failures.

At autopsy of the 4 Denver patients who survived the operation, pulmonary emboli were found that apparently had originated in the bypass tubing used to decompress the blocked systemic and splanchnic venous beds during the removal and replacement of the native liver. Ironically, the bypass which had been an essential component of the canine operation, is not mandatory in most human recipients, or even in dogs if venous collateralization is encouraged by bile duct ligation a month in advance (115).

By the time our fourth and fifth liver recipients were reported to the American Surgical Association in April 1964 (11), all clinical liver transplant activity had ceased in what would be a voluntary 3-1/2 year worldwide moratorium. The self-imposed decision to stop did little to quiet polite but unmistakably disapproving discussions of an operation that had come to be perceived as too difficult to ever be tried again.

THE MORATORIUM

In effect, it now would be necessary to return to ground zero and reexamine all 5 of the themes of Table 1. The central assumption of Theme I had been that portal venous blood contained hepatotrophic molecules. The hypothesis was consistent with our results in 1958-60 in non-immunosuppressed canine recipients of replacement livers (3), and especially with the acute atrophy of Welch's auxiliary grafts in azathioprine-treated dogs (see earlier, and Ref 11). The possibility was now explored of providing the auxiliary allografts with direct access to the portal molecules (116).

But what were the hepatotrophic factors? Using double liver fragment non-transplant models derived from Welch's auxiliary liver operation (Figure 4), it was proved during and after the moratorium that insulin is the principal (although not the only) hepatotrophic molecule in portal blood; that insulin is avidly removed by the liver; and that its primary passage through the hepatic microvasculature is crucial for the maintenance of liver size, ultrastructure, function, and the capacity for regeneration (27,28,116-122). When other molecules subsequently were identified that had insulin-like or diametrically opposite effects (Table 4), hepatotrophic physiology blossomed into multiple research areas of metabolism and regenerative medicine (123,124).

Although the moratorium studies did not support reconsideration of auxiliary liver transplant trials, they added a new dimension to the operation of portacaval shunt which had been used primarily to treat complications of portal hypertension. With the demonstration of the profound effects of portal diversion on protein, carbohydrate (119), and lipid metabolism (121), portacaval shunt was used to favorably alter the course of 3 categories of inheritable metabolic disorders: glycogen storage diseases (125,126), familial hyperlipoproteinemia (127,128), and alpha-1-antitrypsin deficiency (129,130). The dramatic amelioration of the pathophysiology of these diverse conditions (e.g.

hyperlipoproteinemia, Figure 5) presaged their definitive correction with liver replacement (see next section).

Themes II (the surgical operations) and III (immunology) were pursued with both kidney and liver canine transplant models. These efforts included the construction and testing of equipment with which livers could be preserved for one or two days (131), the experimental development and clinical introduction of antilymphoid globulin (ALG) (13,132), and the demonstration that immunosuppression-aided organ tolerance was more frequently induced by the liver than by the kidney (12). In addition, studies of our burgeoning human kidney recipient population clarified the role of HLA matching in all kinds of organ transplantation (14).

Activity also had intensified on the humanism issues (Theme V). The agenda items at medical ethics conferences in 1966-67 (15,16) included human experimentation, living organ donation, informed consent, and the equitable allocation of organs. The most definitive consequence of these discussions was an evolving consensus that the end of life was more appropriately defined by brain death than by the previous criteria of cessation of heart beat and respiration (18).

THE LIVER TRANSPLANT BEACHHEAD

Despite these accomplishments, confidence about our impending liver trial was nowhere near the level that had existed during the run up to the 1963 attempts. The legacy of doubt from the earlier failures was cancelled by a critical new factor. This was the arrival in 1966 of Carl Groth, a 32 year old Fulbright Fellow from Stockholm who joined all of the thematic developments and became a key member of both the donor and recipient teams. With Groth's leadership, multiple examples of prolonged human liver recipient survival were produced in 1967 (Figure 6), using triple drug immunosuppression (azathioprine, prednisone, and ALG) (17).

The first Denver successes were bolstered by the opening in 1968 of a second clinical liver program by Roy Calne in Cambridge, England (133), following preclinical studies in outbred pigs (21,134). The early trials were described in my 1969 book entitled, Experience in Hepatic Transplantation (22), based on our first 25 human liver replacements and 8 performed elsewhere (4 by Calne). Collateral support was provided with the use of the same immunosuppression regimen for the first successful human heart, lung, and pancreas transplantations (135-137) (Table 5). However, the promise of the non-renal procedures, and even of deceased donor kidney transplantation, was unfulfilled for the next dozen years because of immunosuppression-related morbidity and mortality.

Half or more of the liver recipients treated during this time died within the first post-transplant year. The most encouraging observation was that many

patients who survived to this milestone were quietly compiling years of good health thereafter (64,155) (Figure 7). Despite deepening suspicion that progress in the whole field of organ transplantation had permanently stalled, the new French and German liver teams of Henri Bismuth and Rudolf Pichlmayr joined the Denver-Cambridge (Eng) alliance in the early 1970s, followed later in the decade by the Dutch group of Rudi Krom. Much of the medical-scientific, logistic, and administrative framework of hepatic transplantation that exists today was developed by the 5 mutually supportive liver centers during the frustrating period between 1969 and 1979.

Most of the indications for liver transplant candidacy were obvious, including inheritable disorders with a definitive biochemical explanation (e.g. Wilson's disease [23]). The acid test of liver transplantation ultimately would help elucidate the mechanisms or pathophysiology of less well-understood inborn errors: e.g. the 3 diseases that were palliated by portacaval shunt (see earlier). Four patients with alpha-1-antitrypsin deficiency underwent liver transplantation between 1973-1977 (138,139). Liver replacement for treatment of glycogen storage disorders (140,141), hyperlipoproteinemia (44,45), and a growing panoply of other metabolic diseases awaited better immunosuppression.

THE LIVER AVALANCHE

Improvements in therapy were heralded in 1979 by Roy Calne's report of cyclosporine-based immunosuppression in 34 patients, including two liver recipients (33). The side effects of cyclosporine precluded its use as a single agent. However, when it was substituted for azathioprine in our two- or three-drug therapeutic algorithm that included dose-maneuverable prednisone (34), cyclosporine's full potential was realized. Kidney recipients were the first to be treated with liver recipients close behind. Eleven of our first 12 liver recipients treated in Colorado with cyclosporine-based immunosuppression during 1979-80 survived for more than one year (35).

More experience in 1981-82 (now in Pittsburgh) was confirmatory. In December 1981, these findings were reported to C. Everett Koop, the United States Surgeon General, who initiated a Consensus Development Conference for liver transplantation that would include input from the European centers. Prior to the Conference, I prepared a summary of our experience for presentation on November 1, 1982, at the American Association for the Study of Liver Disease (AASLD), and publication in *Hepatology* the same month (36). An updated version was presented to the Consensus Development Conference on June 20-23, 1983.

The consensus committee concluded that liver transplantation had become a "clinical service" as opposed to an experimental procedure (38). The resulting world-wide stampede to develop liver transplant centers was even more dramatic than that of kidney transplantation 20 years earlier. Only 6 years after

the Consensus Conference, a 17 page article equally divided between the October 12 and October 19 issues of the *New England Journal of Medicine* (142) contained a opening statement that, "The conceptual appeal of liver transplantation is so great that the procedure may come to mind as a last resort for virtually every patient with lethal hepatic disease." It already was evident that the need for these operations would greatly exceed both an identifiable source of organs and those qualified to transplant them.

A significant number of the next generation of liver transplant leaders who flocked to Pittsburgh for clinical training during the 1980s were non-surgeons. Their primary connection was with David Van Thiel (Figure 8), the brilliant gastroenterologist who became a founding doyen of transplantation hepatology along with his English counterpart, Roger Williams of the Cambridge-King's College program. During this volatile period, preclinical studies of tacrolimus were begun that would lead to its substitution for cyclosporine (56,57) with fast-track FDA approval in November1993. With tacrolimus, the multivisceral and intestine-alone transplant procedures developed 3 decades earlier in dogs (Figure 3) achieved the status of a genuine "clinical service" (61,62). The timing was perfect. With arrival of my 65th birthday in 1991, I retired from active surgical practice.

THEMATIC EPILOGUE: 1991 - 2009

Most of the advances in liver transplantation during the succeeding 18 years (Table 1) have been derivative from earlier work including the use of partial livers from deceased or living volunteer donors. However, the antecedent contributions with which the taxonomical foundation of organ transplantation was built have been obscured with the advent of the World Wide Web (www). Many of the referenced articles of the foregoing narrative cannot be accessed online in full text, and some have become invisible. With the dearth of electronic information from before the 1990s and the convenience of citing easy internet finds, the recent literature has been replete with observations, events, and concepts that were described more clearly years or decades before. Nevertheless, there have been new trends in organ transplantation, 2 of which were driven mainly by the liver.

The Exegesis Of Alloengraftment

A major gap in immunology (Theme III) when I stopped surgical practice was the inability to explain why organ transplantation had been possible. Because organ recipients were not infused with donor leukocytes, it became dogma by the early 1960s that the donor leukocyte chimerism associated with acquired tolerance in experimental models was not a factor in organ engraftment. The dogma was not challenged until we discovered small numbers of multilineage donor leukocytes (microchimerism) in the blood or tissues of all

studied long-surviving liver, kidney, and other organ recipients (63,64,143). These findings in 1992-93, and an array of supporting experimental studies in congenic rat (144-150) and mouse models (151-154) mandated a change in the previously perceived landscape of transplantation immunology.

It was proposed (63,64,155,156) that organ transplantation was the equivalent of a bone marrow transplantation. The key step leading to rejection, or alternatively alloengraftment, after both kinds of transplantation was hematogenous migration of leukocytes (including stem cells [157-159]) to the recipient's lymphoid organs (Figure 9). Otherwise, the presence of the allograft would not be recognized: i.e. the "immune ignorance" (160,161) first described in a transplant model by Clyde Barker and Rupert Billingham 42 years ago. The seminal mechanism of alloengraftment was exhaustion-deletion of the T cell response (162,163) induced at the host lymphoid sites by the invading cells (Figure 9). Because the migrant donor leukocytes are immune competent, successful alloengraftment involved a double immune reaction in which immune responses of coexisting donor and recipient cells, each to the other, were reciprocally exhausted and deleted under a protective umbrella of immunosuppression (Figure 10).

Our interpretation of the microchimerism was at first highly controversial (164,165) because it was incompatible with multiple theories and hypothesis that made up much of the base of transplant immunology. Resistance to the new concept was eroded when Rolf Zinkernagel in Zurich independently proposed an explanation of acquired tolerance to pathogens that was essentially the same as that of our allotolerance paradigm. In the 1970's, Zinkernagel and Doherty had demonstrated that the MHC-restricted cytolytic T cell response induced by noncytopathic microorganisms was the same as that induced by allografts. These studies were done in highly controlled experimental models of infection with the lymphocytic choriomeningitis virus (LCMV) and other intracellular parasites (166). Their subsequent investigations of tolerance were done with the same models and described in 4 landmark articles between 1993 and 1997 (167-170).

With recognition that the Pittsburgh and Zurich investigations were on parallel pathways, a joint author review was published in a December 1998 issue of the *New England Journal of Medicine* in which analogous scenarios were described of transplantation and pathogen-specific infections (e.g. chronic rejection vis a vis chronic viral hepatitis) (65). The concept developed from transplant and infection models was generalized in the following way: "The migration and localization of antigen govern the immunologic responsiveness or unresponsiveness against infections, tumors, or self --- and against xenografts or allografts" (65). In this view, all outcomes in the divergent circumstances of transplantation including those of microchimerism (150,171,172) were determined by the balance established between the amount of mobile donor leukocytes with access to host lymphoid organs and the number of donor-specific

cytolytic T-cells (CTL) induced at the lymphoid sites (Figure 11, inner graphic) (65).

Long term organ alloengraftment with this generalizable paradigm, was a highly variable form of leukocyte chimerism-dependent tolerance, the completeness of which could be inferred from the amount of immunosuppression necessary to maintain stable function and structure of the transplant (Figure 11). In a second article with Zinkernagel, the Pittsburgh-Zurich immunologic paradigm provided a road map for improved therapeutic strategies of transplant patient management based on 2 principles: recipient pretreatment, and the least possible use of post-transplant immunosuppression (68). When applied clinically for different kinds of organ transplantation (69), these strategies have minimized, or in some cases eliminated, the burden of chronic immunosuppression (173-178). More rational approaches also were developed for the treatment of opportunistic infections caused by noncytopathic microorganisms (70,168,179).

Reporting of Transplantation Outcomes (Theme IV) and Equitable Organ Allocations (Theme V)

A second trend coincided with and was empowered by the rise of the internet. One of the mandates of the 1984 National Transplant Act was the formation of an organ procurement and transplantation network (OPTN). Another was the development of a scientific registry of transplant recipients (SRTR) with which patient and graft survival could be quantified from center to center along with center-specific parameters. After the Department of Health Resources and Services Administration (DHHS) awarded the contract for both functions to the United Network of Organ Sharing (UNOS), disputes about organ allocation within the appointed UNOS committee prevented the development of the required plan. In order to avoid a UNOS default of contract, a document was pieced together from 2 articles In Press describing the renal (180) and non-renal (181) distribution systems already in place in Pittsburgh.

In the contract derived from these manuscripts and presented to DHHS on the eve of the deadline, the overwhelming factor for liver distribution was recipient urgency of need (181). In contrast, time waiting dominated kidney distribution with major credit for HLA matching only when this was complete (180). Although these policies were accepted by DHHS and provisionally implemented in November 1987, they were widely abridged (182) until the final regulations were issued by DHHS on April 2, 1998. During the chaotic intervening decade (see Supplementary Index for a cryptic description of the "liver wars"), UNOS led the opposition to adoption of the regulations and withheld access to SRTR. A Lancet Editorial during the heat of the debates suggested that: "UNOS would better serve the transplant community if it abandoned its stance and began working with DHHS to draw up allocation policies that are practical and fair (183)".

One of the most contentious issues was the conclusion in a large Pittsburgh study published in 1994 that liver transplantation performed too early was associated with a net loss of recipient life years (184,185). These findings led to retention of the "sickest first" policy in both the provisional and final DHHS rules for liver allocation. In the meanwhile, the continued resistance to release of center-specific data, as well as inaccuracies and inconsistencies in the first SRTR reports (1992, 1995, 1997), led to transfer of SRTR management to the University of Michigan-based Arbor Research Collaborative for Health. An Arbor multicenter study in 2005 confirmed the original Pittsburgh findings about the timing of liver transplantation and came to the same policy recommendations (186).

Until now, success with liver transplantation has been judged largely by relatively short term patient and graft survival. A more complete profile has been made possible by the use of the treatment-based evaluation system of Clavien in which the rate and severity of complications (including death) are quantified with a 5-tier scale (71). The value of this objective assessment was exemplified by a recent Pittsburgh study of right lobar living donor liver transplantation (187). The Clavien metric is applicable to all kinds of organ transplantation, and has been generalized to other surgical and medical procedures (188).

CONCLUSION

Liver transplantation began with almost no resources at the same time as the tentative first steps were taken to land a man on the moon. Because human lives would be at stake, both objectives had a sacramental element from the outset: i.e. a solemnly binding commitment to perfection. A need for that pledge still exists.

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TABLE 1 --- MILESTONES OF LIVER TRANSPLANTATION,

COLOR-CODED ACCORDING TO 5 DEVELOPMENTAL THEMES*,**

YEAR	DESCRIPTION	REFERENCE	THEME
1955	First article in the literature on auxiliary liver transplantation	1	I,II
1959-1960	Models described of canine total hepatectomy and liver replacement	2-5	I,II
1960	Canine abdominal multivisceral transplant model described	6,7	I,II
1963	Azathioprine-prednisone cocktail introduced (kidneys first, then livers) with recognition of organ-induced tolerance	8	III
1963	*In situ* preservation-procurement of cadaveric organs described	9,10	II
1963	First attempts to transplant the human liver with maximum survival of 3 weeks	10	IV
1960-1965	Evidence reported of hepatotrophic factors in portal venous blood	3,11	I
1965	Liver induced tolerance under a short course of azathioprine reported in dogs	12	III
1966	Clinical introduction of antilymphoid globulin (ALG) for kidneys, then liver recipients	13	III
1966-1970	Evidence that HLA matching would not be a major factor in cadaveric organ transplantation	14	III
1966-67	First biomedical ethical conferences centered on transplantation	15,16	V
1967	First one-year survivals after human liver replacement	17	IV
1967-1968	Acceptance of brain death concept	18	V
1967-1969	Liver-induced tolerance in pigs without immunosuppression	19-21	III
1969	First textbook on liver transplantation based on 25 Denver cases	22	*ALL*
1969	First inborn error (Wilson's disease) to be cured with liver transplantation	23	I
1973	Surprising first evidence that the liver controls cholesterol homeostasis	24,25	I
1973	Description of the liver's resistance to ABO and cytotoxic antibody-mediated rejection	26	III
1973-1975	Principal portal blood hepatotrophic factor identified as insulin	27,28	I
1976	Causes of failure analyzed among first 93 Colorado cases of liver transplantation	29	IV
1976	Improved slush liver preservation permitted long-distance procurement	30,31	II
1979	Systematic use of arterial and venous grafts for cadaver liver revascularization	32	I
1979	Cyclosporine introduced for organ transplantation including 2 liver recipients	33	III
1980	Cyclosporine-steroid cocktail introduced clinically	34	III
1981	80% one year liver recipient survival reported using cyclosporine-prednisone	35	IV
1982	Review of progress in liver transplantation generates widespread interest of hepatologists	36	IV
1983	Introduction of pump-driven venovenous bypass without anticoagulation during liver transplantation	37	II
1983-1995	USA consensus development conference conclusion that liver transplantation is a service (1983) is followed by the US National Organ Transplantation Act of 1984	38	V
1984	Standardization of *in situ* preservation-procurement techniques for multiple organ cadaver donors (Derivative from Refs 9, 10)	39,40	II
1984	Reversibility reported of B cell malignancies (PTLD) in liver and other organ recipients	41	III
1984	Reports of reduced-size liver grafts for pediatric recipients	42,43	II
1984	Liver transplantation of patient with hypercholesterolemia verified hypothesis that the liver is the site of cholesterol homeostasis	44,45	I

1987-1989	First successful transplantation of liver-inclusive multivisceral grafts	46,47	IV
1987	University of Wisconsin (UW) solution improves preservation of liver and other organs	48-50	II
1987	Successful extensive use of livers from "marginal" donors reported	51	IV
1988	Published Pittsburgh point systems used verbatim for UNOS contract for cadaver kidney and liver distribution in compliance with Organ Transplant Act of 1984	52,53	V
1989	Popularization of the "piggy back" variation of liver transplantation	54	II
1989	Liver-pancreas "cluster allograft" described after upper abdominal excenteration	55	II
1989	Clinical introduction of FK 506 (tacrolimus)-based immunosuppression	56,57	III
1989	First report of split cadaver liver for transplantation into 2 recipients	58	II
1990	First successful use of living volunteer liver donors (left side fragments)	59,60	II
1992-1993	Practical use of multivisceral transplantation made feasible by tacrolimus	61,62	IV
1992-1993	Discovery of donor leukocyte microchimerism in liver (and other organ) recipients, places organ and bone marrow cell transplantation on common ground.	63,64	III
1998	Delineation of analogies between transplantation and infection immunology	65	III
1994-1999	Live donor transplantation of large right side liver fragments	66,67	IV, V
2001	Mechanism-based tolerogenic immunosuppression proposed	68	III
2003	Clinical use of tolerogenic immunosuppression	69	III
2005	Mechanisms elucidated of accelerated recurrent viral hepatitis in allografts	70	III
2005	Use of Clavien's metric for evaluating liver transplant outcomes	71	IV,V

***1. Green: Hepatotrophic Physiology, 2. Red: Transplant Models,**
3. Blue: Immunology, 4. Pink: Survival Results, 5. Brown: Humanism Issues

****With major co-themes, the text color is of the dominant one**

Abbreviations: UW = University of Wisconsin; PTLD = Post-transplant lymphoproliferative disorders

TABLE 2

CHARACTERISTICS OF THE FIRST SUCCESSFUL TRANSPLANTATION OF KIDNEY ALLOGRAFTS WITH >6 MONTHS SURVIVAL AS OF MARCH 1963

PHYSICIAN	REF	SITE	DATE	DONOR RELATIONSHIP	GRAFT SURVIVAL
Joseph E. Murray	91	Boston, Massachusetts	January 24, 1959	Fraternal twin	20 years[b]
Jean Hamburger	103	Paris, France	June 29, 1959	Fraternal twin	26 years[b]
Rene Kuss	105	Paris, France	June 22, 1960	Unrelated	18 months[b]
Jean Hamburger[a]	104	Paris, France	December 19, 1960	Mother	22 months[b]
Rene Kuss[a]	105	Paris, France	March 12, 1961	Unrelated	18 months[b]
Jean Hamburger[a]	104	Paris, France	February 12. 1962	Cousin	15 years[c]
Joseph E. Murray	106,107	Boston, Massachusetts	April 5, 1962	Unrelated	17 months[b,d]
Thomas E. Starzl	8,108-9	Denver, Colorado	1962-1963	First Series: A mixture	$\geq$ 45 years

[a]Kuss and Hamburger described periodic administration of adrenal cortical steroids with these patients.
[b]Patient death occurred at or shortly after listed time.
[c]Patient underwent successful retransplantation in the 1970s; elected to French Parliament.
[d]First successful with drugs-only immunosuppression (no radiation).

TABLE 3

FIRST RECIPIENTS OF REPLACEMENT LIVERS

AGE	DATE	CITY (REF)	LIVER DISEASE	SURVIVAL (DAYS)	MAIN CAUSE OF DEATH
3	3-1-63	Denver (10)	Biliary Atresia	0	Intra-op Bleeding
48	5-5-63	Denver (10)	Hepatoma, Cirrhosis	22	Pulmonary Emboli, Sepsis
68	6-3-63	Denver (10)	Duct Cell Carcinoma	7.5	Pulmonary Emboli
52	7-10-63	Denver (11)	Hepatoma, cirrhosis	6.5	GI bleeding, pulmonary emboli/edema, liver failure
58	9-16-63	Boston (88)	Colon metastases	11	Pneumonitis, hepatic abscesses, failure
29	10-4-63	Denver (11)	Hepatoma	23	Sepsis, bile peritonitis, pulmonary emobli
75	1-?-64	Paris (114)	Colon metastases	0	Intraoperative hemorrhage

TABLE 4

HEPATOTROPHIC FACTORS REVEALED BY 1994 WITH PORTAL DIVERSION, DOUBLE LIVER FRAGMENT, OR PARTIAL HEPATECTOMY MODELS*
Annotated in Hepatology 20:747-757, 1994 (Ref 124)

Hepatotrophic

Hormones:
- Insulin

Growth factors:
- Cytosol substrate and ALR
- IGF II
- TGF-α [a]
- HGF [a]

Immunosuppressants:
- Cyclosporine
- Tacrolimus

Immunophilins:
- $FKBP_{12}$

Anti-hepatotrophic

Growth factors:
- TGFβ [b]

Immunosuppression:
- Rapamycin [b]

*It is noteworthy that numerous humeral and cellular mechanisms involved in liver size homeostasis and regeneration (not shown here) are the same as those involved in immunologic responsiveness (rejection) and unresponsiveness (tolerance).
[a]Mitogenic in tissue culture
[b]Inhibitory in tissue culture

TABLE 5

THE DOMINO EFFECT IN 1968-69 OF THE 1967 FIRST SUCCESSFUL HUMAN LIVER TRANSPLANTATIONS

ORGAN	CITY	DATE	PHYSICIAN/ SURGEON	REF
Kidney	Boston	1/24/59	Merrill/Murray	91
Liver	Denver	7/23/67	Starzl	17
Heart	Cape Town	1/2/68	Barnard	135
Lung*	Ghent	11/14/68	Derom	136
Pancreas**	Minneapolis	6/3/69	Lillehei	137

***Patient died after 10 months; all others in table lived >one year with functioning graft. The first >one year survival of isolated lung recipients was not reported until 1987.**

****Kidney and pancreas allografts in a uremic patient.**

FIGURE LEGENDS

Figure 1 --- Auxiliary liver homotransplantation in dogs (the Welch procedure). Note that the portal venous inflow of the extra liver is from the inferior vena caval bed while the native liver retains a normal blood supply. It was suspected from the beginning that this was a major flaw in the design of the procedure. From: Ann Surg 160:411-439, 1964.

Figure 2 --- Complete liver replacement in the dog circa 1958-9. The fact that this was a canine rather than a human operation is evident only from the small multiple lobes of the allograft and the biliary drainage with cholecystoduodenostomy. In my first report (3), an "outflow block" syndrome resembling endotoxin shock was described if donor body weight was less than half that of the recipient (one cause of today's "small for size" syndrome).

Figure 3 --- Bottom Center: Multivisceral allograft transplanted in dogs in 1959 (6,7) and in humans for the first time 3 decades later (46). With removal of different organs from the common vascular stem, this original procedure has had many subsequent variations. Lower Left: Liver-intestinal transplantation (47,62). Top Middle: Cluster of upper abdominal organs (55). Right: Mid gut organs except the liver. From: Liver Transplant & Surg 4:1-14, 1998.

Figure 4 --- The double liver models that led to progressively precise identification of the hepatotrophic factors that influenced liver size, ultrastructure, function, and the capacity for regeneration: (A) Welch's index operation of auxiliary liver allotransplantation (see also Figure 1); (B) non-transplant split liver model that differentiated the effect on the liver of systemic venous (vena caval) versus splanchnic (portal) blood; (C) separation with the double liver fragment model of the qualities of venous blood from the upper and lower abdominal viscera; and (D) selective infusion of candidate hepatotrophic molecules into one or the other of 2 liver fragments, both of which had an arterial supply only. From: Liver Transplant & Surg 4:1-14, 1998.

Figure 5 --- The dramatic effect of portacaval shunt on serum cholesterol concentration in a child with homozygous familial hyperlipoproteinemia. These observations (24) and canine studies of lipid synthesis with the models shown in Figure 4 (25) suggested that the liver was the principal site of cholesterol homeostasis. Although we considered familial hyperlipoproteinemia to be a candidate disease for liver replacement from the mid 1970s, this was not accomplished until February 14, 1984 (44,45) by which time more evidence that this was an appropriate step was obtained in New York, Bethesda, and Dallas. Interactions over more than a dozen years between experts in cholesterol metabolism in these cities and the author (TES) are described in the chapter

"The Little Drummer Girls" of The Puzzle People (128). From: Lancet 2:940-944, 1973

Figure 6 --- The first 3 human recipients with prolonged survival following liver replacement in July and August, 1967. The adult, Carl Groth, was a Swedish surgeon-in-training whose tenures in Denver as a Fulbright Scholar (1966-68) and faculty member (1970-71) were near the beginning of his Olympian career. After returning to Stockholm to occupy a Chair in transplantation surgery created for him at the Karolinska Institute, Groth developed the multiorgan transplant program that produced the first liver transplantations in Sweden. His numerous honors include the King's Medal of his country and the Medawar Prize, the highest distinction of the international Transplantation Society.

Figure 7 --- World's longest surviving liver recipient whose 40th post-transplant anniversary will take place January 22, 2010. The primary disease diagnosis was biliary atresia, but the right lobe of her excised liver contained an incidental 2.7 x 1.8 centimeter hepatoma. The serum alpha fetoprotein level was 6 mg/cm at one post-transplant month, trace-present at 4 months, and undetectable since (Ref 189). The patient's companion, now a retired United States Marine, is her husband of many years. The statue behind them is Roberto Clemente (1934–1972), the greatest baseball right fielder of all time who was killed bringing food by air flight to victims of the catastrophic Nicaraguan earthquake.

Figure 8 --- David Van Thiel (1941-), gastroenterologist-hepatologist without whose herculean efforts, the University of Pittsburgh liver transplantation program could not have been established.

Figure 9 --- The cell migration and localization of organ and bone marrow cell transplantation. Organs (here a liver) are composites of architecturally fixed cells and mobile multilineage cells of bone marrow origin ("passenger leukocytes") that include pluripotent hematolymphopoietic stem cells (157-159). Within minutes after organ transplantation, the passenger leukocytes simulate a bone marrow cell infusion by migrating selectively to recipient lymphoid organs where they induce the depleted antidonor T cell response. Although the clonal response normally destroys the invading donor cells and their outlying source organ (rejection), the response may be exhausted and deleted if it is too weak to eliminate the invading donor cells during the first few weeks of maximal cell migration. Perpetuation thereafter of survival of the bystander organ allograft requires persistence of enough donor leukocytes to maintain the initial exhaustion-deletion. Importantly, the invading donor cells are immune competent and their response against the recipient also must be exhausted and deleted for a successful transplant outcome (see Figure 10).

Figure 10 --- The kinetics of immunosuppression-aided exhaustion and deletion of the contemporaneous host versus graft (HVG, upright curve) and graft versus host (GVH, inverted curve) responses in organ recipients following the cell migration shown in Figure 8. Although HVG is the dominant response in most organ recipients (expressed as rejection), serious or lethal GVH reactions (expressed as graft versus host disease [GVHD]) are not rare in recipients of lymphoid-rich organs (liver, intestine). In naturally immune deficient or cytoablated bone marrow cell recipients, GVHD is avoided by using histocompatible (HLA-matched) donors. Therapeutic failure after either organ or bone marrow cell transplantation implies the inability to control one, the other, or both of the responses. From New Engl J Med 339:1905-1913, 1998.

Figure 11 --- The many faces of transplantation tolerance.
Outer Circle: The continuum of experimental and clinical donor leukocyte chimerism-associated tolerance models that can be traced back to observations in 1945 in freemartin cattle (upper left) whose fused placentas permitted fetal cross-circulation, blood chimerism, and reciprocal immune nonreactivity.

Inner Graphic: Permutations of tolerance defined as balances between persisting migratory donor leukocytes and the number of antidonor T cells undergoing steady state exhaustion-deletion. The achievement of balances and the resulting clinical phenotypes are influenced by the dose, type, and timing of immunosuppressive therapy and by the dose, type, timing, route, and localization of the migrant donor cells. The single most important factor leading to the macrochimerism of bone marrow cell transplantation versus the microchimerism of most organ (and composite tissue) recipients is enfeeblement of recipient immune reactivity before the arrival of donor cells in the first instance and after their arrival in the second. The non-specific potential "stabilizing factors" in the left-directed arrow above the human silhouette include special cells (e.g. T-regulatory), enhancing antibodies, graft secretions, and endogenous cytoprotective molecules.

Figure 1

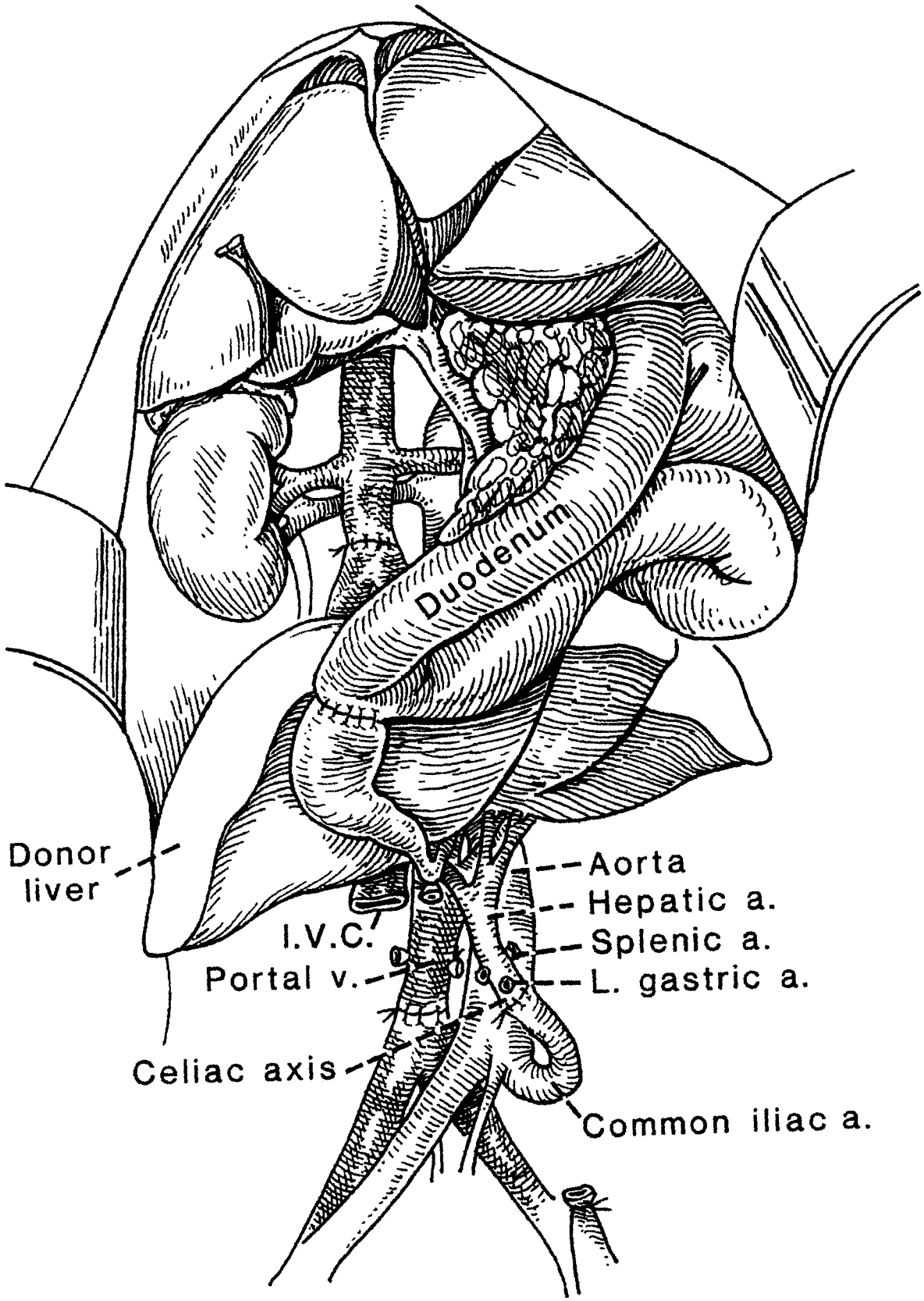

Duodenum
Donor liver
Aorta
Hepatic a.
I.V.C.
Splenic a.
Portal v.
L. gastric a.
Celiac axis
Common iliac a.

Figure 2

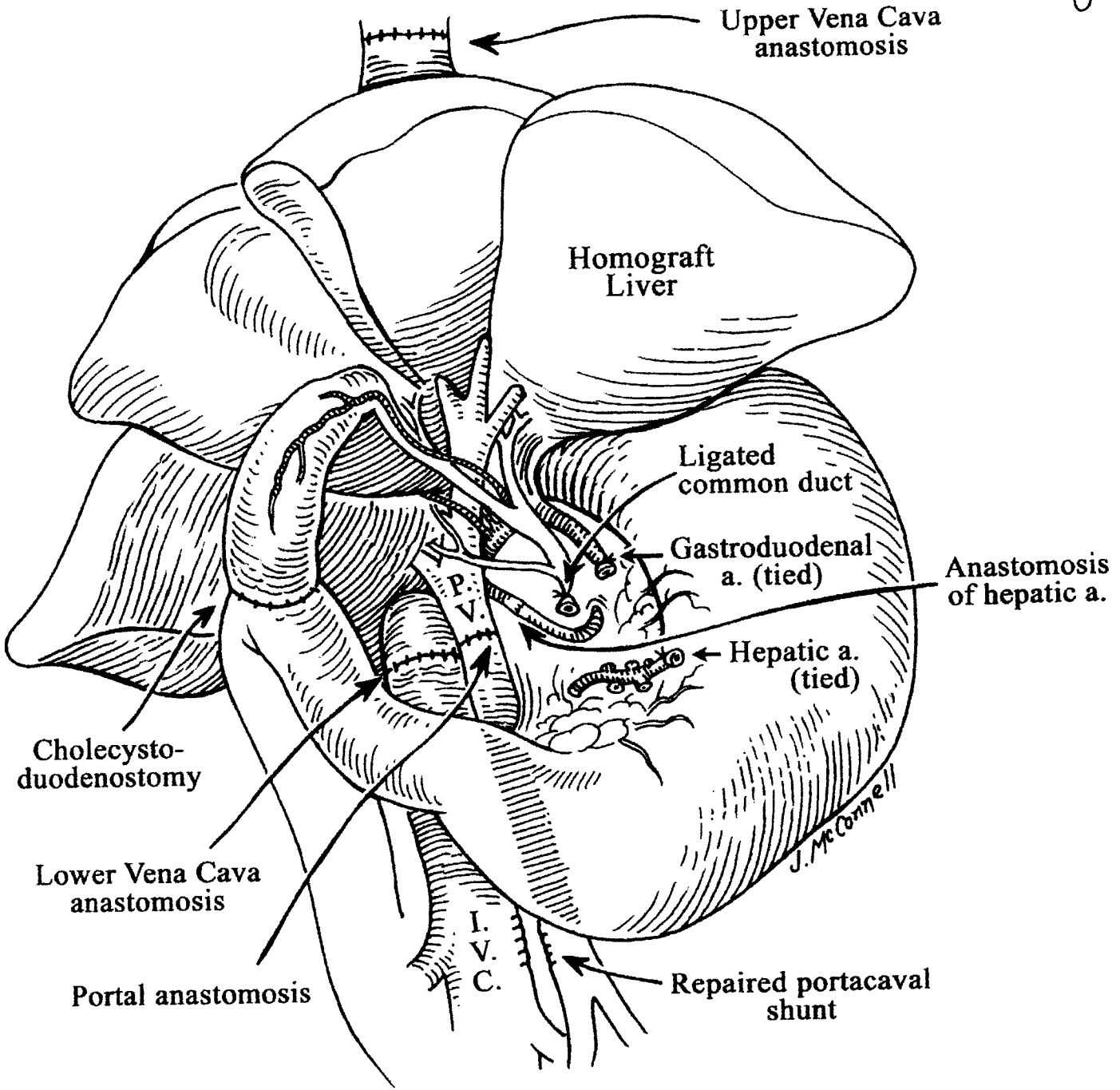

Upper Vena Cava anastomosis
Homograft Liver
Ligated common duct
Gastroduodenal a. (tied)
Anastomosis of hepatic a.
P. V.
Hepatic a. (tied)
Cholecysto-duodenostomy
Lower Vena Cava anastomosis
Portal anastomosis
I. V. C.
Repaired portacaval shunt
J. McConnell

FIG 3

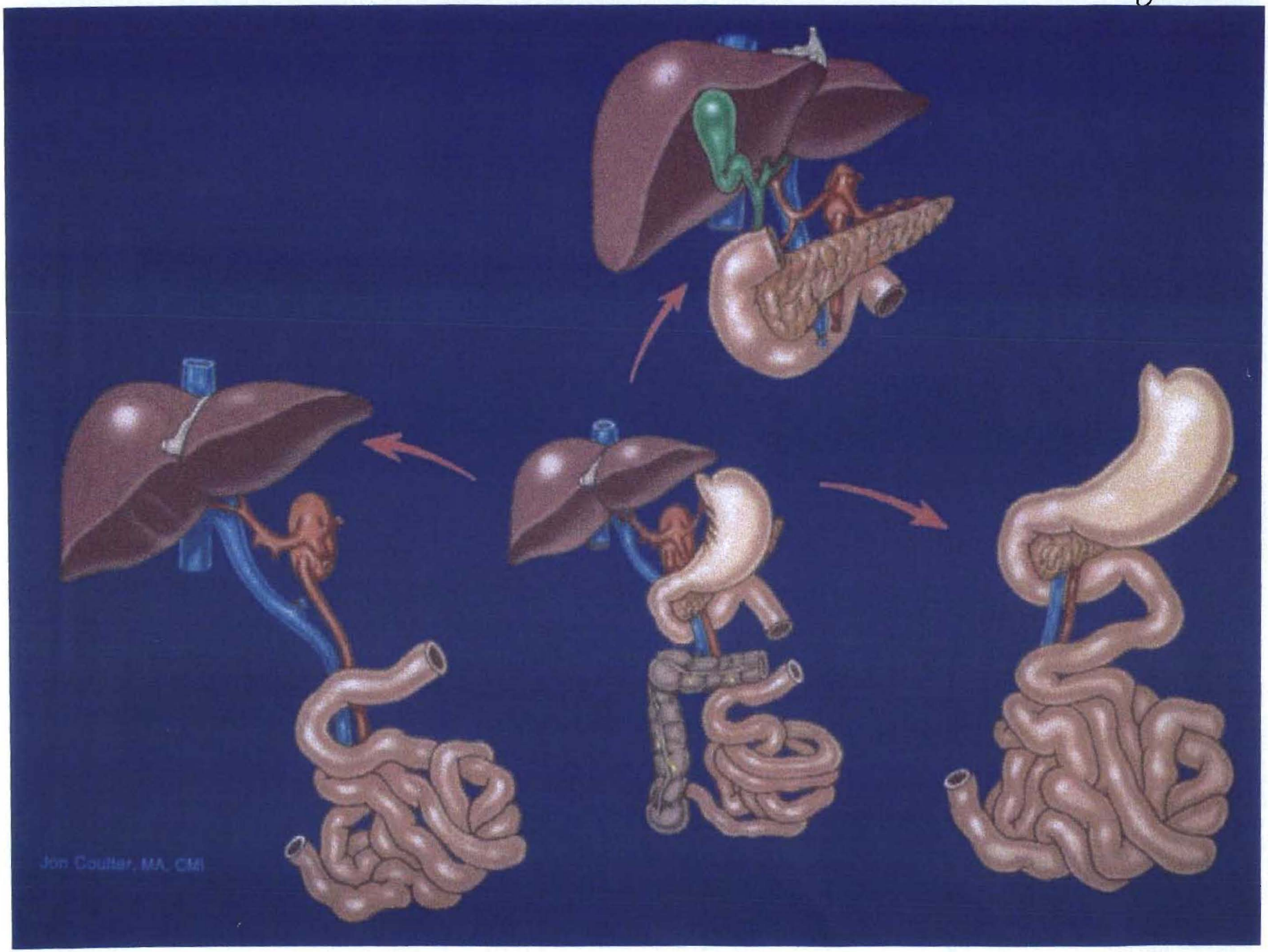


Fig4

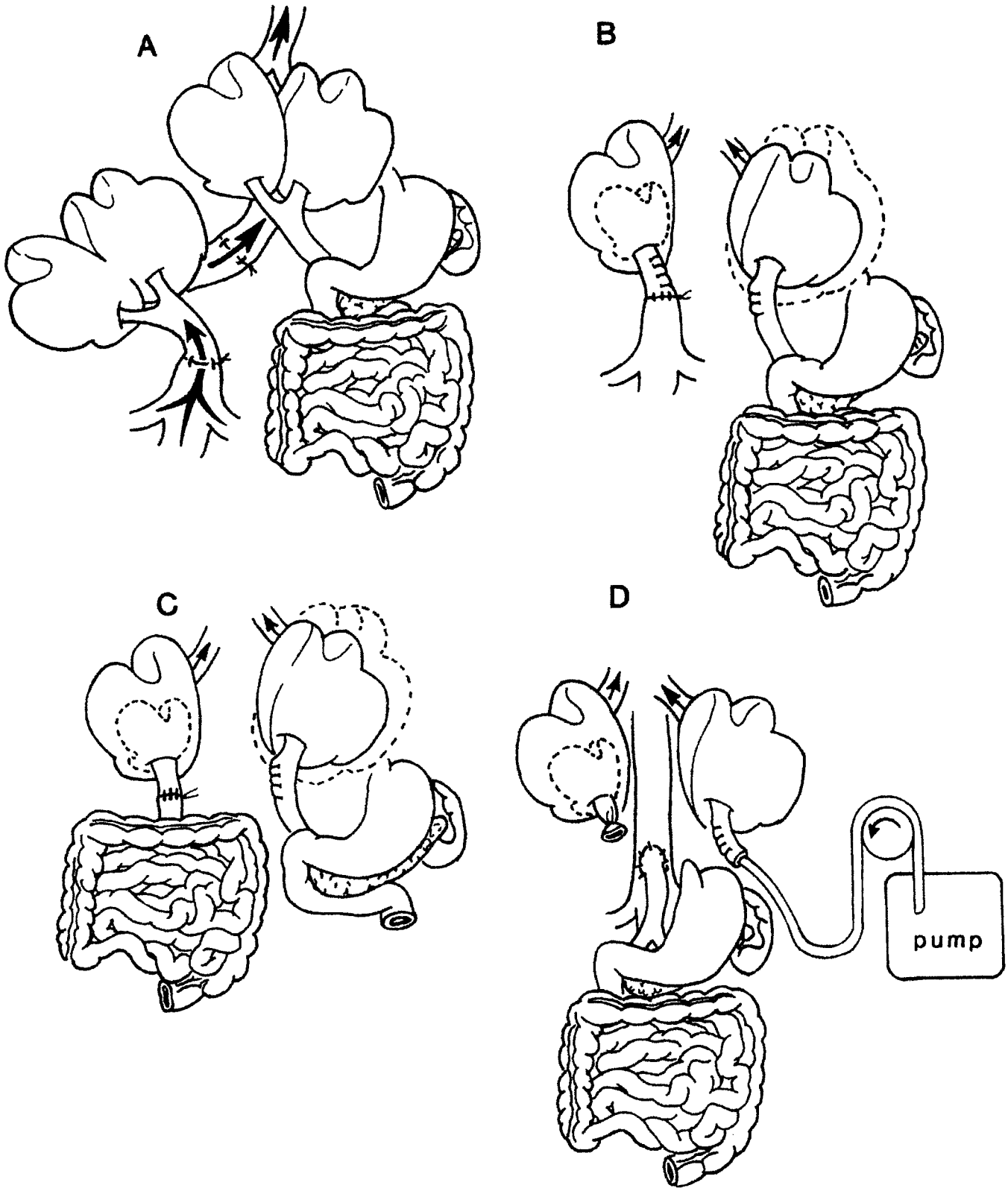


Figure 5

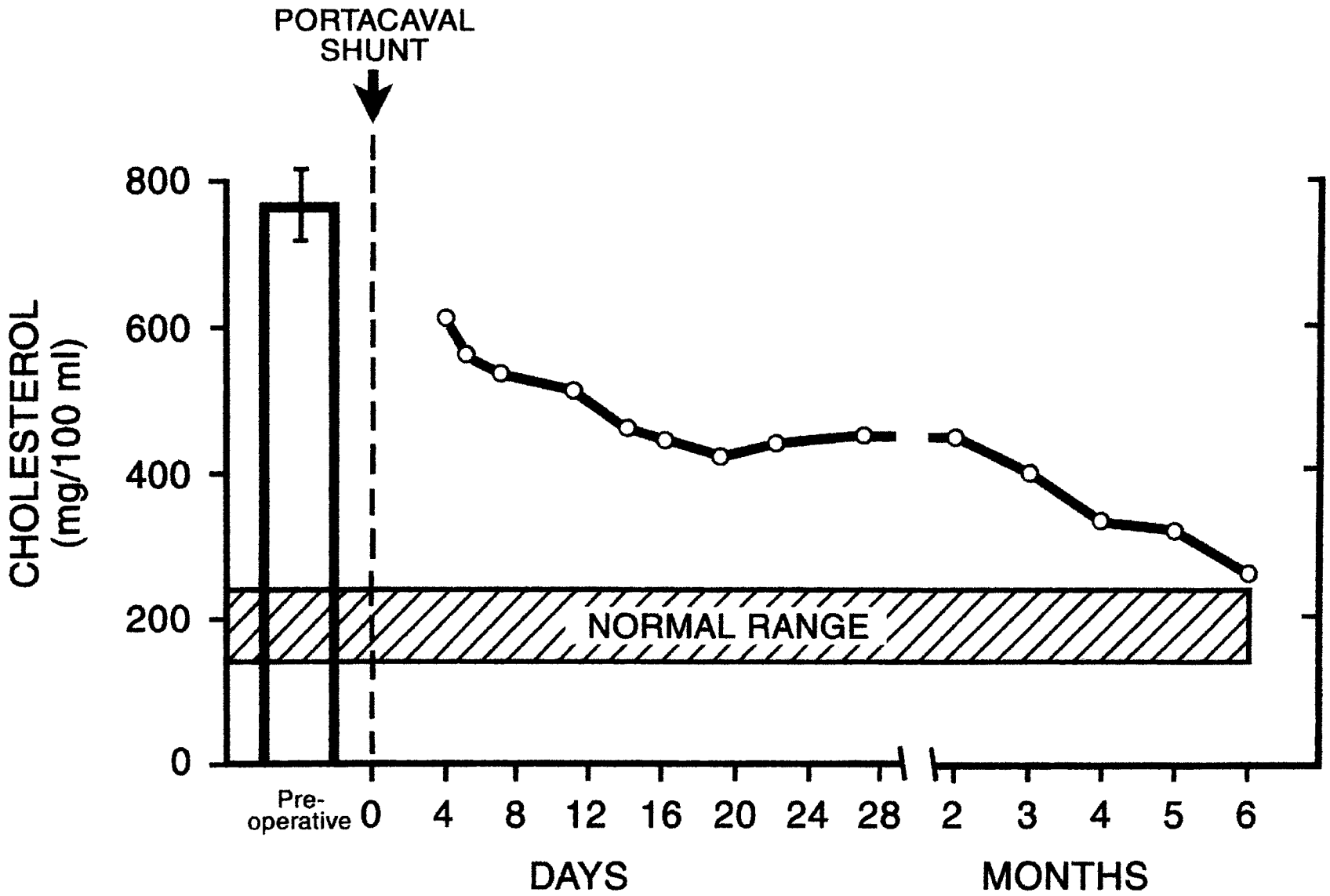

PORTACAVAL
SHUNT
CHOLESTEROL
(mg/100 ml)
800
600
400
200
0
NORMAL RANGE
Pre-
operative
0
4
8
12
16
20
24
28
2
3
4
5
6
DAYS
MONTHS

FIGURE 6

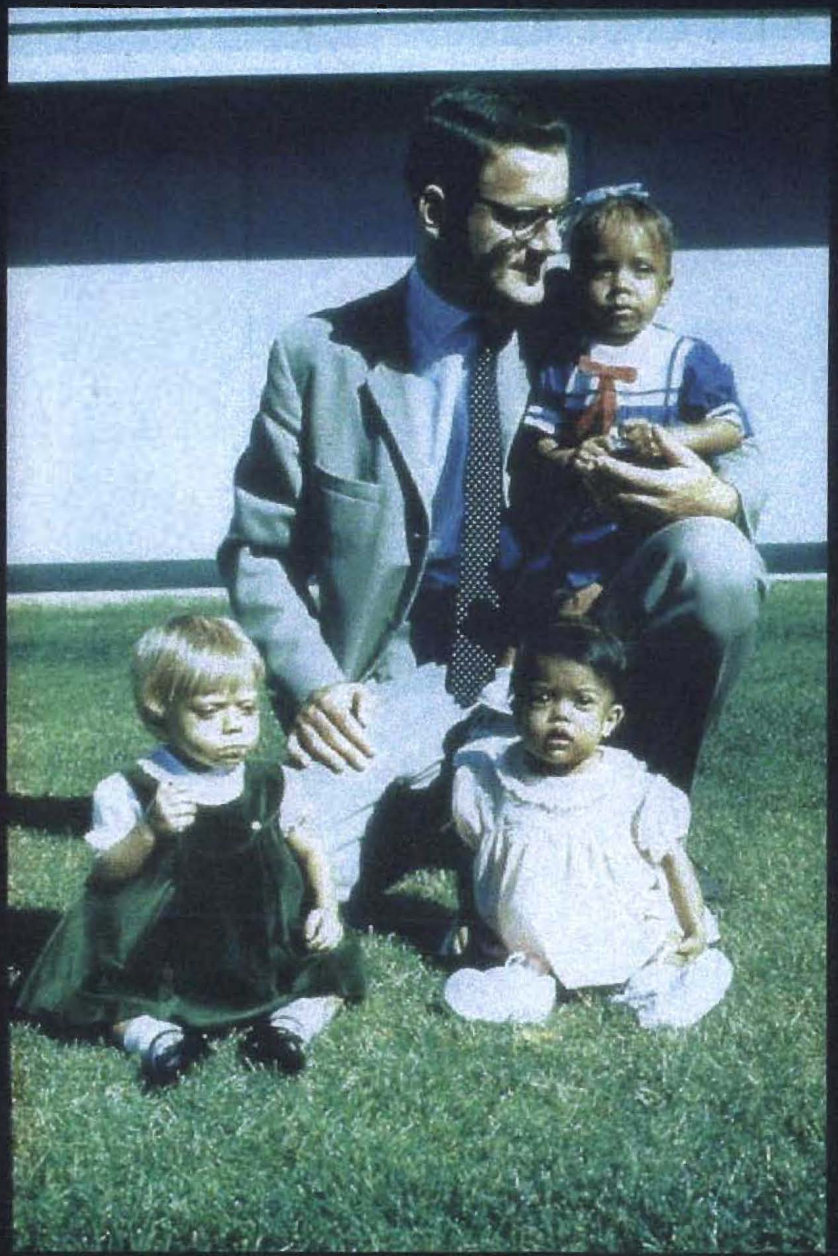


Figure 7

Fig 7B

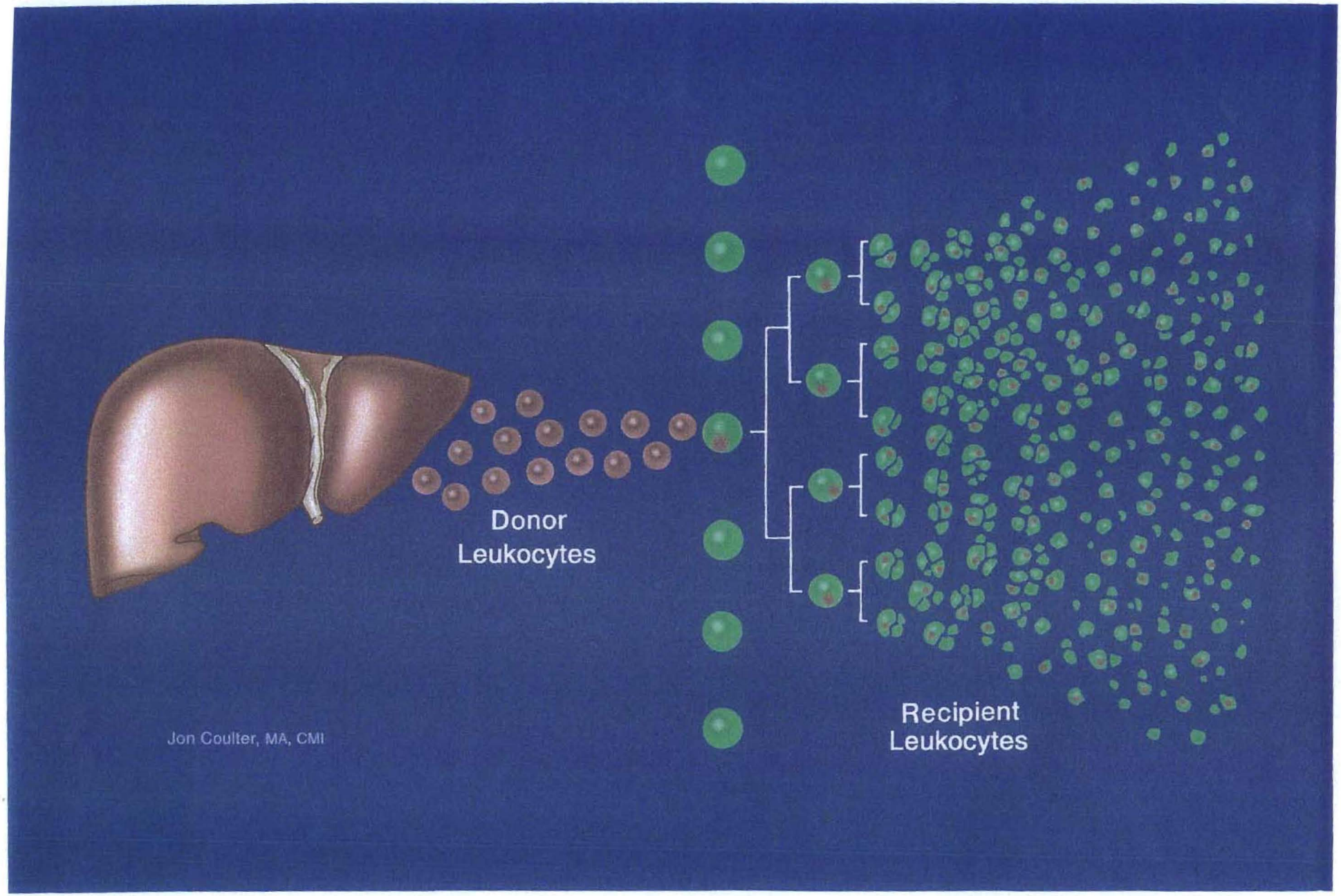


Figure 10

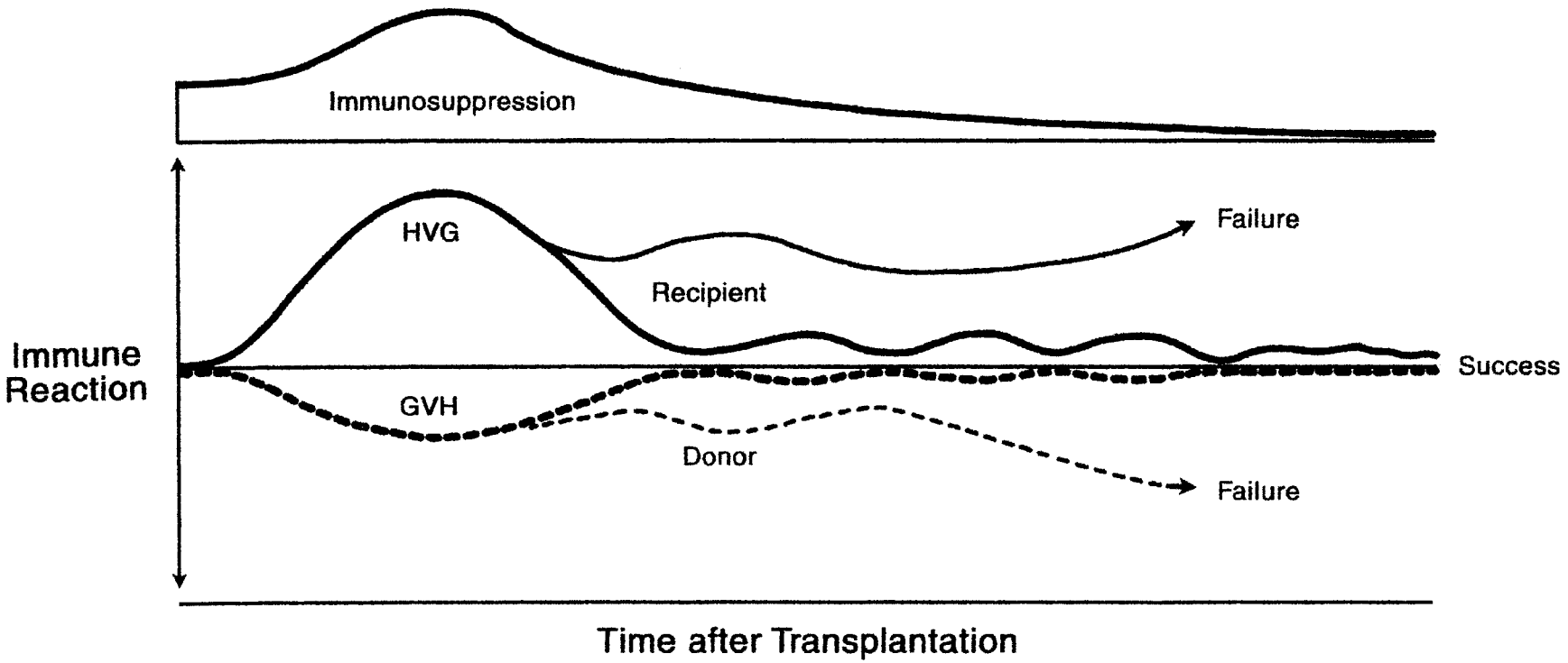
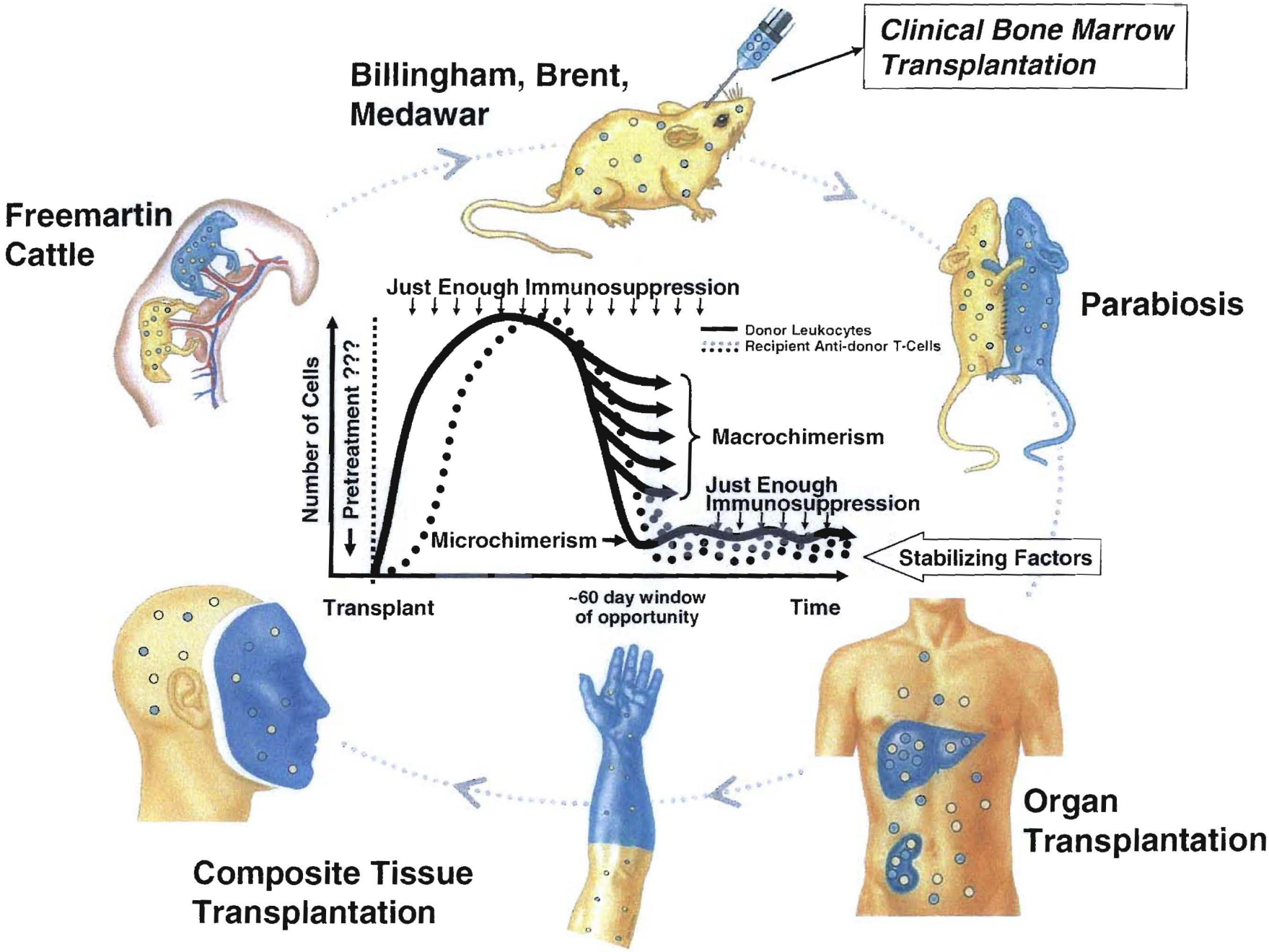

Immunosuppression
HVG
Failure
Recipient
Immune Reaction
Success
GVH
Donor
Failure
Time after Transplantation

Figure 11


Clinical Bone Marrow Transplantation
Billingham, Brent, Medawar
Freemartin Cattle
Parabiosis
Just Enough Immunosuppression
Donor Leukocytes
Recipient Anti-donor T-Cells
Number of Cells
Pretreatment ???
Macrochimerism
Just Enough Immunosuppression
Microchimerism
Stabilizing Factors
Transplant
~60 day window of opportunity
Time
Organ Transplantation
Composite Tissue Transplantation

SUPPLEMENTARY APPENDICES

1. Supplementary Appendix #1: The Neuroscience Interval

   Item A: A 1991 letter written by the author (TES) in response to a request by Dr. Louise Marshall who was writing a history of the UCLA Brain Institute.
   Item B: A related letter written in December 1951 from Professor H.W. Magoun to Dr. Alfred Blalock, supporting the candidacy of TES for a Johns Hopkins Internship. This letter was found by Dr. Henry T. Bahnson in 1989 when he was cleaning out his office after retiring from the Surgical Chair at the University of Pittsburgh. Dr. Bahnson did not know who was responsible for the underlines, but thought that it probably was Dr. Blalock.

2. Supplementary Appendix #2: Dust cover written by TES for the book, *"Defying the Gods"* by Scott McCartney (Macmillan Publishing Company, 1994) based on the program founded by Dr. Goran Klintmalm (a former fellow of Dr. Starzl) at Baylor University Hospital, Dallas.

University of Pittsburgh
SCHOOL OF MEDICINE
Department of Surgery

Supplementary Appendix #1 (PART A)
STARZL-Fung manuscript

September 16, 1991

Louise H. Marshall
University of California, Los Angeles
Brain Research Institute
Center for the Health Sciences
10833 Le Conte Avenue
Los Angeles, CA 90024-1761

Dear Ms. Marshall:

I will try to touch on the issues in your letter to me of August 23, 1991. Please bear in mind that I have not worked in neurophysiology for more than 40 years. Consequently my perspective never matured beyond the primitive state of knowledge which existed in 1949-1951. I made no recent effort to educate myself about subsequent developments, fearing that this would change my memory of now-distant events. In addition, I would have to be re-educated to comprehend the more sophisticated later literature.

By coincidence, I wrote an autobiography last January which was written about transplantation, primarily for the lay public rather than the profession. I hope that the book will be published in 1992 in English, at the same time as translated Italian and Japanese versions. In it, Chapter 3 (pages 30-47) is concerned mostly with the time spent during 1949-1951) in Magoun's Northwestern and UCLA (Long Beach VA) laboratories.

If you are interested, Chapters 19-21 have the inside story of my near move to UCLA, 30 years later. Paul Terasaki and Jim Maloney were major figures during this latter time, and of course I have sent them the book for an accuracy check which it passed. Finally, almost all of Chapter 12 is about Paul Terasaki in the 1965-1970 era.

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Magoun was a legendary figure at Northwestern where Neuroanatomy was taught separately from gross anatomy. The course was under Magoun's direct and very detailed supervision. Some of the men who later helped create your Brain Institute were at Northwestern at the time, although most of them did not play a large role in Magoun's neuroanatomy course and were not part of Magoun's nuclear research group. Included were Earl Eldred and Bill (Robert W.) Porter. Eldred and Porter did Ph.D.'s in the Department of Anatomy, but under the supervision of other faculty members.

Other than Magoun, the most senior person in the official Neuroanatomy Section was Ray Snider whose interest was highly focused (some said monolithically so) on the cerebellum. Eldred's main research was with him. Snider did not have the vast range of knowledge possessed by Magoun, nor the creativity. These deficits, and I emphasize that the term was relative only to the luminescence of Magoun, prompted invidious comparisons between the two which must have undermined Snider's self confidence and made his life miserable. He seemed easily irritated, always near the explosion point.

Bill Neimer was next in the seniority line. With his sunken eyes, raven black hair, and gaunt frame, he sometimes resembled a cadaver when he was immobile, or Boris Karloff (which is what the students nicknamed him) when he moved. The reality was that he was just about the kindest and most gentle man whom I have ever met. When Magoun went to California, Bill Neimer took a faculty appointment at Creighton University in Omaha --- about 90 miles from my home town of Le Mars, Iowa. Whenever I was in Omaha during the succeeding years, I visited him. He seemed very happy there.

Magoun's attention to his teaching responsibilities was greater than I have ever witnessed at any level of the education process. He gave most of the formal lectures in his neuroanatomy course, and each one was a masterpiece. Scheduled for one hour, the talks lasted exactly 55 minutes, and always were accompanied by beautiful visual aids. Until I worked with him in the research laboratory, I did not know that he wrote these lectures and memorized them with the same care as he might have taken for a plenary address at a major international congress. In addition, he always was present for the laboratory sessions, and his final "practical" examination, complete with dozens of specimens, was the supreme event of the semester.

I was a good student generally, and perhaps especially so in neuroanatomy. Because of his attention to the students, Magoun was aware of this. In the spring of 1949, toward the end of my sophomore year, he asked me if I wanted to be a summer research fellow. For the personal and consequent economic reasons which I described in Chapters 2 and 3 of my autobiography, I was looking for a job which would allow me to stay in Chicago instead of going home to Iowa. During the previous summer, I had worked as a copywriter at the Chicago Tribune where I was invited, and even recruited, to return for a much higher salary. Magoun's advice was never to make a decision about work which was based on money. As a consequence, I joined him to continue the work on the reticular formation which he had begun with Giuseppe Moruzzi.

By the time I came in May 1949 to Magoun's 7th floor laboratory in the Montgomery Ward Building, his foremost collaborator, Giuseppe Moruzzi had returned to Italy. I had seen Moruzzi from time to time in the preceding year and was left with an impression (which probably is wildly at variance with the facts) of a youngish, slightly portly, very active and intense individual with hawk-like features and an army style haircut. Leon Schreiner, the budding neurosurgeon who did the chronic experiments of reticular formation ablation with Don Lindsley (motor and sensory both), was still in evidence, largely as an observer of previously operated cats which were a miserable lot.

Schreiner had the attributes of a movie star because of his good looks, long wavy hair, and a short but powerful build. He also had a dominant and engaging personality. His destiny was to be in University life, but somewhere along the way this was derailed. I think that he later worked at Walter Reed Hospital with David McRioch, but after that he went into the private practice of neurosurgery in Cheyenne, Wyoming. About 15 years later, when I was Chief of Surgery at the Denver VA Hospital I saw him again. He seemed bitterly unhappy, not only about his professional world, but also in his personal life. I was alarmed, but after this I lost track of him.

It was my misfortune not to have more than casual contact with Don Lindsley either in Chicago or California. Although I met Lindsley in Chicago, his work with Magoun appeared to have come to a hiatus at the time, and of course his arrival at UCLA was not long before the conclusion of my visit there in the spring and summer of 1951. Looking back

on it, I fit into a hole between Lindsley's collaboration with Magoun at Northwestern, and resumption of these joint Magoun-Lindsley activities in Los Angeles. The consequence is that I undervalued Lindsley's two papers in EEG Clin Neurophysiol, although I always cited them. Last week, I reread them for the first time in 40 years and realized that they were magnificent.

There were other people at Northwestern whom I should mention. John Brookhart was in the Department of Physiology, where he taught neurophysiology as if it were in a different universe than Magoun's course. Here also, I failed to appreciate Brookhart's distinction until later when I spent the summer of 1951 with Brookhart's star pupil, Dave Whitlock.

I never met Bowden and Knowles who were the "mystery" authors on the three seminal papers from Northwestern which appeared in 1949 in EEG Clin Neurophysiol. Wendell Krieg, a neuroanatomist who published books with artistic stereoscopic reconstructions of the brain, worked on a higher floor of the Montgomery Ward Building, but he might as well have been on Mars. There was a very cool interface between Magoun's group and Krieg's.

My view of the magical environment of Northwestern in 1949 was that Magoun was the shark under whose fins we all swam. Magoun already was the master of the reticular formation because of his work on the extrapyramidal motor system. The classic monograph on this subject by Ruth Rhines and Magoun had been published recently by Charles C. Thomas. The frontispiece was a picture of a man with hemiplegia. Magoun used the tragic photo to begin his book, and the first line of the text (which I cite from memory, probably with minor accuracies) read "In an autumn that is appropriately sere . . . etc."

What followed was a description of the partially paralyzed patient, but what stuck was the first line which reminded me of the beginning of Stephan Crane's famous story in which the survivor described his first impression of seeing muddy waves against the yellow sky. I realized that Magoun was an artist. Thereafter, it was easy to recognize what he had written, no matter who the ostensible first author was. I remember resisting his editorial changes on papers which I wrote because I did not want to be a mere mimic. One of Magoun's stylistic quirks was to begin sentences with the preposition <u>for</u> ("For we now understand .

. . "). He slaved over manuscripts, eliminating redundancies.

To me, Magoun's 1949 paper with Moruzzi was the cornerstone of his monumental contributions toward an understanding of the behavioral significance of the reticular formation. The idea of an extraleminscal sensory system which ran through the reticular formation already was there from some of Magoun's own previous observations, those of Ransom, and more obscurely in the seminal observations of Bremer. However, these were patches in the crazy quilt until the paper of Moruzzi and Magoun made everything comprehensible. Moruzzi apparently had added a technologic component (electrophysiology) to Magoun's classic anatomic techniques which made it possible to give substance to the concept. I was led to believe, or perhaps I merely assumed, that in turn this technology had been imparted to Moruzzi by Lord Adrian (England).

Such a historical backdrop, if it is accurate (and I believe it to be), helps explain the idolatry for Magoun exhibited by those whose reflections later appeared in the history of the first quarter century of the UCLA Brain Institute. Like me, all of Magoun's co-workers appeared to see him as the locomotive of the train to which they were permitted and encouraged to attach and contribute great or small things in their own right. The article by Moruzzi and Magoun contained the synthesis of Magoun's life's work and in my opinion is one of the truly great articles in the history of science. I have been puzzled through the years why Magoun did not become a Nobel Laureate when other related work (that of Hess, for example, in the same field) resulted in this distinction.

In my autobiography (Chapter 3), I described the events in the summer of 1949 which permanently changed my life. With his principal collaborators gone or inactive, Magoun devoted much time to my training, beginning by showing me the neuropathologic techniques of brain preparation which he used to study the tracks left by stimulating, recording, and electrocoagulation needles which were inserted into the brain stem.

The map for anatomic localization was an atlas of the cat brain prepared by a Spaniard (or possibly South American) named Jimenez-Castellanos who had recently left Northwestern. The readings and drawings of the needle tracks were done in a tiny room which contained a microscope with an overhead projector, the images from which were

traced on fine paper. During the summer, a young staff neurosurgeon named Charlie Taylor joined us on a sabbatical from the University of Toronto.

My original assignment was to systemically apply single shock and high frequency stimulation to areas in the thalamus and reticular formation, and to record the electrical changes in various cortical and subcortical areas. The objective was to determine how the impulses from the reticular formation reached their cortical destination. The conclusion was that there were both transthalamic and capsular pathways.

The basis for the second paper was Magoun's suspicion that the transthalamic route was the same as the "diffuse thalamic projection system" discovered several years earlier by Dempsey and Morison of Harvard. However, the Boston experiments had been performed under barbiturate anesthesia (Dial) which depressed the reticular formation fairly specifically and prevented delineation of the true character of this system or how it might modulate cortical or subcortical electrical activity. In both the first and second study, we used Bremer's encephale isole preparation. However, for the diffuse thalamic project we used repetitive slow stimulation to show a series of projections, primarily to the association cortices, from the medially located diffuse thalamic projection nuclei.

These experiments involved stimulation of subcortical areas with recording at a more cephalic level. They did not address what was feeding the reticular formation from below. One afternoon in June or July, 1949, before I was disciplined enough to refrain from deviating from protocol, a much more important observation surfaced. For no good reason, I switched the leads around so that the stimulating electrode was used for recording.

I was startled to see that substantial electrical activity could be picked up in the reticular formation and that this was significantly altered by noise such as that caused by a door slamming, a toy cricket, or an animal cry. I can remember bursting into Magoun's office, and how excited he was to hear the news. He came inside the wire cage with me where we spent a long time looking for artifacts. At first we searched for movement of the cat's ears, but the findings were unchanged by giving a large dose of a curare-like drug.

In Magoun's earlier paper with Moruzzi, conclusion 9 in the summary was "The possibility that the cortical arousal reaction to natural stimuli is mediated by collaterals of afferent pathways to the brain stem reticular formation, and thence through the ascending reticular activating system, rather than by intracortical spread following the arrival of afferent impulses at the sensory receiving areas of the cortex, is under investigation". The same hypothesis, and circumstantial support for it, was an important part of the two 1949 Lindsley papers. Now Magoun knew that these collateral pathways which had been very difficult to demonstrate with classical anatomic techniques, were susceptible to systematic electrophysiologic exploration.

The magnitude of the opportunity was stunning. Shortly afterward, I went to the Dean's office and gave notice that I was dropping out of medical school for at least one year. From this time until his departure for California in the late spring of 1950, Magoun and I worked all day, almost every day of the week, doing the experiments which we published together in the Journal of Neurophysiology in 1951. At noon, we invariably walked the several blocks to the Allerton Cafeteria on Michigan Avenue where we had lunch as I described in Chapter 3 of the autobiography. Because we were together so much, and because there was a physical resemblance, the preposterous rumor found its way back to me that I was Magoun's illegitimate son from some earlier youthful venture.

Quitting medical school was not easy to explain to anyone at Northwestern, or for that matter to my family in Iowa. Although I had discontinued all financial support from my father (see Chapter 3), I honored and respected him above all others. Magoun realized the quandary and wrote a touching letter to my father which he kept at his bedside for many years after he became invalided. The letter was lost when he died in 1976, but I remember it well and would blush to quote it. Magoun was determined that I should stay in research and explained why in his letter to my father. Eventually, I was half ashamed to follow a different pathway.

It may be that I came to know Magoun better than almost anyone else. I learned from him firsthand the price of having a creative vision. He lived in a flat on the south side of Chicago where he tried to juggle the needs of his family with the pressures caused by his discoveries and work. His wife, Jean, already was chronically ill. A beautiful teenage daughter (and I do not use the adjective

lightly) married someone of whom he disapproved. He yearned for a more tranquil life. Whether he found this peace in California, you would know better than I.

At scientific meetings, Magoun radiated charm and confidence, but behind the facade I thought that he was shy. During his Chicago period, he was the nuclear figure in a neuroscience brain trust which was interinstitutional. Weiner (the father of cybernetics) often came there from Boston. Others included Warren McCulloch, Perciful Bailey, Ralph Gerard, and several people from a downstate psychiatric institute in Mantino, Illinois. I am sure that they were all brilliant, but one thing I noticed in their meetings was that they fell silent when Magoun spoke.

I am sure that you will not want to include the following anecdote, but I will relate it anyway because it was the most devastating putdown I have ever witnessed in my life. One day, Magoun took me to a neurophysiology meeting at the University of Chicago, where Ralph Gerard worked. Gerard could scarcely be missed in a crowd because he was extremely overweight. Apparently believing that Magoun was sensitive about being bald, Gerard rushed over and greeted him by saying "Tid, your head has gotten as bald as my wife's ass". I remember how Magoun flushed, and I knew that he was genuinely offended. Gravely he examined his own scalp, as if comparing it to something, and then replied, "By God, Ralph, I think you're right". I never saw Gerard again, but I doubt if he forgot the riposte and the roar of laughter which followed. I still smile.

Magoun left Northwestern in May or early June, 1950. We were unable to finish our manuscripts because all of the experiments had not been completed. Throughout the summer, I worked on these and eventually sent drafts to Magoun in California which he revised them and added the often reproduced Figure 8 in the afferent collateral paper. Some time in the autumn, after I had returned to my junior year of medical school, Magoun wrote that he could provide a traveling fellowship for me if I wanted to come to UCLA the following May (1951).

My papers from the Northwestern period, and the later ones at UCLA were as follows:

1. Starzl TE and Carpenter W: Diffuse thalamic projections to the telencephalon. Anat Rec (Abstract) 106:250, 1950.

2. Starzl TE and Magoun HW: Organization of the diffuse thalamic projection system. J Neurophysiol 14:133-146, 1951.

3. Starzl TE, Taylor CW and Magoun HW: Ascending conduction in reticular activating system, with special reference to the diencephalon. J Neurophysiol 14:461-477, 1951.

*4. Starzl TE, Taylor CW and Magoun HW: Collateral afferent excitation of reticular formation of brain stem. J Neurophysiol 14:479-496, 1951.

5. Starzl TE and Whitlock DG: Diffuse thalamic projection system in monkey. J Neurophysiol 15:449-468, 1952.

6. Starzl TE, Neimer WT, Dell M and Forgrave PR: Cortical and subcortical electrical activity in experimental seizures induced by metrazol. J Neuropathol Exp Neurol 12:262-276, 1953.

*Of these, the one on collateral afferent excitation was the most important, or so I thought then and still believe. The introduction (next page) describes the ambiguous situation as we encountered it. The summary (the page after that) was so brief because the findings and implications were so clean. I carried the article in my heart for the rest of my life, never believing that I could do so well again.

COLLATERAL AFFERENT EXCITATION OF RETICULAR FORMATION OF BRAIN STEM

T. E. STARZL, C. W. TAYLOR* AND H. W. MAGOUN†

Department of Anatomy, Northwestern University Medical School,‡ Chicago, Illinois

(Received for publication December 26, 1950)

THE demonstrable capacity of afferent stimulation to arouse a sleeping subject, and the obvious benefits of reducing sensory inflow in predisposing to sleep, are in seeming disharmony with recently discovered influences for wakefulness exerted by the central reticular core of the brain stem. Direct stimulation of this part of the neuraxis reproduces the electrical pattern of wakefulness in the cerebral cortex (14) while at the same time it facilitates lower motor activity (16), and so arouses the nervous system generally (9).

The ascending course of this reticular activating system is distinct from that of afferent pathways in the brain stem (19) and selective destruction of its cephalic portion is followed by the EEG synchrony and behavioral somnolence, hitherto attributed to deafferentation of the cerebrum (7, 8). Such consequences do not follow selective interruption of ascending somatic and auditory paths in the midbrain and after this latter injury both somatic and auditory stimuli are still capable of awakening the sleeping animal and activating its EEG (7, 8).

It seemed likely that the apparent conflict might be resolved if evidence were forthcoming that collaterals from afferent paths turned into the reticular activating system in the brain stem and exerted their admittedly important arousing and awakening influences, indirectly, by modifying its activity.

The present study has explored this possibility by probing the brain stem for alterations in electrical activity evoked by somatic and auditory stimuli. The findings establish the existence of collaterals from these sensory systems to the brain stem reticular formation, the rich wealth of which has never previously been suspected, though indications for it have been afforded by earlier anatomical investigation (2, 11, 13) and by study of the atypical route of conduction of the 'secondary response' to sciatic stimulation (5).

Though the results are presented here only with reference to the problem under discussion, it is felt that implications of these findings may be broad indeed, for they appear to enlarge outlooks in afferent conduction far beyond those which have been envisioned within the circumscribed limits imposed by classical sensory paths.

* Department of Neurosurgery, University of Toronto. Medical Research Fellow, National Research Council of Canada.

† School of Medicine, University of California at Los Angeles.

‡ Aided by a grant from the Commonwealth Fund.

Reprinted from
J. Neurophysiol., 1951 *14*: 479–496

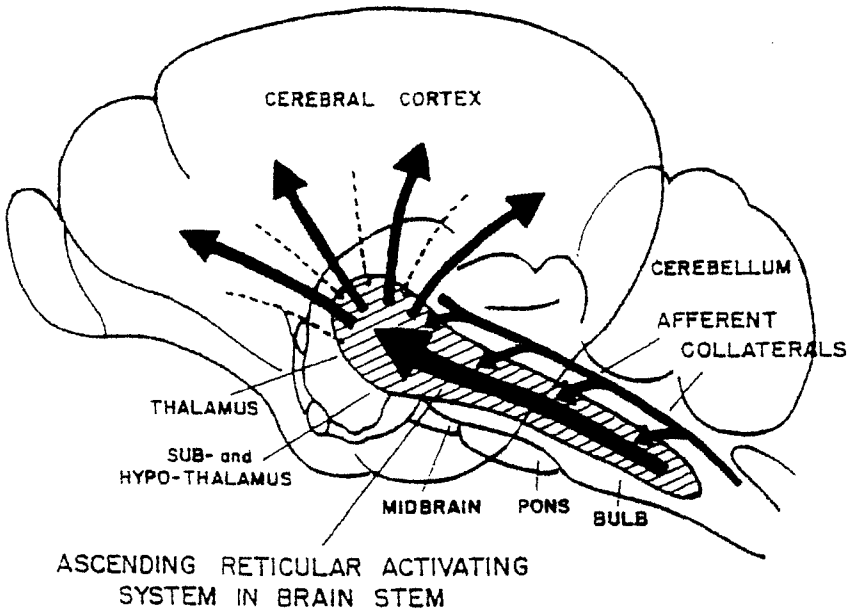


FIG. 8. Outline of brain of cat, showing distribution of afferent collaterals to ascending reticular activating system in brain stem.

SUMMARY

The distribution of afferent collaterals to the reticular formation of the brain stem has been investigated in the cat by probing for potential changes evoked by somatic and auditory stimulation.

In the case of each modality, a rich supply of collateral connections to the midbrain tegmentum, sub- and hypothalamus and ventromedial thalamus was encountered. These findings offer an explanation for a number of the generalized consequences of afferent stimulation which have been difficult to understand in terms of conduction within classical sensory paths. Specifically, they indicate that the arousing and awakening influences of sensory stimulation may be exerted indirectly, and at a subcortical level, by collateral excitation of the reticular activating system in the brain stem.

Reprinted from
J. Neurophysiol., 1951 *14*: 479-496

Throughout the entire period from 1948 until my departure for California, I had worked as an industrial surgeon at night, as I described in my autobiography. I quit this job, picked up my two sisters in Iowa, and drove to the Long Beach VA Hospital which had the only available laboratory facility. There I met Jack French and Mr. Edwards (the Hospital Director) and the other people who were laying the groundwork for the UCLA Brain Institute. There was no activity going on, but provisions had been made for monkeys and for operating facilities.

Dave Whitlock, a graduate student who had just completed his Ph.D. requirements, arrived from the University of Oregon with his wife, Peggy. I lived on the VA Hospital base. The Whitlock's had a small house in Long Beach where I spent many evenings. I tracked Dave from place to place after this, and eventually was able to nominate him for the Chairmanship of Anatomy at the University of Colorado where I was working myself. He accepted the job and we were reunited almost 20 years later.

My primary objective in Long Beach was to map the projections of the diffuse thalamic projection system in the primate, because the monkey had much more extensive cortical association areas than the cat. The results were largely confirmatory of those in the cat, although there was a much stronger localization of the medial thalamic nuclei projections to specific cortical association areas as well as an overall dominance in the frontal lobes and cingulate gyrus.

In a second study in cats, we tried to determine if metrazol seizures were initiated in the subcortical areas and radiated to the cortex. This was an attempt to verify a hypothesis by Jasper about the deep initiation of seizures, but to our disappointment these appeared to start in the cortex and could be invoked best by stimulation of the classical sensory pathways. The seizures then spread across the cortex and antidromically to the diencephalon.

I cannot remember a more happy time than the summer of 1951. The place where I lived on the VA Hospital base was Spartan, but it was clear that French and Magoun had created an idyllic place to work. Play was not totally ignored. There was a small golf course on the station, and just across Highway One were numerous alluring places to go late at night. The Pike (an amusement park, now gone) was at the height of its popularity. Twenty miles to the south was

Christian's Hut where we had an overly hedonistic farewell party the weekend before I left.

Magoun was concerned at one time that I was neglecting my social life. It would have relieved him (or possibly the opposite) if I had shared all secrets. I did not know anyone of my own age when I arrived, and after a few days I drove up the Pasadena Freeway and on to the Los Angeles County Hospital where I conducted a survey of the first 8 or 10 interns and residents whom I encountered. I asked them "Who is the most attractive student nurse in the hospital?". All but 2 or 3 identified a young lady named Marilyn Conner. I tracked her to the ward where she was working the night shift, explained exactly how I had identified her, and asked her if she would join me for a snack after work (which she did). Unfortunately, she was in love with a medical student at the University of California, San Francisco, and soon was borrowing money from me to take the train on the weekends to see him.

During my last week in Los Angeles, she learned that her San Francisco friend had become engaged to someone else, emancipating her from further obligations and leaving her free as she saw it to join me in Chicago. Somehow, it did not fit my preconceived romantic scenario, and I never saw her again. Jack French met Marilyn at about this time, probably at the Christian's Hut party. He was unattached and I believe that they saw each other after this. Apparently, Jack was very popular, and was just coming off of a romance with Ava Gardner when I arrived.

About 35 years later, I was saddened to receive a letter from Marilyn who now lives some place in Oregon. She had developed renal failure, and was inquiring about the best place to have a kidney transplantation. In her long letter, she told me of her numerous adventures in life. Now she had grown old and sick. Even the most beautiful flowers bloom and wither like all the rest.

During the end of my stay in Los Angeles, Magoun approached me about taking a fellowship at the Karolinska Institute with Ragnar Granit, instead of returning to my senior year. I knew by this time that I wanted to practice surgery, primarily because the complex technical procedures required to do the experiments with Magoun had seemed so easy to me. Incidentally, Magoun himself was a master surgeon, more skillful in the performance of fine work, in my opinion, than any surgeon whom I have ever watched in the clinical operating room.

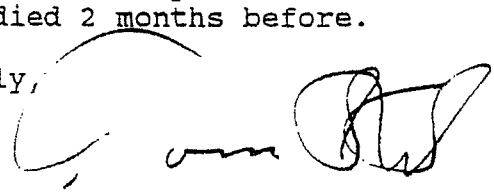
Until he left Northwestern, Magoun did all of his own experiments, and was an active participant in the smallest detail of the benchwork. He had an obsession for accuracy which caused some people to believe he had a fiery temper. His pursuit of an idea was so passionate that I believe he suffered intensely at the time of his highest creativity. I realized from talking to him that he did not intend to return to this way of life, and that probably I would be the last person he would work with shoulder to shoulder. He was only 43 years old. As it turned out, he had many other useful ways to serve out the remaining 40 years.

On the way back from Los Angeles, I drove to Salt Lake City, and gave a paper at the autumn meeting of the American Physiology Society. It was a sad departure, because I realized that I might never see Magoun again. In fact, I met him only once when he came to a neurophysiology conference at Northwestern in the late 1950's. He was grayer then, but otherwise much the same. Now at the peak of his prestige, he was surrounded by admirers who were speaking a language which I no longer understood.

I do not remember Joe Bogen. If you would like to know more, please write again. What I did in the rest of my life is in the book, and in the enclosed Chapter which I contributed to Paul Terasaki's recent history of transplantation (UCLA Press). It was all an anticlimax. At the back of the chapter is an abbreviated C.V.

In my book (pages 40-41) I tried to explain my debt to Magoun, in fewer words than in this letter, and possibly better. I was planning to send the book to him, but when I asked Don Lindsley's son about him last May, I learned that he had died 2 months before.

Sincerely,



Thomas E. Starzl, M.D., Ph.D.
Professor of Surgery

TES/ps

Supplementary Appendix #1 (Part B): Starzl-Fung manuscript

UNIVERSITY OF CALIFORNIA

LOS ANGELES 24, CALIFORNIA

Department of Anatomy
School of Medicine
December 20, 1951

Dr. Alfred Blalock
Johns Hopkins Hospital
Baltimore 5, Maryland

Dear Doctor Blalock:

I am writing you in connection with the application of Mr. Thomas E. Starzl for an internship at Johns Hopkins Hospital in the year 1952 to 1953. Mr. Starzl will graduate in medicine from Northwestern University School of Medicine in June, 1952, and will receive his Ph.D. at the same time. I have been closely acquainted with Mr. Starzl during three of his years at Northwestern and again last summer at UCLA.

Mr. Starzl is a fine-appearing, clean-cut, personable young man who is one of the most outstanding medical students with whom it has ever been my pleasure to be acquainted. He has constantly stood at or near the top of his class, and he is a prodigious worker who has far exceeded the ordinary accomplishments of medical students.

Mr. Starzl has spent each of his summers and a year between the sophomore and junior years of his medical program in research work in the experimental neurology laboratory under my supervision. I have never known a young man who showed such capability in rapidly grasping the background of a problem. His imagination in conceiving new ideas for exploration is outstanding, and he possesses a remarkable ability to design the experimental approaches to test such possibilities. In each research team with which he was associated, he rapidly assumed leadership and carried the main burden of the work. His research accomplishment for a young man of his age is, in my opinion, unique. He is the chief author of three published papers and one additional paper now accepted for publication. Two other major projects to which he contributed heavily are now being prepared for publication. In all of this experimental animal work Mr. Starzl has been constantly alert to the implications of the program for clinical medicine. In his present clerkship at Passavant Hospital in Chicago, he writes of the clinical investigative activity which he is undertaking in addition to the regular program.

Mr. Starzl is intent on entering surgery as a career, and I am confident that he will become one of the outstanding figures in this field in the future. I would rate him as absolutely the top man that I have encountered during some twenty years of association with medical students. I recommend him to the attention of your internship committee in the very highest possible terms.

Very sincerely yours,

H. W. Magoun

H. W. Magoun
Professor and Chairman
Department of Anatomy

mmm:dal

Medicine/Current Affairs Supplementary Appendix #2 Starzl-Fung Manuscript

Thank you for sending me the advance copy of Scott McCartney's outstanding book. I would not be surprised to see it show up on the bestseller list. It has dramatic inherent interest, and in addition it could not have appeared at a better time in the political process of policy determination.

The patient histories are touching, but similar accounts are in other books on transplantation—some written by organ recipients. The unique feature of Mr. McCartney's narrative is his subplot exposing how the transition of a new technology occurs from its developmental phases to commercialization. As Mr. McCartney has frankly stated, no advance, however promising, can be diffused into our health care system unless it is economically advantageous to the involved institution and to the medical personnel whose livelihood and variable lifestyles depend on cash flow.

In *Defying the Gods*, the transplanted organ under the journalistic microscope is the liver. However, in my book *The Puzzle People* (1992), I wrote, "It was uncanny how much the liver transplant gold rush of 1984 resembled that of kidney transplantation twenty years earlier. As before, there was a shortage of gold miners . . . The fresh crop of youthful men and women inherited the earth, or at least that part of it where they landed and staked their claims, hard-eyed now and determined to limit the numbers of new intruders who came close behind."

Thus, not far below the tragic surface of patient illness can be found the war for turf. In this case, the ultimate coin of the marketplace became the organs without which the services that generated cash flow could not be rendered. The battlefield was governed by the United Network of Organ Sharing (UNOS), whose directorship was made up not by the patients who needed the organs but by those who aspired to transplant them. Mr. McCartney has looked at the mercurial combatants in these struggles with a balanced and generally kind eye. All the while, he has made clear the entrepreneurial drives of a whole range of health care providers who frequently could be seen to change sides when their own supply of the precious livers expanded or retracted as rules of organ allocation changed.

Seemingly forgotten by many was the simple principle that organs must go where patients wait—or die while waiting if the principle is abrogated. With Mr. McCartney's help, it may still be possible to have equity.

—**Thomas E. Starzl, M.D., Ph.D.** *Professor of Surgery, University of Pittsburgh School of Medicine*
Director, Pittsburgh Transplantation Institute

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