HAWAII MEDICAL JOURNAL

Special Issue:
Organ
Transplantation

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HPAS   Hawaii Patient Accounting Services
"Setting Hawaii's physicians free"

Contents

◢ Editorials

Doctor, we need your organs! And your help!

This special issue of the *Journal* is devoted to organ transplantation in Hawaii and is dedicated to **Livingston Wong MD.** Livy, the father of Hawaii organ transplantation, and **Alan Cheung MD** have brought to the *Journal* a very special series of manuscripts. They have reviewed the past, updated the present, and will stimulate the reader to the future potential of organ transplantation.

It was in 1963 when your editor, then a dermatology resident at New York University, first became interested in organ transplantation. At that time, we were doing only preliminary work with tissue culture of basal cell cancers.[1]

Then in 1969, while at the Honolulu Medical Group, The Research and Education Foundation and the University of Hawaii School of Medicine sponsored Hawaii's first Organ Transplantation Symposium. We invited some of the most renowned authorities to speak at our symposium. They included: **Thomas Starzl MD, Robert A. Good MD, Irving Page MD,** and **David Rubsamen MD, LLB.** Local speakers included **Arnold Siemsen MD, Richard Mamiya MD,** and **Richard Kekuni Blaisdell MD.**

The Editorial Board hopes this special issue of the *Journal* will promote more interest in organ donations. Call the Hawaii Lions Eye Bank or the Makana Foundation at 536-7416 and the Organ Donor Center of Hawaii at 599-7630 for brochures and information for distribution to your patients. We need those organs!

References
1   Walker DG, Goldstein N, Kopf AW, Wright JC. Epithelial outgrowth from tissue culture of basal cell epitheliomas. *J Invest Derm.* 1994;42:435-441.

Mahalo

Hawaii Medical Journal
Advertisers

Organ transplantation overview

This year marks the 25th anniversary of organ transplantation in Hawaii.

In August 1969, St. Francis Medical Center in Honolulu performed the state's first kidney transplant. From the beginnings of transplantation here, which has evolved to include heart, bone marrow, liver and combined pancreas and kidney transplants, the people of Hawaii now are provided the latest services in transplantation.

This special issue on organ transplantation is designed to educate and inform the practitioners of Hawaii about what's happening in transplantation.

As in any major clinical endeavor, organ transplantation requires the participation and commitment of numerous people working as a team. They include:

1. A team of nurse coordinators, social workers, and financial advisors aiding the physicians in evaluating potential candidates, caring for post-operative patients, and following patients for the rest of their lives. This is essential for recognition of potential complications, such as rejection and infection.

2. Laboratory staff and facilities performing: (a) HLA tissue typing capability and association with the ASHI; (b) specific immunological and drug monitoring; (c) anatomic/histologic pathology to identify and grade rejection and graft-versus-host disease.

3. Transplant organ procurement agency for evaluating potential cadaveric donors, obtaining appropriate consent from family members in a sensitive manner, and overseeing the entire process of organ donation. They see to it that organs are procured and allocated according to the bylaws of the national organization, UNOS (United Network for Organ Sharing).

4. Operating room staff capable of procuring organs (liver, heart, pancreas, and kidneys) and tissue (bone, bone marrow, cornea, tendons) for transplantation. This team must properly perfuse the organs, place them in preservation solution, store them for varying lengths of time, and prepare them for transportation.

5. A team of qualified surgeons to implant these organs.

6. A medical center with specialized patient rooms and trained, dedicated personnel to care for these challenging patients.

7. A team of physicians, including surgeons, internists, and specialists, capable of monitoring immunosuppressive medications and recognizing rejection and other potential complications.

8. Nurse transplant coordinators instrumental in data collection. Transplant patients must be monitored and statistics must be submitted to national and international registries. This allows our program to be measured against other programs. Our data also will contribute to both the U.S. and world experiences for each type of transplant. This will lead to a better understanding of every aspect of transplantation and ultimately improved patient care. Submission of data is often tedious and burdensome for transplant coordinators, but this is absolutely essential.

We thank all of the above individuals and institutions for their support and team work. We would also like to thank all of the contributing authors for their fine work, and Dr Norman Goldstein for this opportunity to share our excitement and experience on organ transplantation in Hawaii.

Livingston M.F. Wong MD
Alan H.S. Cheung MD

Birth of Moloka'i

Another amazing birth attributed to the goddess Hina was that of the wondrous hog-child, *Kamapua'a*. A pig at birth, Kamapua'a was a *kupua* or shape-changer and could assume either the body of a hog, a handsome young man, or even a fish.

Hina's hog-child had many fantastic, comical and violent adventures. He was a notorious thief and relentless womanizer; his greatest conquest was the volcano goddess, *Pele*, with whom he had a tempestuous affair. Pele and Kamapua'a had a child, and this grandson of Hina became the god of thieves and medical practitioners.

The collected adventures of Kamapua'a are an excellent example of a *ka'ao* or a lengthy story recited from memory. It is said that the Ka'ao of Kamapua'a took 16 hours to recite; such incredible feats of memory were common to old Hawaiian storytellers.

Generations of Caring

Growing With Hawaii

Thanks to our 'ohana of dedicated physicians, St. Francis Medical Center has grown with Hawaii's families.
Since our founding in 1927, we've expanded from 13 doctors to more than 700 medical specialists.

Today, we're a household name in areas such as organ transplants, cardiology, cancer treatment, renal services and hospice care. For the future, we're dedicated to pioneering the latest medical advances to keep your family healthy.

St. Francis Medical Center... your partner in health, united in caring.

St. Francis Medical Center
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Congratulations on the 25th anniversary of organ transplantation in Hawaii. I feel certain that the physicians of Hawaii join me in expressing our appreciation to the authors featured in this special issue of *Hawaii Medical Journal* for bringing us current information regarding transplants. Too often the medical profession goes unrecognized for their accomplishments in improving the quality of life for Hawaii's citizens. Its sad to see that so few in our community realize the role organized medicine has played in shaping the health care system in our State.

In the State Legislature, hundreds of bills have been passed or held based on testimony presented by our physicians. Over the years, for example, physicians have been instrumental in developing the emergency medical services system, helping to implement a school health system in all public schools, nurturing the child protective services system with its child abuse laws as well as founding unique programs to help prevent child abuse.

The freedom to choose one's physician was fostered by HMA for the Workers' Compensation program as well as the Medicaid program.

In cooperation with the Department of Health, American Cancer Society and the Medical School, the Hawaii Tumor Registry has tracked cancer cases since the 1950s.The development of the Hawaii Claims Conciliation Panels which hear all medical tort cases prior to entering the court system has saved thousands of dollars in litigation costs: The tort laws regarding informed consent, access to medical records, protection for physicians who serve on peer review committees, or who are good samaritans have all come about through the efforts of HMA physicians.

HMA initially developed a coding system, known as the RVS or Relative Value System, which has enabled physicians and insurers to speak a common language when claims for services are filed. And when all the professional liability insurers moved from Hawaii, HMA searched for ways to offer coverage to Hawaii physicians and was successful in encouraging the Medical Insurance Exchange of California to provide coverage for Hawaii physicians.Our peer review committees have reviewed complaints made by patients against HMA members in an effort

to bring some resolution to problems: All at no cost to the patient.The continuing medical education accreditation program was begun by Hawaii Medical Association; hospitals, specialty societies, and others are surveyed and accredited by the HMA program.These are but a few of the achievements of the medical profession in Hawaii. Physicians will continue to be advocates for their patients and for a health care system second to none. We hope *Hawaii Medical Journal* will continue to acknowledge the contributions of Hawaii Medical Association to Hawaii physicians and the community.

🐾 Military Medicine

Benjamin W. Berg MD
Department of Medicine
Tripler Army Medical Center

Central Identification Laboratory

At Fort Kamehameha, a small army enclave on the edge of sprawling Hickam Air Force Base, is located the world's only forensic science laboratory dedicated solely to the recovery and identification of U.S. service members lost in past military conflicts. The U.S. Army Central Identification Laboratory, Hawaii—more commonly known as CILHI—is the last and most permanent incarnation in a long line of "CILs" dating back to World War II. In 1973 the army established a Central Identification Laboratory at Camp Samae San, Thailand and charged that organization with the responsibility of identifying the remains of personnel killed or carried as missing from the Vietnam War. In 1976 the laboratory was moved to Hawaii and the organization's role subsequently expanded to include the identification of remains from World War II and the Korean Conflict in addition to those recovered from Southeast Asia.

The laboratory currently employs 8 civilian forensic anthropologists, a civilian forensic odontologist, and 2 military dentists for the purpose of affecting identifications of skeletal and dental remains. A military staff of approximately 140 organize and execute the search-and-recovery operations and administer the nonscientific aspects of the organization.

An integral component of the forensic identification process is the acquisition and curation of antemortem medical and dental records for those individuals whose identification is sought. CILHI's Casualty Data Section maintains available medical and dental records for the 2,238 U.S. service members unaccounted for from the war in Southeast Asia and the approximately 8,200 individuals carried as missing from the Korean War. In addition, antemortem records for World War II losses can be ordered as needed from other U.S. government record centers.

The goal of the CILHI is to determine or estimate enough individual characteristics to establish a favorable comparison between the biological remains under study and the antemortem records of a known individual. Most commonly this involves a positive dental match combined with supportive anthropological determinations of such characteristics as sex, race, age, and stature. Less commonly, individual characteristics such as handedness, pathological conditions (eg, arthritis, anemia), traumatic wounds (eg, healed fractures), and congenital disorders (eg, deformed, missing, or supernumerary elements) can be diagnosed. Certain occupations or habits might also be detectable from skeletal remains. Habitual pipe smokers, for instance, can sometimes be detected by deviation in the occlusal angle of the teeth used to clamp the pipestem.

Other information derived from the forensic analyses might include circumstances of death (eg, a gunshot wound versus a high-speed impact).

More recently, CILHI has begun utilizing the emerging technology of DNA analysis. While still a relatively new science—at least with regards concerning DNA typing of bone samples—DNA analysis promises a new approach to many difficult cases that have eluded identification in the past.

While the obstacles at times appear daunting, the future actually is bright. New and emerging technological advances combined with increasing access to former combat theaters previously inaccessible to the U.S. augurs well for the identification of U.S. service members lost in past conflicts and with that, the resolution of perhaps the most-personal and private side of war.

The views expressed in this article are those of the author and do not reflect the official policy or position of the Department of the Army, Department of Defense, or the U.S. Government.

📖 Historical Notes

John A. Breinich
Hawaii Medical Library

With this special issue of the *Journal* dedicated to transplantation, it is appropriate to look back at the first successful kidney transplant in Hawaii 25 years ago. On August 10, 13, and 17, 1969, a team of physicians at St. Francis Hospital conducted the first kidney transplants. The surgical transplant team was led by Drs Livingston Wong, Herbert Chinn, Glenn Kokame, Richard Pang, and Walton Shim. Dr Arnold Siemsen was director of the hemodialysis center at St. Francis and was behind the kidney transplant program at the hospital. The first procedure ended in rejection, but the second and third transplants were successful. Since that time, kidney transplantations have become routine. Other more recent firsts include Hawaii's first bone marrow transplant on March 31, 1978, the first heart transplant on March 11, 1987, and the first liver transplant on September 26, 1992.

In November 1970, the Makana Foundation (*makana* can be translated as gift or to give freely in Hawaiian) was established by John J. Stanford and others who felt the need to do something in the community to assist in matching donors and recipients with needed organs. In 1980 the Foundation merged with the Hawaii Lions Eye Foundation and is still involved today in this work. Their primary activity is in eye tissue, and they work closely with the Organ Donor Center of Hawaii, established in 1987.

Highlights of the HMA Council Meeting of January 7, 1994

The HMA Council met January 7, 1994. Members present were: Drs A. Don, F. Holschuh, C. Lehman, J. Spangler, J. Chang, C. Kam, R. Stodd, A. Kunimoto, P. Blanchette, B. Shitamoto, R. Goodale, T. Smith, D. Canete, P. Chinn, W. Dang Jr, P. Hellreich, M. Shirasu, K. Thorburn, C. Wong, J. Betwee, C. Kadooka, W. Chang, W. Dang, G. Goto, J. Lumeng, J. McDonnell, S. Wallach, M. Montoya, M. Lau, N. Goldstein. HMA Alliance president Susan Foo and medical student A. Mateo. Guests: Drs W. Foo, G. Yuen, S. Vitousek, A. Oki; R. Neupauer and R. Caron from MIEC; Mmes E. Don, K. Yuen, S. Wong. Staff: J. Won, B. Kendro, N. Jones, L. Tong, J. Asato, J. Estioko, Diane Shiraishi (recording secretary).

The Council heard a report from Dr Sharon Vitousek on the proposed medical assessment program. Significant funding totaling $460,000 has been committed by HMSA, various hospitals, and HDS; HMA was asked to contribute. Council voted to contribute $5,000.

Dr Norman Goldstein, newly appointed editor of the *Hawaii Medical Journal*, reported that the *HMJ* is progressing within its new guidelines, being typeset and prepared in–house and printed by Pacific Printers. Dr Goldstein requested names of physicians willing to review and read articles prior to their publication.

Ron Neupauer, vice president of underwriting for Medical Insurance Exchange of California (MIEC), reported that MIEC has worked with physicians since 1981. The numbers of policies in Hawaii increased from 150 in 1982 to 700 in 1984 and has remained between 800 to 900 from 1985 to 1992. The highest number of MIEC Hawaii claims reported were in 1986, 1991, and 1993. MIEC has been very supportive of HMA, has presented seminars over the years, and looks forward to continuing those seminars in the future.

Mrs Susan Foo, president of the HMA Alliance, reported that group is actively working on a large fund-raising banquet scheduled for Sunday, March 13. The HMA will join the festivities by presenting the 1993 Distinguished Medical Reporting Awards that night. The proceeds of this event will be donated to an endowment fund for medical education and research at the John A. Burns School of Medicine.

Dr Fred Holschuh discussed the need for pre-test counseling for HIV/AIDS in emergency departments. The HMA HIV/AIDS Committee will work on developing simplified pre-test counseling guidelines. The International AIDS Conference will be held in Japan in 1994 and a team of experts will stopover in Hawaii for a conference. HMA Council voted to support the conference by donating $500.

The Hawaii Federation of Physicians and Dentists published a red alert in December 1993 with specific mention of HMA and its activities. The red alert suggested that several unrelated activities were part of a generalized plan. President Andrew Don responded to the red alert with a letter to the Federation clarifying HMA's position on the subjects mentioned in the alert.

The Nurse Prescribing Committee was asked to further discuss this issue and report back to Council at its next meeting.

Corporate papers for the Independent Physicians Network of Hawaii Inc (IPN) commonly referred to as the IPA, have been completed but not filed as yet. Further organization and funding were discussed and Council voted that fewer than 24 stockholders can purchase shares of stock up to a total of $50,000 to provide funding for profiling the organization.

HMA Alliance

Susan L. Foo, President

Sex, politics, religion—enough controversy can be generated dealing with each subject alone, so consider what happens when a group of doctors' wives begin to sound off about topics such as the current state of health system reform, not allowing themselves to be intimidated by a few sacred cows that might be standing in the way! Recently, some criticism was voiced about the Alliance being too *strong* or *outspoken,* or wandering too far off the fashion show/fund-raiser circuit.

To loosely paraphrase HMA President Andy Don's remarks at his inauguration, physicians have an obligation to be the guardians of quality medical care in this country.

The politicizing of medicine was not really welcomed by the vast majority of medical families, but since it is now reality, members of the HMA Alliance who have some real-life contact with current problems feel an obligation to expose them so solutions can be found. In the midst of so much change occurring so quickly in the medical profession, controversy is inevitable.

For some, running away from it all has seemed like the best bet: Can't do anything about it, so no use getting involved. The increasing hassles of governmental or legal intrusions into the practice of medicine still affect them, but they try not to think about it and adapt as well as they can.

Another segment of the medical community sees a big steam-roller coming toward them: Can't stop it, might as well try to find some way to jump on, avoid getting hurt. The problem is, they also add their collective weight to the moving object heading toward the others down the road.

Still another group of physicians and their spouses see that change in the practice of medicine is inevitable, and firmly believe they must voice their opinions because they will still have the responsibility of implementing health policy at the everyday, routine level: Eyeball-to-eyeball with a sick patient.

Here in Hawaii, many bills directly affecting the quality of medical care are working their way through the legislative process. We owe it to ourselves and the people of Hawaii to become familiar with the hot topics of the day: Managed care, global budgets, gatekeepers and PCP's prescriptive authority for non-MDs, etc.

But above all, we should grasp the opportunity to contribute our valuable perspectives gained through years of experience with the delivery of health care to the continuing debate about health system reform. Not everyone will agree with a given opinion, but the HMA Alliance welcomes a lively debate. We're all in it together, we're family, and our combined energy certainly makes a positive difference in this community!

Susan Chong Wong Esq
HMA Alliance Legislative Committee

Medical School Hotline

John A. Burns School of Medicine
Naleen N. Andrade MD
Associate Professor and Associate Chair
Department of Psychiatry

Developments in Psychiatry

In July 1990, the John A. Burns School of Medicine's Department of Psychiatry embarked on two distinct, yet complementary tracts of service: training and research.

The first track involved forming the State/University Collaboration between the Department of Health's Behavioral Health Administration and the Department of Psychiatry. The second involved establishing the Native Hawaiian Mental Health Research Development Program.

The state/university collaboration program

Hawaii's State/University Collaboration is part of the national program between the American Psychiatric Association and the National Association of State Mental Health Program Directors, whose goal is to improve the quality of psychiatric care within public mental health systems.

The Collaboration began with a primary focus of reorganizing and strengthening the psychiatric services at the Hawaii State Hospital through joint-appointed psychiatric faculty and has carefully moved into selected outpatient community mental health centers on the islands of Oahu, Kauai, Molokai, and Hawaii.

The psychiatric gains made at the State Hospital in Kaneohe are substantial. Prior to the State/University Collaboration, Hawaii State Hospital had a 50% vacancy rate of psychiatrists, no permanent clinical director, no forensic psychiatry expertise, no alcohol and substance abuse expertise, and no geriatric and neuropsychiatric expertise. To date, all vacant psychiatric positions have been filled with qualified full-time, joint-appointed psychiatry faculty who provide direct service, teaching, and outcomes-related research. Furthermore, faculty with expertise in forensics, geriatrics, neuropsychiatry, and substance abuse have been recruited. Hawaii State Hospital has become one of the most exciting training sites for the Department of Psychiatry, and we hope to see the quality of services, training and research continue to be strengthened through the State/University Collaboration, the Department of Psychiatry has made a significant contribution to Hawaii's public mental health system for adults. It is our hope that in the coming year similar growth will occur within the State's Child and Adolescent Mental Health Division.

Native Hawaiian mental health research program

Since 1987, the Department of Psychiatry has built a cadre of mental health researchers to conduct Native Hawaiian mental health research. By federal policy, particular focus was given to recruit and develop Native Hawaiians; five Native Hawaiians

are the co-principal investigators. Two federal grants were awarded: In 1990, a two-year NIH supplemental research grant, through the University's Research Centers for Minority Institutions (RCMI) program for $303,000 and in 1992, a three-year National Institute of Mental Health (NIMH), Minority Institutions Research Development Program (MIRDP) for $885,769. These grants fund a longitudinal epidemiologic study of about 6,000 adolescents and provide the first epidemiologic data on Hawaiian adolescents. Three papers written by the researchers have been accepted for presentation at the May 1994 American Psychiatric Association meeting in Philadelphia. Plans are currently underway to expand the MIRDP project and submit a Minority Research Center grant proposal to NIMH within the next several months. In addition to Native Hawaiians, these future proposals will include Asians, another designated special population.

"You don't eat them.
Just spill them on the
floor three times a day
and pick them up
one at a time."

25 Years of Kidney Transplantation in Hawaii

Alan H.S. Cheung MD, Mary S. Wheeler MSN, Fong-Liang Fan MD, Whitney M.L. Limm MD, Linda L. Wong MD, Richard K.S. Pang MD, Herbert Y.H. Chinn MD, Livingston M.F. Wong MD

The first kidney transplant in Hawaii was performed in August 1969. In the following 25 years, more than 433 kidney transplants were performed. The most common etiology leading to transplantation was chronic glomerulonephritis. Patient and graft survivals after a kidney transplant have progressively improved, particularly after the introduction of cyclosporine in 1984. The overall one-year patient and graft survival rates now are 96% and 85%, respectively; these results exceed the national averages.

Introduction

The first kidney transplant in Hawaii was performed in August 1969 on a 43–year–old man with a diagnosis of membranous glomerulonephritis. Prior to the transplant, he had been maintained on hemodialysis for 17 months. The early efforts of Drs Livingston Wong, David Hume, Arnold Siemsen, and Herbert Y.H. Chinn brought about this surgical procedure; combined with excellent follow-up care provided by the nephrologists, the quality of life for many patients with end-stage renal disease has improved. The growth and development of this new technology was crucial in Hawaii where geographic isolation might otherwise force many patients to travel to the Mainland for kidney transplantation or to remain on dialysis without surgery.

The objectives of this study were to: 1. Examine St. Francis Medical Center's experience from a historical perspective; 2. Compare the results with available national statistics; 3. Review briefly the indications, techniques, and immunosuppression used in kidney transplantation.

Methods

Between August 1969 and December 1993, a total of 433 kidney transplants were performed at St. Francis Medical Center in Honolulu. The approach to patient care, including recipient

and donor selection, timing of the transplant, surgical techniques, immunosuppressive protocols, treatment of rejection, and ancillary care have been similar to those described in detail in the literature.[1,2,3,4,5,6,7] Of these 433 transplants, 405 were available for analysis using the UCLA/United Network of Organ Sharing (UNOS) Scientific Registry.

The UNOS Scientific Registry was created in October 1987 following enactment of legislation contained in the Transplant Act of 1984 and records all kidney transplants performed in the United States. Prior to 1987, kidney transplantation registry data was maintained by Dr Terasaki at the UCLA Tissue Typing Laboratory. This retrospective review used the UNOS Kidney Transplant Registry data base and locally available charts at St. Francis Medical Center.

Because of the number of study patients, data was stratified into historical periods:

1. Era I–August 1969 to December 1983. This is referred to as the pre–cyclosporin A (Pre–CsA) period. Immunosuppression consisted of steroids and azathioprine. A total of 186 transplants were performed during this period.

2. Era II–January 1984 to December 1989. The powerful new drug, cyclosporin A (CsA) was introduced and used on all transplant patients to prevent graft rejection, in addition to steroids and azathioprine. OKT3 also was available to treat acute rejections. A total of 137 transplants were performed during this time period.

3. Era III–January 1990 to December 1992. A total of 89 transplants were performed during this time period. The same immunosuppressive regimen as Era II was used.

4. Era IV–January 1993 to December 1993. A total of 21 transplants were done this past year. The same immunosuppressive regimen as Era II and III was used.

Patient and graft survival rates for each era were calculated by statistical analysis using the Kaplan-Meier method for estimating survival. Graft loss was defined as the earliest return to maintenance dialysis, retransplantation, or death and all causes of death were included in the analysis.

Results

The number of kidney transplants performed each year since the premier transplantation in 1969 and the source of donor

kidneys are shown (Fig 1). Only living-related donor (LRD) kidney transplants were performed in 1969 and 1970. Most of the donor organs came from cadavers (CAD), with a total of 344 cadaver– versus 88 living–related donor kidneys. The patients' ages ranged from 3.5 years to 70 years and 58% were men and 42% were women. The majority of the patient population was Asian (Table 1). Most of these patients had ABO blood type A and were non-diabetic. Some of the common causes of renal failure for our population are listed (Table 2).

The overall patient survival rates were stratified by era. Prior to 1984, prednisone and azathioprine, or *conventional therapy* were used for immunosuppression. After 1984, CsA was added to the immunosuppressive regimen. The overall patient survival rates have improved with each era (Fig 2). The one-year patient survival now is about 97%.

The overall kidney graft survival rates also were stratified (Fig 3). The one-year kidney graft survival in the pre-CsA era was only 45%; now it exceeds 85%.

Both the patient and kidney graft survival rates were better for patients with a living-related donor (LRD) as compared to a cadaver donor (Fig 4 to 7). The current one-year patient survival with an LRD is 100% versus 97% with a CAD. The current one-year kidney graft survival with an LRD is 100% versus 84% with a CAD.

The UNOS Scientific Renal Transplant Registry also provided data based on 41,240 renal transplants performed at 237 U.S. transplant centers between October 1987 and November 1992.[8] These national statistics were compared to Hawaii's: The national overall one-year patient and kidney graft survival rates for cadaver transplants were 93% and 73%, respectively; compared to our most recent results of 95% and 85%, respectively.

The UNOS Scientific Renal Transplant Registry also provided a "1991 Report of Center–Specific Graft and Patient Survival Rates".[9] This report was the first attempt to determine center–specific kidney transplant survival rates for all kidney transplant programs in the United States. In this report, UNOS provided graft and patient survival rates for patients who received a kidney transplant from October 1, 1987 to December 31, 1989. The report analyzed 19,990 kidney transplants performed at 219 separate U.S. transplant programs during this time. In this report, our one-year patient survival of 93% and one-year graft survival of 83% were equivalent to or better than the UNOS national averages (Table 3). The results compare very favorably with those of larger centers in California.

In 1993, 21 kidney transplants were performed in Hawaii: 17 patients received cadaveric organs and 4 received organs from living-related donors. All of the patients have survived to date. Twenty of 21 patients currently have functioning grafts for an overall graft survival rate of 95%. Stratifying the data based on organ source reveals that 100% of the LRD grafts are still functioning and 94% of the CAD organs (16/17) are still functioning.

Discussion

Since the first kidney transplant was performed in Hawaii, kidney transplantation has become the treatment of choice for selected patients with end-stage renal failure. As the sole transplant center for Hawaii, St. Francis Medical Center continues to address the needs of patients with end-stage renal disease. In this retrospective review, the lessons learned over the past 25 years have been tremendous. This retrospective analysis will reflect past accomplishments, compare our current results with those of other centers in the country, and offer a glimpse into the future of kidney transplantation for patients in Hawaii.

As the overall patient and graft survival rates have improved over the years, a milestone improvement seems to be that of better immunosuppression. The survival data improved dramatically after 1984 with the introduction of CsA. This new immunosuppressive regimen presumably allowed for a lower incidence of graft loss from rejection. Although not included in our data, during this period other centers have noted a lower incidence of infection from the lower use of nonspecific immunosuppressive drugs such as prednisone and azathioprine.[7] This might help explain our improved one-year patient survival now at 96% and one-year graft survival now at 85%. Although it is not clear in the data, probably other factors contributed to this improvement including the increased experience of the transplant team, improved ancillary support, better intensive care management, and newer antibiotics such as ganciclovir for treatment of severe CMV infections.

The living-related donor kidney transplants continue to do much better than the cadaveric transplants in long-term graft survival. This is true in all other reports because a living-related donor allows for better HLA matching and shorter ischemic times, thereby avoiding preservation injury from acute tubular necrosis (ATN).

Retrospective reviews and comparison reports are important both to show where we have been and where we could be headed in the future. Data from UNOS compiling national statistics and large center reports have been most helpful.[8,9] In the past, our program had been criticized for its geographic isolation and small size, and it was unfairly assumed that our results would not be as good as those of larger centers. However, our one-year patient survival is equivalent to the national average and our one-year kidney graft survival exceeds the national average. As compared to larger programs in California, our results clearly speak for themselves. This should be very reassuring to the people of Hawaii who rely on St. Francis Medical Center exclusively for their transplantation needs.

Briefly, over the past 25 years, both hemodialysis and renal transplantation have advanced to the point where patients with end-stage renal disease can be managed with good long-term success rates. Recent data indicate that patient survival after transplantation is far superior to that of dialysis. In addition, kidney transplantation continues to be a more cost-effective treatment than dialysis. Perhaps more important, quality of life after successful transplantation is markedly better than dialysis. Thus, in 1994 all patients with end-stage renal disease should be considered as transplant candidates. The only absolute contraindications are active infection, active intravenous drug abuse, positive HIV status, and systemic malignancy. Relative contraindications include hepatitis, history of poor compliance

with medications, or advanced systemic diseases. As the technical aspects of renal transplantation have been perfected, patients in either age extreme or more advanced disease processes have been accepted as candidates.

Preoperative evaluation.—An extensive evaluation of all patients referred for transplantation is performed, including a detailed history and physical exam, routine laboratory studies, chest radiograph, electrocardiogram, blood and human leukocyte antigen (HLA) typing and viral serology. Certain candidates might require more extensive preoperative evaluation such as diabetic patients or patients with potential cardiac and/or pulmonary diseases. Patients older than 65 years constitute an increasingly larger group in the population in general and in those requiring dialysis or transplantation in particular. Careful evaluation of this group must be considered. Once a patient has been accepted for kidney transplantation, donor status is evaluated. Living-related donors are preferred because of the improved survival rates, ability to schedule cases electively, and the shortage of cadaver organs. If no living donor is available, patients are then placed on the cadaver donor waiting list.

Perioperative care.—Current preservation techniques allow kidney storage for up to 72 hours with good success rates. Cold–storage time still is minimized, however, to reduce the incidence of delayed graft function. For this reason, once the cadaver kidney is procured, the recipient is admitted and transplanted as quickly as possible. HLA and blood typing of the donor are performed and preliminary cross matches are done using recipient serum. Once this matching is completed, the kidneys are assigned to the 2 recipients with a negative cross match and the highest number of points according to the allocation system developed by UNOS. This includes the degree of HLA antigen match, length of waiting time, and panel–reactive antibody (PRA). The recipient is admitted to the hospital on an urgent basis; chest radiograph, electrocardiogram, and routine preoperative laboratory tests are performed and a final crossmatch is done. If needed, the recipient is dialyzed prior to surgery. Transplantation occurs within 12 to 24 hours of hospital admission.

Operative procedure.—A central venous pressure monitor is routinely placed in all recipients in order to manage preoperative and postoperative fluids. A Foley catheter is inserted preoperatively and immunosuppressive medications and antibiotics are administered prior to the beginning of the actual surgery. The technical approach to kidney transplantation has remained the same since the procedure was first successfully performed in 1954.

Briefly, a left or right lower-quadrant incision is made and the iliac vessels are dissected free extraperitoneally. The renal artery and vein from the donor kidney are anastamosed to the patient's iliac artery and vein, respectively. Revascularization is performed as quickly as possible to minimize ischemia time to the kidney. Before unclamping the revascularized kidney, the patient is fluid–resuscitated to maintain a systolic blood pressure of 140 mm Hg and central venous pressure to 12 mm Hg.

Table 1 Patient Demographics

Race	Percent
Asian	48.0
White	30.0
Filipino	17.0
Polynesian	4.1
Black	0.6
Hispanic	0.3

ABO Blood Type	Number (Percent)
O	141 (35.0)
A	166 (41.0)
B	64 (16.0)
AB	33 (8.0)
Data Unavailable	2 (0.2)
Total	**405 (100.0)**

Renal Disease	Number (Percent)
Diabetes Mellitis	37 (9.1)
Non-Diabetic	368 (90.9)
Total	**405 (100.0)**

Table 2 Causes of Renal Failure

Primary Diagnosis	Number (Percent)
Chronic Glomerulonephritis	220 (51.3)
Diabetes Mellitus	40 (9.3)
Systemic Lupus	36 (8.4)
Polycystic Kidney	22 (5.1)
Pyelonephritis	5 (1.2)

Table 3 Overall Actual Survival Rates from Oct 1, 1987 to Dec 31, 1989

	UNOS	Hawaii	CPMC*	UCSF**
Number of Kidney Transplants with Follow-up	19,588	54	344	521
1-Year Graft Survival (Percent)	80	83	80	77
Number of Kidney Transplants with Follow-up	18,930	54	342	518
1-Year Patient Survival (Percent)	93	93	93	93

* California Pacific Medical Center, San Francisco
** University of California, San Francisco

KIDNEY TRANSPLANTS IN HAWAII
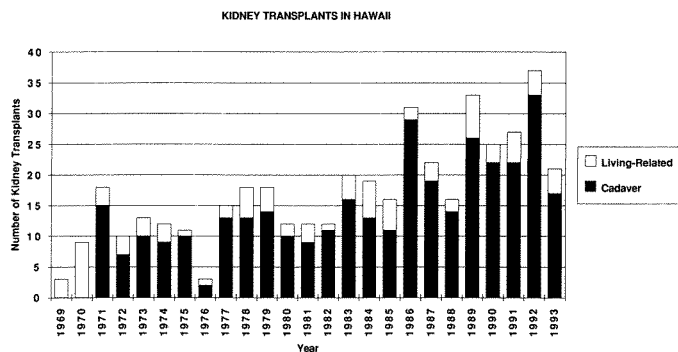
Figure 1.—A breakdown of 433 kidney transplants performed at St. Francis Medical Center by year and donor source.

CUMMULATIVE PATIENT SURVIVAL
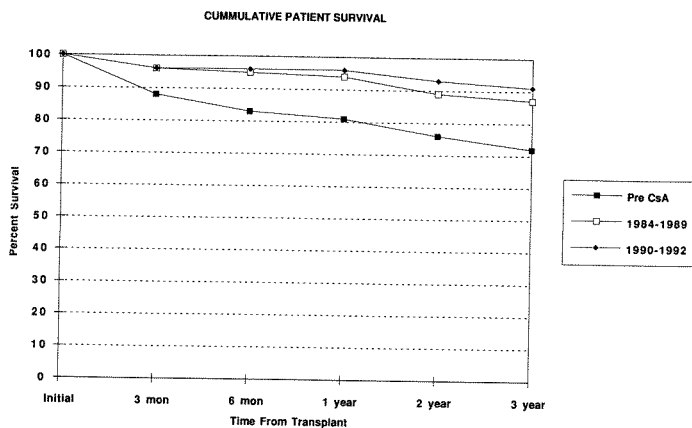
Figure 2.—Overall patient survival rates for recipients of kidney transplants at St. Francis Medical Center. The different eras include Pre CsA (1969 to 1983) and Post CsA (1984 to 1989 and 1990 to 1992).

CUMMULATIVE KIDNEY GRAFT SURVIVAL
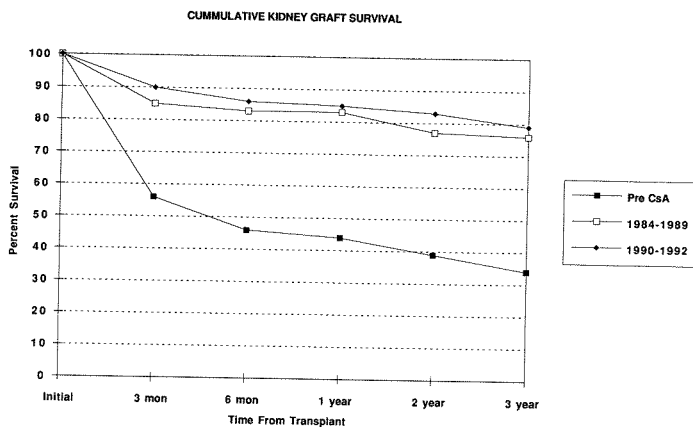
Figure 3.—Overall graft survival rates for recipients of kidney transplants at St. Francis Medical Center.

**PATIENT SURVIVAL
LIVING-RELATED DONORS**
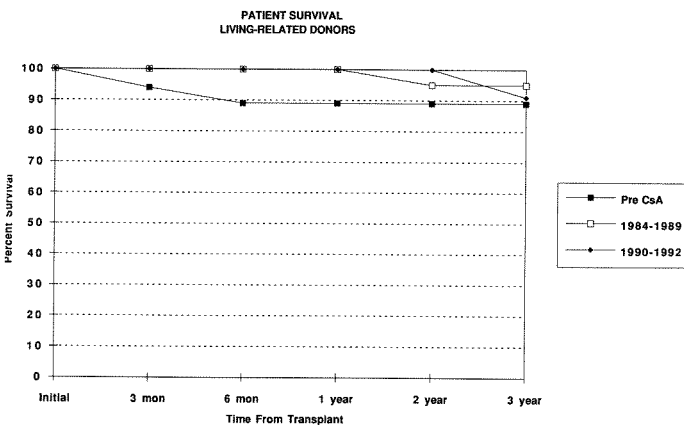
Figure 4.—Patient survival rates for recipients with a living-related donor kidney transplant.

**PATIENT SURVIVAL
CADAVER DONORS**
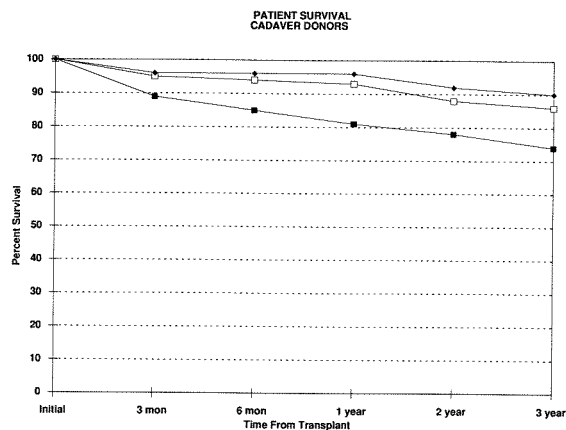
Figure 5.—Patient survival rates for recipients with a cadaver donor kidney.

**GRAFT SURVIVAL
LIVING-RELATED DONORS**
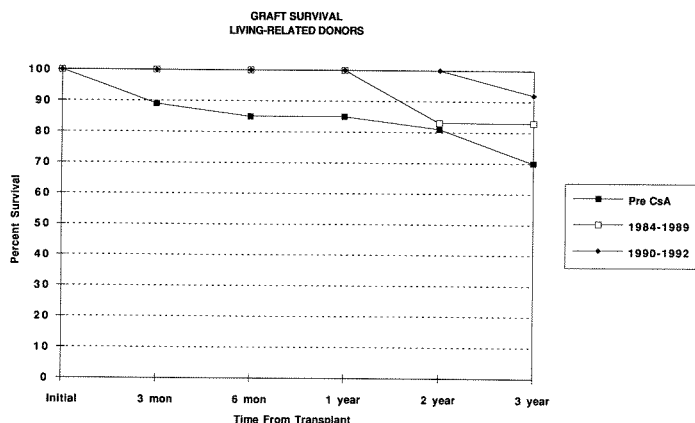
Figure 6.—Graft survival rates for recipients of a living-related donor kidney transplant.

GRAFT SURVIVAL
CADAVER DONORS

FIG 7

Legend:
- Pre CsA
- 1984-1989
- 1990-1992
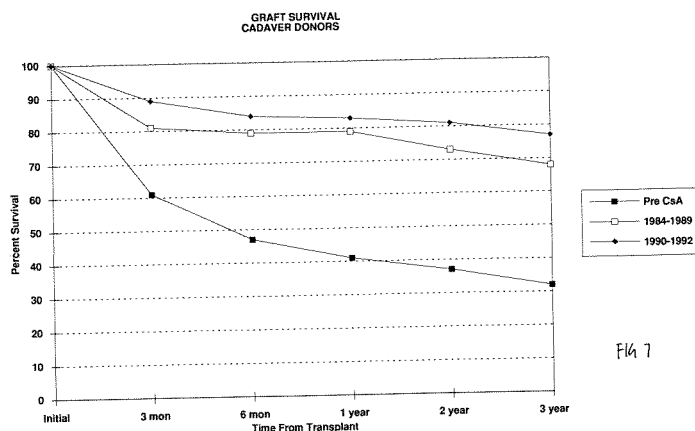
Figure 7.—Graft survival rates for recipients of a cadaver kidney transplant.

Furosemide (Lasix) and mannitol are administered as needed. The ureter is then implanted into the bladder via one of several techniques including the posterior Leadbetter-Politano or the Litch technique.

Postoperative care.—All patients require support in the intensive care unit during the first 24 to 48 hours. Most patients are extubated immediately after completion of the procedure, the fluid and electrolyte status are carefully monitored, and the hourly urine output is recorded and replaced cc for cc during the first 24 to 48 hours. After the first 24 hours, volume replacement is gradually decreased until maintenance replacement levels are reached. Patients with delayed graft function require special attention. Inadequate fluid resuscitation can result in acute tubular necrosis (ATN); overly aggressive fluid replacement can result in pulmonary edema or congestive heart failure.

Medications.—Standard postoperative medications include immunosuppression; the current regimen includes prednisone, azathioprine (Imuran) and CsA in all patients. In addition, OKT3 or ATGAM immunotherapy can be used in cadaver recipients with delayed graft function. These drugs are standard and have been described elsewhere. Other standard medications include H2 blockers and trimethoprim-sulfamethoxazole (Bactrim) to prevent *pneumocystis carinii* and to decrease the incidence of urinary tract infection. Prophylactic antibiotics, CMV prophylaxis and occasionally fluconazol for fungal prophylaxis are used for postoperative care.

Early complications.—Delayed graft function from a preservation injury, ATN, or rejection can occur. A rapid diagnosis using ultrasound or renal scan needs to be done to rule out any technical problems. General complications might occur as with all other surgical procedures. Wound complication such as hematoma, seromas, and infections are of significant concern since these patients are immunosuppressed. Wound complication rates are less than 2%. The most devastating early postoperative complication is bleeding or thrombosis which can present with a sudden onset of anuria. Urologic complications including ureter disruption, urinary leaks and distal ureter stenosis with

obstruction can be seen. And as in all organ transplants, acute rejection can occur at any time within the first 3 to 6 months. Chronic rejection and recurrence of original kidney disease also can occur. A kidney biopsy is frequently required to define the cause of a late rise in the serum creatinine level and to direct treatment as needed.

Conclusions

Kidney transplantation has evolved into a treatment of choice for selected patients with end-stage renal disease. With improvements in patient management, HLA matching, and immunosuppressive protocols, the future of renal transplantation will include high risk groups such as the very young or the elderly. It is imperative that all patients with end-stage renal disease be given the option of kidney transplantation. As will be discussed later in this issue of the *Journal*, organ donation remains the major obstacle in kidney and solid organ transplantation. In Hawaii, there are more than 100 patients awaiting kidney transplant. All health professionals can make a difference by selecting and referring appropriate recipients and referring appropriate donors. This *gift of life* must be available to the people of Hawaii.

Acknowledgements

As with any large clinical endeavor, numerous individuals from all specialties must work together to make the vision possible. We owe special thanks to all the nephrologists in Hawaii for their excellent care of patients with end-stage renal disease. Also, the staff of St. Francis Medical Center has been instrumental to our success.

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9. *1991 Report of Center-Specific Graft and Patient Survival Rates;* U.S. Department of Health and Human Services, Public Health Service, Health Resources and Service Administration.

Now indicated for both...

Chronic hepatitis B
and
Chronic hepatitis Non-A, Non-B/C
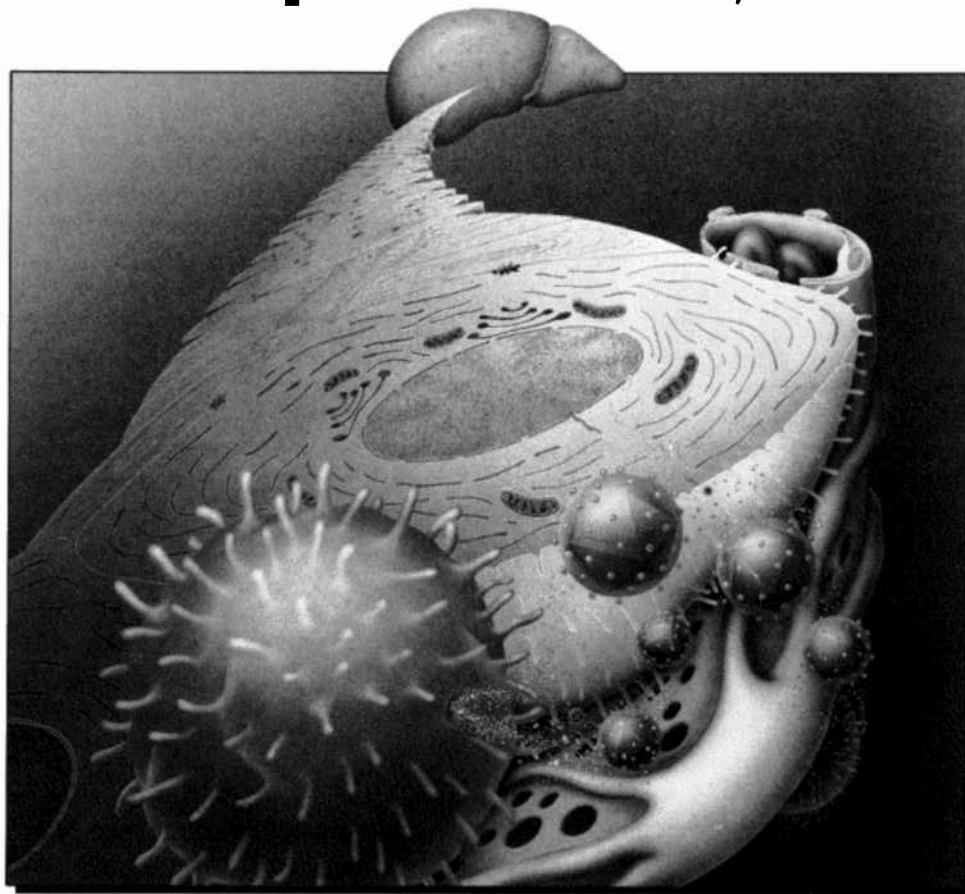
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INTRON® A
Interferon alfa-2b recombinant
For Injection
BRIEF SUMMARY

INDICATIONS AND USAGE

Chronic Hepatitis Non-A, Non-B/C (NANB/C)   INTRON A Interferon alfa-2b, recombinant for Injection is indicated for the treatment of chronic hepatitis Non-A, Non-B/C (NANB/C) in patients 18 years of age or older with compensated liver disease who have a history of blood or blood product exposure and/or are HCV antibody positive. Studies in these patients demonstrated that INTRON A therapy can produce clinically meaningful effects on this disease, manifested by normalization of serum alanine aminotransferase (ALT) and reduction in liver necrosis and degeneration.

A liver biopsy should be performed to establish the diagnosis of chronic hepatitis. Patients should be tested for the presence of antibody to HCV. Patients with other causes of chronic hepatitis, including autoimmune hepatitis, should be excluded. Prior to initiation of INTRON A therapy, the physician should establish that the patient has compensated liver disease. The following patient entrance criteria for compensated liver disease were used in the clinical studies and should be considered before INTRON A treatment of patients with chronic hepatitis NANB/C:

- No history of hepatic encephalopathy, variceal bleeding, ascites, or other clinical signs of decompensation

- Bilirubin   ≤2 mg/dL
- Albumin   Stable and within normal limits
- Prothrombin Time <3 seconds prolonged
- WBC   ≥3000/mm³
- Platelets   ≥70,000/mm³

Serum creatinine should be normal or near normal.

Prior to initiation of INTRON A therapy, CBC and platelet counts should be evaluated in order to establish baselines for monitoring potential toxicity. These tests should be repeated at weeks 1 and 2 following initiation of INTRON A therapy, and monthly thereafter. Serum ALT should be evaluated after 2, 16, and 24 weeks of therapy to assess response to treatment (see **DOSAGE AND ADMINISTRATION**).

Patients with preexisting thyroid abnormalities may be treated if thyroid stimulating hormone (TSH) levels can be maintained in the normal range by medication. TSH levels must be within normal limits upon initiation of INTRON A treatment and TSH testing should be repeated at 3 and 6 months (see **PRECAUTIONS – Laboratory Tests**).

Chronic Hepatitis B   INTRON A Interferon alfa-2b, recombinant for Injection is indicated for the treatment of chronic hepatitis B in patients 18 years of age or older with compensated liver disease and HBV replication. Patients must be serum HBsAg positive for at least 6 months and have HBV replication (serum HBeAg positive) with elevated serum ALT. Studies in these patients demonstrated that INTRON A therapy can produce virologic remission of this disease (loss of serum HBeAg), and normalization of serum aminotransferases. INTRON A therapy resulted in the loss of serum HBsAg in some responding patients.

Prior to initiation of INTRON A therapy, it is recommended that a liver biopsy be performed to establish the presence of chronic hepatitis and the extent of liver damage. The physician should establish that the patient has compensated liver disease. The following patient entrance criteria for compensated liver disease were used in the clinical studies and should be considered before INTRON A treatment of patients with chronic hepatitis B:

- No history of hepatic encephalopathy, variceal bleeding, ascites, or other signs of clinical decompensation

- Bilirubin   Normal
- Albumin   Stable and within normal limits
- Prothrombin Time <3 seconds prolonged
- WBC   ≥4000/mm³
- Platelets   ≥100,000/mm³

Patients with causes of chronic hepatitis other than chronic hepatitis B or chronic hepatitis NANB/C should not be treated with INTRON A Interferon alfa-2b, recombinant for Injection. CBC and platelet counts should be evaluated prior to initiation of INTRON A therapy in order to establish baselines for monitoring potential toxicity. These tests should be repeated at treatment weeks 1, 2, 4, 8, 12, and 16. Liver function tests, including serum ALT, albumin and bilirubin, should be evaluated at treatment weeks 1, 2, 4, 8, 12, and 16. HBeAg, HBsAg, and ALT should be evaluated at the end of therapy, as well as 3 and 6 months posttherapy, since patients may become virologic responders during the 6 month period following the end of treatment. In clinical studies, 39% (15/38) of responding patients lost HBeAg 1 to 6 months following the end of INTRON A therapy. Of responding patients who lost HBsAg, 58% (7/12) did so 1 to 6 months posttreatment.

A transient increase in ALT ≥2 times baseline value (flare) can occur during INTRON A therapy for chronic hepatitis B. In clinical trials, this flare generally occurred 8 to 12 weeks after initiation of therapy and was more frequent in responders (63%, 24/38) than in nonresponders (27%, 13/48). However, elevations in bilirubin ≥3 mg/dL occurred infrequently (2%, 2/86) during therapy. When ALT flare occurs, in general, INTRON A therapy should be continued unless signs and symptoms of liver failure are observed. During ALT flare, clinical symptomatology and liver function tests including ALT, prothrombin time, alkaline phosphatase, albumin, and bilirubin, should be monitored at approximately 2 week intervals (see **WARNINGS**).

DOSAGE AND ADMINISTRATION

Chronic Hepatitis Non-A, Non-B/C (NANB/C)   The recommended dosage of INTRON A Interferon alfa-2b, recombinant for Injection for the treatment of chronic hepatitis NANB/C is 3 million IU three times a week (TIW) administered subcutaneously or intramuscularly.

Normalization of serum alanine aminotransferase (ALT) may occur in some patients as early as two weeks after initiation of treatment; however, current experience suggests that patients responding to INTRON A therapy with a reduction in serum ALT should complete 6 months (24 weeks) of treatment. The optimal dose and duration of therapy are currently under investigation.

In clinical trials, 54% (51/95) of the patients at a dose of 3 million IU TIW responded with a reduction in serum ALT after 6 months of INTRON A therapy. Since most of these patients (49/51) responded within the first 16 weeks of treatment, consideration could be given to discontinuing INTRON A therapy in patients who fail to respond after 16 weeks. The effect of dose escalation in these patients is under investigation.

If severe adverse reactions develop during INTRON A treatment, the dose should be modified (50% reduction) or therapy should be temporarily discontinued until the adverse reactions abate. If intolerance persists after dose adjustment, INTRON A therapy should be discontinued.

Patients who relapse following INTRON A therapy may be retreated with the same dosage regimen to which they had previously responded.

Chronic Hepatitis B   The recommended dosage of INTRON A Interferon alfa-2b, recombinant for Injection for the treatment of chronic hepatitis B is 30 to 35 million IU per week, administered subcutaneously or intramuscularly either as 5 million IU daily (QD), or 10 million IU three times a week (TIW), for 16 weeks.

If severe adverse reactions or laboratory abnormalities develop during INTRON A therapy the dose should be modified (50% reduction), or discontinued if appropriate, until the adverse reactions abate. If intolerance persists after dose adjustment, INTRON A therapy should be discontinued.

For patients with decreases in granulocyte or platelet counts, the following guidelines for dose modification were used in the clinical trials:

INTRON A Dose	Granulocyte Count	Platelet Count
Reduce 50%	<750/mm³	<50,000/mm³
Interrupt	<500/mm³	<30,000/mm³

INTRON A therapy was resumed at up to 100% of the initial dose when granulocyte and/or platelet counts returned to normal or baseline values.

At the discretion of the physician, the patient may self-administer the medication. (See illustrated **PATIENT INFORMATION SHEET** for instructions.)

Preparation and Administration of INTRON A Interferon alfa-2b, recombinant for Injection
Reconstitution of lyophilized INTRON A Interferon alfa-2b, recombinant for Injection Inject the amount of Diluent for INTRON A Interferon alfa-2b, recombinant for Injection (bacteriostatic water for injection) stated in the appropriate chart below (diluent is supplied in either a vial or syringe, see **HOW SUPPLIED** below), into the INTRON A vial. Swirl gently to hasten complete dissolution of the powder. The appropriate INTRON A dose should then be withdrawn and injected intramuscularly or subcutaneously. (See **PATIENT INFORMATION SHEET** for detailed instructions.)

After preparation and administration of the INTRON A injection, it is essential to follow the procedure for proper disposal of syringes and needles. (See **PATIENT INFORMATION SHEET** for detailed instructions.)

Chronic Hepatitis Non-A, Non-B/C

Vial Strength	mL Diluent	Final Concentration
3 million IU	1	3 million IU/mL
†18 million IU multidose	3.8	6 million IU/mL

†This is a multidose vial to deliver 18 million IU of INTRON A Interferon alfa-2b, recombinant for Injection when reconstituted with 3.8 mL of the diluent provided.

Chronic Hepatitis B

Vial Strength	mL Diluent	Final Concentration
5 million IU	1	5 million IU/mL
10 million IU	1	10 million IU/mL

Stability INTRON A Interferon alfa-2b, recombinant for Injection provided as lyophilized powder in vials ranging from 3 to 50 million IU per vial, is stable at 45°C (113°F) for up to 7 days. After reconstitution with Diluent for INTRON A Interferon alfa-2b, recombinant for Injection (bacteriostatic water for injection) the solution is stable for one month at 2° to 8°C (36° to 46°F). The reconstituted solution is clear and colorless to light yellow.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. INTRON A Interferon alfa-2b, recombinant for Injection may be administered using either sterilized glass or plastic disposable syringes.

CONTRAINDICATIONS

INTRON A Interferon alfa-2b, recombinant for Injection is contraindicated in patients with a history of hypersensitivity to interferon alfa or any component of the injection.

WARNINGS

General   Moderate to severe adverse experiences may require modification of the patient's dosage regimen, or in some cases termination of INTRON A therapy. Because of the fever and other "flu-like" symptoms associated with INTRON A administration, it should be used cautiously in patients with debilitating medical conditions, such as those with a history of pulmonary disease (eg, chronic obstructive pulmonary disease), or diabetes mellitus prone to ketoacidosis. Caution should also be observed in patients with coagulation disorders (eg, thrombophlebitis, pulmonary embolism) or severe myelosuppression.

Patients with platelet counts of less than 50,000/mm³ should not be administered INTRON A Interferon alfa-2b, recombinant for Injection intramuscularly, but instead by subcutaneous administration.

INTRON A therapy should be used cautiously in patients with a history of cardiovascular disease such as unstable angina or uncontrolled congestive heart failure. Those patients with a recent history of myocardial infarction and/or previous or current arrhythmic disorder who require INTRON A therapy should be closely monitored (see **Laboratory Tests**). Cardiovascular adverse experiences, which include hypotension, arrhythmia, or tachycardia of 150 beats per minute or greater, and transient reversible cardiomyopathy have been observed in some INTRON A treated patients. Transient reversible cardiomyopathy was reported in approximately 2% of the AIDS-Related Kaposi's Sarcoma patients treated with INTRON A Interferon alfa-2b, recombinant for Injection. The incidence of these complications in patients with preexisting heart disease is unknown. Hypotension may occur during INTRON A administration, or up to two days posttherapy, and may require supportive therapy including fluid replacement to maintain intravascular volume. Supraventricular arrhythmias occurred rarely and appeared to be correlated with preexisting conditions and prior therapy with cardiotoxic agents. These adverse experiences were controlled by modifying the dose or discontinuing treatment, but may require specific additional therapy.

Patients with a preexisting psychiatric condition, especially depression, or a history of severe psychiatric disorder should not be treated with INTRON A Interferon alfa-2b, recombinant for Injection.[1] INTRON A therapy should be discontinued for any patient developing severe depression or other psychiatric disorder during treatment. Central nervous system effects manifested by depression, confusion and other alterations of mental status have been observed in some INTRON A treated patients, and suicidal ideation and attempted suicide have been observed rarely. These adverse effects have occurred in patients treated with recommended doses as well as in patients treated with higher INTRON A doses. More significant obtundation and coma have also been observed in some patients, usually elderly, treated at higher doses. While these effects are usually rapidly reversible upon discontinuation of therapy, full resolution of symptoms has taken up to three weeks in a few severe episodes. Narcotics, hypnotics, or sedatives may be used concurrently with caution and patients should be closely monitored until the adverse effects have resolved.

Patients with preexisting thyroid abnormalities whose thyroid function cannot be maintained in the normal range by medication should not be treated with INTRON A Interferon alfa-2b, recombinant for Injection. Therapy should be discontinued for patients developing thyroid abnormalities during treatment whose thyroid function cannot be normalized by medication.

Hepatotoxicity, including fatality, has been observed rarely in INTRON A treated patients. Any patient developing liver function abnormalities during treatment should be monitored closely and if appropriate, treatment should be discontinued.

Chronic Hepatitis Non-A, Non-B/C (NANB/C) and Chronic Hepatitis B   Patients with decompensated liver disease, autoimmune hepatitis or a history of autoimmune disease, and patients who are immunosuppressed transplant recipients should not be treated with INTRON A Interferon alfa-2b, recombinant for Injection. There are reports of worsening liver disease, including jaundice, hepatic encephalopathy, hepatic failure and death following INTRON A therapy in such patients. Therapy should be discontinued for any patient developing signs and symptoms of liver failure.

Chronic hepatitis B patients with evidence of decreasing hepatic synthetic functions, such as decreasing albumin levels or prolongation of prothrombin time, may be at increased risk of clinical decompensation in association with a flare of aminotransferases during INTRON A treatment. In considering these patients for INTRON A therapy, the potential risks must be evaluated against the potential benefits of treatment.

PRECAUTIONS

General   Acute serious hypersensitivity reactions (eg, urticaria, angioedema, bronchoconstriction, anaphylaxis) have been observed rarely in INTRON A treated patients; if such an acute reaction develops, the drug should be discontinued immediately and appropriate medical therapy instituted. Transient rashes have occurred in some patients following injection, but have not necessitated treatment interruption.

While fever may be related to the flu-like syndrome reported commonly in patients treated with interferon, other causes of persistent fever should be ruled out.

There have been reports of interferon exacerbating preexisting psoriasis; therefore, INTRON A therapy should be used in these patients only if the potential benefit justifies the potential risk.

Variations in dosage, routes of administration, and adverse reactions exist among different brands of interferon. Therefore, do not use different brands of interferon in any single treatment regimen.

Drug Interactions   Interactions between INTRON A Interferon alfa-2b, recombinant for Injection and other drugs have not been fully evaluated. Caution should be exercised when administering INTRON A therapy in combination with other potentially myelosuppressive agents such as zidovudine.

Laboratory Tests   In addition to those tests normally required for monitoring patients, the following laboratory tests are recommended for all patients on INTRON A therapy, prior to beginning treatment and then periodically thereafter.
- Standard hematologic tests — including hemoglobin, complete and differential white blood cell counts and platelet count.
- Blood chemistries — electrolytes, liver function tests, and TSH.

Those patients who have preexisting cardiac abnormalities and/or are in advanced stages of cancer, should have electrocardiograms taken prior to and during the course of treatment.

Mild to moderate leukopenia and elevated serum liver enzyme (SGOT) levels have been reported with intralesional administration of INTRON A Interferon alfa-2b, recombinant for Injection (see **ADVERSE REACTIONS** section); therefore, the monitoring of these laboratory parameters should be considered.

Baseline chest X-rays are suggested and should be repeated if clinically indicated.

For specific recommendations in chronic hepatitis NANB/C and chronic hepatitis B, see **INDICATIONS AND USAGE** section.

Carcinogenesis, Mutagenesis, Impairment of Fertility   Studies with INTRON A Interferon alfa-2b, recombinant for Injection have not been performed to determine carcinogenicity.

Interferon may impair fertility. In studies of interferon administration in nonhuman primates, menstrual cycle abnormalities have been observed. Decreases in serum estradiol and progesterone concentrations have been reported in women treated with human leukocyte interferon.[2] Therefore, fertile women should not receive INTRON A therapy unless they are using effective contraception during the therapy period. INTRON A therapy should be used with caution in fertile men.

Mutagenicity studies with INTRON A Interferon alfa-2b, recombinant for Injection revealed no adverse findings.

Studies in mice, rats, and monkeys receiving INTRON A injections for up to one month have revealed no evidence of toxicity. However, due to the known species-specificity of interferon, the effects in animals are unlikely to be predictive of those in man.

Pregnancy Category C INTRON A Interferon alfa-2b, recombinant for Injection has been shown to have abortifacient effects in *Macaca mulatta* (rhesus monkeys) in all dose groups studied (7.5 million, 15 million, and 30 million IU/kg), although it was only statistically significant *versus* control at the mid and high dose groups (corresponding to 90 and 180 times the intramuscular or subcutaneous dose of 2 million IU/m2). There are no adequate and well controlled studies in pregnant women. INTRON A therapy should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers It is not known whether this drug is excreted in human milk. However, studies in mice have shown that mouse interferons are excreted into the milk. Because of the potential for serious adverse reactions from the drug in nursing infants, a decision should be made whether to discontinue nursing or to discontinue INTRON A therapy, taking into account the importance of the drug to the mother.

Pediatric Use Safety and effectiveness have not been established in patients below the age of 18 years.

ADVERSE REACTIONS

Chronic Hepatitis Non-A, Non-B/C (NANB/C) In patients with chronic hepatitis NANB/C, alopecia, injection site reactions, rash, depression, and irritability apparently increased in incidence with continued treatment; residual mild alopecia persisted posttreatment.

Infrequently, patients receiving INTRON A therapy for chronic hepatitis NANB/C developed thyroid abnormalities, either hypothyroid or hyperthyroid. In clinical trials <1% (4/426) developed thyroid abnormalities. The abnormalities were controlled by conventional therapy for thyroid dysfunction. The mechanism by which INTRON A Interferon alfa-2b, recombinant for Injection may alter thyroid status is unknown. Prior to initiation of INTRON A therapy for the treatment of chronic hepatitis NANB/C, serum TSH should be evaluated. Patients developing symptoms consistent with possible thyroid dysfunction during the course of INTRON A therapy should have their thyroid function evaluated and appropriate treatment instituted. INTRON A treatment may be continued if TSH levels can be maintained in the normal range by medication. Discontinuation of INTRON A therapy has not always reversed thyroid dysfunction occurring during treatment.

Chronic Hepatitis B In patients with chronic hepatitis B, some type of adverse reaction occurred in 98% of the 101 patients treated at 5 million IU, QD and 90% of the 78 patients treated at 10 million IU, TIW. Most of these adverse reactions were mild to moderate in severity, were manageable, and were reversible following the end of therapy.

Adverse reactions classified as severe (causing a significant interference with normal daily activities or clinical state) were reported in 21% to 44% of patients. The severe adverse reactions reported most frequently were the flu-like symptoms of fever (28%), fatigue (15%), headache (5%), myalgia (4%), and rigors (4%), and other severe flu-like symptoms which occurred in 1% to 3% of patients. Other severe adverse reactions occurring in more than one patient were alopecia (8%), anorexia (6%), depression (3%), nausea (3%), and vomiting (2%).

To manage side effects, the dose was reduced, or INTRON A therapy was interrupted in 25% to 38% of patients. Five percent of patients discontinued treatment due to adverse experiences.

ABNORMAL LABORATORY TEST VALUES BY INDICATION
Dosing Regimens
Percentage (%) of Patients

	Chronic Hepatitis NANB/C 3 million IU TIW N = 87-158	Chronic Hepatitis B 5 million IU QD N = 96-101	Chronic Hepatitis B 10 million IU TIW N = 75-103
Laboratory Tests			
Hemoglobin	15%	32%*	23%*
White Blood Cell Count	18%	68%†	34%†
Platelet Count	9%	12%‡	5%‡
Serum Creatinine	2%	3%	0%
Alkaline Phosphatase	3%	8%	4%
Serum Urea Nitrogen	1%	—	—
Granulocyte Count			
• Total	37%§	71%§	61%§
• 1000 – <1500/mm³	—	31%	32%
• 750 – <1000/mm³	—	23%	18%
• 500 – <750/mm³	—	15%	9%
• <500/mm³	—	2%	2%

* Decrease of ≥2 g/dL
† Decrease to <3000/mm³
‡ Decrease to <70,000/mm³
§ Neutrophils plus bands

General The adverse experiences listed in the following table were reported to be possibly or probably related to INTRON A therapy during clinical trials. Most of these adverse reactions were mild to moderate in severity and were manageable. Some were transient and most diminished with continued therapy.

The most frequently reported adverse reactions were flu-like symptoms, particularly fever, headache, chills, myalgia, and fatigue. More severe toxicities are observed generally at higher doses and may be difficult for patients to tolerate.

TREATMENT-RELATED ADVERSE EXPERIENCES BY INDICATION
Dosing Regimens
Percentage (%) of Patients*

ADVERSE EXPERIENCE	CHRONIC HEPATITIS NANB/C 3 million IU TIW N = 159	CHRONIC HEPATITIS B 5 million IU QD N = 101	CHRONIC HEPATITIS B 10 million IU TIW N = 78
Application-Site Disorders			
injection site inflammation	7	3	—
other (<5%)	injection site bleeding, injection site pain, injection site reaction		
Blood Disorders (<5%)	granulocytopenia, hemolytic anemia		
Body as a Whole			
facial edema	1	3	1
weight decrease	<1	2	5
other (<5%)	lymphadenopathy, peripheral edema, thirst		
Cardiovascular System Disorders (<5%)	extrasystoles, hypotension, palpitations, tachycardia		
Endocrine System Disorders (<5%)	aggravation of diabetes mellitus, thyroid disorder		
Flu-like Symptoms			
fever	43	66	86
headache	43	61	44
myalgia	42	59	40
fatigue	19	75	69
increased sweating	3	1	1
asthenia	24	5	15
rigors	27	38	42
arthralgia	19	19	8
dizziness	9	13	10
influenza-like symptoms	9	5	—
back pain	3	—	—
dry mouth	4	6	5
chest pain	1	4	—
malaise	3	9	6
other (<5%)	chest pain substernal, rhinitis, rhinorrhea		
Gastrointestinal System Disorders			
diarrhea	13	19	8
anorexia	13	43	53
nausea	23	50	33
taste alteration	1	10	—
abdominal pain	6	5	4
loose stools	3	2	—
vomiting	3	7	10
constipation	<1	5	—
gingivitis	—	1	—
dyspepsia	3	3	8
other (<5%)	abdominal distention, eructation, flatulence, gastric ulcer, gingival bleeding, gum hyperplasia, increased appetite, melena, stomatitis, stomatitis ulcerative, taste loss		

Disorder		Chronic Hepatitis NANB/C 3 million IU TIW	Chronic Hepatitis B 5 million IU QD	Chronic Hepatitis B 10 million IU TIW
Liver and Biliary System Disorders (<5%)	jaundice, right upper quadrant pain and very rarely, hepatic encephalopathy, hepatic failure, and death			
Musculoskeletal System Disorders				
musculoskeletal pain		—	9	1
other (<5%)	arthrosis, leg cramps			
Nervous System and Psychiatric Disorders				
depression		8	17	6
paresthesia		1	6	3
impaired concentration		4	8	5
confusion		1	—	—
irritability		4	16	12
somnolence		1	14	9
anxiety		1	2	—
insomnia		4	11	6
nervousness		—	3	—
decreased libido		—	5	1
other (<5%)	abnormal coordination, abnormal dreaming, abnormal gait, aggressive reaction, agitation, dysphonia, emotional lability, feeling of ebriety, hot flashes, hyperesthesia, hyperkinesia, hypertonia, hypokinesia, paroniria, personality disorder, syncope, tinnitus, vertigo			
Reproduction System Disorders (<5%)	amenorrhea, impotence, menorrhagia, uterine bleeding			
Resistance Mechanism Disorders				
herpes simplex		—	5	—
other (<5%)	conjunctivitis			
Respiratory System Disorders				
dyspnea		<1	5	—
coughing		<1	4	—
pharyngitis		1	7	1
nonproductive coughing		—	1	—
nasal congestion		—	4	—
other (<5%)	epistaxis, sneezing			
Skin and Appendages Disorders				
dermatitis		—	1	—
alopecia		17	26	38
pruritus		6	6	4
rash		6	8	1
dry skin		<1	3	—
other (<5%)	acne, cyanosis of the hand, cold and clammy skin, dermatitis lichenoides, erythema, increased hair growth, melanosis, nail disorders, photosensitivity, purpura, urticaria, vitiligo			
Urinary System Disorders (<5%)	increased BUN, micturition frequency, nocturia, polyuria			
Vision Disorders (<5%)	abnormal vision, blurred vision, diplopia, dry eyes, eye pain, photophobia			

*Dash (—) indicates not reported

HOW SUPPLIED

INTRON A Interferon alfa-2b, recombinant for Injection, 3 million IU per vial and Diluent for INTRON A Interferon alfa-2b, recombinant for Injection (bacteriostatic water for injection) 1 mL per vial or syringe; boxes containing 1 INTRON A vial and 1 vial of Diluent for INTRON A Interferon alfa-2b, recombinant for Injection (bacteriostatic water for injection) (NDC 0085-0647-03), boxes containing 1 INTRON A vial and 1 syringe of Diluent for INTRON A Interferon alfa-2b, recombinant for Injection (bacteriostatic water for injection) (NDC 0085-0647-04).

INTRON A Interferon alfa-2b, recombinant for Injection INTRON® A, Pak-3, containing 6 INTRON A vials, 3 million IU per vial, and 6 syringes of Diluent for INTRON A Interferon alfa-2b, recombinant for Injection (bacteriostatic water for injection) for Chronic Hepatitis Non-A, Non-B/C (NDC 0085-0647-05).

INTRON A Interferon alfa-2b, recombinant for Injection, 5 million IU per vial and Diluent for INTRON A Interferon alfa-2b, recombinant for Injection (bacteriostatic water for injection) 1 mL per vial or syringe; boxes containing 1 INTRON A vial and 1 vial of Diluent for INTRON A Interferon alfa-2b, recombinant for Injection (bacteriostatic water for injection) (NDC 0085-0120-02), boxes containing 1 INTRON A vial and 1 syringe of Diluent for INTRON A Interferon alfa-2b, recombinant for Injection (bacteriostatic water for injection) (NDC 0085-0120-03).

INTRON A Interferon alfa-2b, recombinant for Injection INTRON® A, Pak-5, containing 14 INTRON A vials, 5 million IU per vial, and 14 syringes of Diluent for INTRON A Interferon alfa-2b, recombinant for Injection (bacteriostatic water for injection) for Chronic Hepatitis B (NDC 0085-0120-04).

INTRON A Interferon alfa-2b, recombinant for Injection, 10 million IU per vial and Diluent for INTRON A Interferon alfa-2b, recombinant for Injection (bacteriostatic water for injection) 2 mL per vial; boxes containing 1 INTRON A vial and 1 vial of Diluent for INTRON A Interferon alfa-2b, recombinant for Injection (bacteriostatic water for injection) (NDC 0085-0571-02).

INTRON A Interferon alfa-2b, recombinant for Injection INTRON® A, Pak-10, containing 6 INTRON A vials, 10 million IU per vial, and 6 syringes of Diluent for INTRON A Interferon alfa-2b, recombinant for Injection (bacteriostatic water for injection) for Chronic Hepatitis B (NDC 0085-0571-06).

INTRON A Interferon alfa-2b, recombinant for Injection, 18 million IU multidose vial and Diluent for INTRON A Interferon alfa-2b, recombinant for Injection (bacteriostatic water for injection) 3.8 mL per vial; boxes containing 1 multidose vial of INTRON A Interferon alfa-2b, recombinant for Injection and 1 vial of Diluent for INTRON A Interferon alfa-2b, recombinant for Injection (bacteriostatic water for injection) (NDC 0085-0689-01).

Store INTRON A Interferon alfa-2b, recombinant for Injection both before and after reconstitution between 2° and 8°C (36° and 46°F).

Allogeneic and Autologous Bone Marrow Transplant Experiences in Hawaii

Livingston M.F. Wong MD, Robert T.S. Jim MD, Kevin K. Loh MD,
Robert W. Wilkinson MD, Clayton D.K. Chong MD

Allogeneic bone marrow transplant (BMT) was first performed successfully at St. Francis Medical Center in 1978. Since that time, 91 BMTs have been performed for aplastic anemia, leukemia, lymphoma, and Stage II, III and IV breast cancers. This article will explain the methods, complications and results of BMT in Hawaii.

Methods

Bone marrow transplant experience in Hawaii has been that of purged or non-purged autologous and allogeneic. Autologous is defined as marrow taken from the patient. It is purged with chemotherapeutic agents or monoclonal antibodies if marrow is involved with tumor, or non-purged if marrow is not involved with tumor. The marrow is stored after being frozen with liquid nitrogen. The patient is treated with total body irradiation, fractionated 225 rads for 5 doses and/or with chemotherapeutic agents such as cyclophamide (CTX), etoposide (VP 16), busulfan (BU), and carmustine (BCNU) in escalated doses (4 to 10 times normal doses). After chemotherapy and/or radiation, the marrow is thawed and re-infused into the patient through a central venous catheter.

Allogeneic transplant is performed between a donor and recipient. The healthy donor usually is an HLA-identical sibling, although HLA-identical unrelated donors recently have been used. The 6th chromosome harboring the HLA locus must be identical or with no more than 1 mismatch in the 6 antigens. The ABO blood type locus in the 9th chromosome can be crossed and a mismatch also may result in similar good results. In Hawaii, a donor is found by HLA typing of family members or through local and national registries. The donor must be free of hepatitis, AIDS, and in good physical condition. The recipient must be young and otherwise healthy with no infectious disease, diabetes, cardiac disease or severe respiratory problems. Once a

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donor/recipient pair is identified, the recipient undergoes total body irradiation of fractionated 225 rads for 5 doses, and/or receives chemotherapy with CTX, VP 16, BU, or BCNU. Following this, the patient is allowed to rest for 48 hours. The donor marrow is then harvested and infused into the recipient within 24 hours. The amount of marrow given is 3×10^8 of nucleated cells per kilogram of recipient weight.

After infusion of marrow, the recipient is maintained in a special room with Hepafilter air conditioning and 10 mm of positive pressure. The patient is maintained on a specific diet consisting of no fresh fruits or vegetables, and all meals are thoroughly cooked to avoid this source of infection. Specific oral antibiotics and antifungal medications are given prophylactically. Visitors must comply with strict rules for washing their hands and must wear masks and gloves to avoid contaminating these immunosuppressed patients. Hospitalization for 30 to 500 days generally is needed to reconstitute marrow and obtain a WBC > 4,000 cells/mm³. The patient is given granulocyte-colony stimulating factor (G-CSF) or granulocyte and macrophage-colony stimulating factor (GM-CSF) in order to stimulate WBC production. RBCs are slower to reconstitute and platelets may require 3 to 6 months before the count becomes normal.

Although the WBC count may become normal, the function of these cells can be depressed for as long as a year. These patients will require monthly intravenous immunoglobulin and cyclosporine for 6 months. If all goes well, at the end of the 6 months, these patients are on no medication and can behave almost normally. At the end of 1 year, the majority who survive in a disease-free state are as healthy as any in their age group.

Results

Sixty-seven allogeneic bone marrow transplants have been performed at St. Francis Medical Center (SFMC) for various stages of leukemia, aplastic anemia, and lymphoma since 1978 and the majority of these were for advanced disease. When broken down by age groups, stage of disease, and type of disease, the numbers of patients for each category would be a relatively small 3 to 5 for each category. Comparisons for such small numbers would not be meaningful. At present, 23 are alive, in complete remission and disease-free: One patient is

alive with recurrent disease; of the 23 who are alive, 19 are back to full employment and activity, 2 are at home and 2 remain hospitalized.

Sixteen autologous harvests have been performed at SFMC, followed by 11 transfusions: Five of these patients are in remission and disease-free and 6 have died. Four autologous purged BMTs have been performed; 2 have survived in complete remission (disease-free). The first was done in conjunction with Kapioloni Medical Center for Women and Children.

Discussion

Autologous BMT, purged or non-purged, has been performed in Hawaii for: Leukemia in remission, lymphoma with minimal or no bone involvement, and breast cancer as an adjutant therapy in those patients with 10 or more positive nodes or metastatic disease. Allogeneic BMT is performed for aplastic anemia, acute leukemias, chronic leukemias, and lymphoma. Currently, there appears to be no benefit of allogeneic BMT in solid tumors.

The results from our center are comparable to many U.S. centers. The success rate for bone marrow transplant is quite variable and depends on: 1) age, 2) disease type: acute myelogenous leukemia (AML), chronic myelogenous leukemia (CML), acute lymphoblastic leukemia (ALL), Lymphoma - B-cell, T-cell, Hodgkin's or non-Hodgkin's, 3) stage of disease (first remission, relapse, second remission, second relapse, accelerated disease or blastic crisis), and 4) overall physical condition of the patient.

1) **Age.** Allogeneic BMTs generally are limited to the younger patient. Those patients under 20 years of age have the best results. Intermediate results occur in 20 to 30-year olds, and BMT is contraindicated in those over 45 years of age because of the high morbidity and mortality.

2) **Type of disease.** Aplastic anemia has excellent results bordering on 75% complete remission after BMT. Good results are obtained from AML and CML, with long-term disease-free states. BMT for ALL results in high recurrence rates and lower long-term disease-free states. The outcome for lymphoma depends largely on the extent of disease and the presence of chromosomal abnormalities. Extensive disease with chromosomal abnormalities invariably yields poor long-term disease-free states.

3) **State of disease.** Optimal results for allogeneic BMT occur when done early after diagnosis when the disease is in first remission. Transplantation done in blastic crisis yields 10% or less long-term disease-free remission.

4) **Patient condition.** The overall physical condition of the patient is important to the success of BMT. Patients with other diseases such as diabetes, cardiac problems, cerebrovascular disease, hepatitis, and AIDS are disqualified from allogeneic BMT because of the associated high morbidity and mortality.

Thus, the ideal candidate for BMT would be an otherwise healthy 20 year-old with AML in first remission. This would yield the lowest mortality and 50% to 60% long-term disease-free state. Likewise, a 30-year old with CML who is transplanted

before the third year of diagnosis and not in accelerated phase or blastic crisis also would be a good candidate.

Complications from BMT are numerous; the more frequent ones are listed here:

1. **Graft versus host disease (GVHD).** This occurs when the graft views the body as foreign and attempts to reject either the body as a whole or specific organs. This process is a function of activated T-lymphocytes which attack the liver, gastrointestinal tract, lungs, and skin. GVHD can be fatal even in HLA-identical donors and mortality can be as high as 10% and varies with age. Younger patients experience GVHD less than older patients. GVHD also brings about GVL (Graft versus Leukemia), a beneficial response. Radiation and chemotherapy are a Log kill of leukemic cells. The probability of all tumor being eliminated by chemotherapy or radiation is small. With GVL, in all likelihood, the graft will be able to eradicate any remaining leukemic cells.

2. **Pharyngitis.** Severe pharyngitis is caused by high-dose chemotherapy and total body irradiation. This pharyngitis lasts for 2 to 3 weeks and keeps the patient from being able to swallow, drink, or eat; total parenteral nutrition is needed during this period.

3. **Infections.** Bacterial infections are common early complications; however, long-term antibiotic therapy for these may result in later fungal infections. Viral infection such as cytomegalovirus, adenovirus, and herpes zoster tend to occur years later. Appropriate therapy is needed to prevent and treat each of the specific organisms.

4. **Rejection.** Rejection of the graft can occur causing prolonged aplasia and accompanying complications. A second graft could be required to achieve good engraftment.

5. **Sterility.** High-dose chemotherapy and/or fractionated Total Body Irradiation will cause sterility, although male and female hormones will be produced in the usual amounts.

6. **Drug effects.** Use of immunosuppressive medications can result in many untoward effects. Use of steroids can result in Cushingoid appearance, peptic ulcer disease, and cataracts. Cyclosporine in high doses can result in seizures, hypertension, headaches, and nephrotoxicity.

7. **Other complications.** There are many other complications that occur less frequently: Hypothyroidism, veno-occlusive disease, de novo tumors such as lymphoma and leukemias, and interstitial pneumonia.

The program in Hawaii has been approved for Southwest Oncology Group (SWOG), Eastern Cooperative Oncology Group (ECOG), and Pediatric Oncology Group (POG) protocols. Site visits have been performed by SWOG and ECOG, and they have provided full approval for allogeneic and autologous BMT under research protocol.

Under the leadership of Y.K. Paik MD, this program has developed a National Marrow Donor Pool (NMDP) of local donors. Donor marrow has been collected in Hawaii and sent to Canada, Washington, Tennessee, and California.

✐ News and Notes Henry Yokoyama MD

Life in these parts

Paul Harvey on KHVH radio reports: "We are now sending a new unmanned, *unwomaned* probe to the moon."

A physician father's anguish

Nine-month old **Chad Kurahara** developed fever, rash, red eyes and chapped lips just before Christmas. His dad, pediatric rheumatologist **David Kurahara**, who had studied Kawasaki Syndrome for the past 7 years, said, "When he got the red eyes, I knew it was Kawasaki. When you realize it is Kawasaki and you don't know if he has aneurysms or whether he's going to develop them, that's pretty scary." (Ed. We pray it had a happy ending)

Gang Tattoos

Sgt **Rodney Goo**, "gang detail's boss", was one of 10 Americans awarded the National Child Labor Committee's 1994 Lewis Hine Award. Goo's 7 officer school-education detail started a pilot program to remove gang tattoos from youngsters wanting to quit gangs. (**Norman Goldstein** is doing it at no charge so long as patients sign a contract promising they will stay out of gangs and off drugs.)

Healthy genes?

Ben and **Rosaline Kanealii,** both pretty pure Hawaiians in their mid-70s are our precious patients. They had 15 children, but 2 died in infancy and a third died in an accident, early in childhood. So their remaining 12 children beget 55 grandchildren, 68 great grandchildren and 4 great great grandchildren—all doing well.

Iniki aftermath: Wilcox Memorial Health Center hopes to consolidate the 80 physicians on Kauai. The Center purchased the Garden Island Medical Group (with its 11 physicians) in January and is continuing discussions with the Kauai Medical Group (with it's 47 physicians). The remaining 22 physicians are mostly independent and a few are associated with HMSA's Kuhio Medical Clinic in Lihue.

Arnold Siemsen's heritage

St. Francis Medical Center has renamed it's newly renovated Renal Institute of the Pacific, the Siemsen Dialysis Center in honor of Arnold who established the dialysis center in 1968 and was medical director until his retirement in 1990.

Our peripatetic neurosurgeon **Ralph Cloward,** on a recent trip to Australia, picked up the following poem entitled: **The Bush Doc**
A ringer* rode up to a pub,
A raging thirst was his.
He tied up his horse, lifted it's tail
and under it planted a kiss.

The Doc had seen some strange things
In this land of sweat and sin.
But what he saw that ringer* do
Well, it fairly got him in!

For this was an act that intrigued the doc,
Who was ever alert for new tips.
"Er, excuse me" he said,
"Why did you do that?"
The ringer* replied, "Sore lips."

"Does that heal them?",
the doctor inquired,
His professional interest quickening.
The ringer* grinned at him,
"No", he drawled, "that's only to Stop me from licken 'em."

*Ringer: Australian for cowboy.

Professional moves

October: Straub announced its newest physicians and their clinic assignments:
Internist **Boyuan Cao**—Urgent care, Kaneohe
Internist **Thomas Cheek**—Medicine, Hawaii Kai
FP **Florante DeLeon**—Urgent care, Westridge
Psychiatrist **John Guo**—King Street
Neurosurgeon **Yoshio Hosobuchi**—King Street
FP **Kenneth Kau**—King Street
Internist **Robert Koerner**—Urgent care, Hawaii Kai
Oncologist/Hematologist **Randal Liu**—King Street
General and vascular surgeon **Elna Masuda**—King Street
Internist **Antonius Mulia**—Pali Momi
FP **Sasha Myers**—King Street
Internist **Robert Westlake**—Mililani

FP **Barbara Ferguson** opened the Naalehu Clinic, West Hawaii. Neurologist **Thomas Drazin** opened at Queen's POB II.

December: Internist **Francis Ikezaki** retired as of Dec 30 with the message, "Fond aloha and good health to all my loyal patients." Internist **Russell Tom** opened at Kapiolani Medical Center at Pali Momi. Internist **Mark Kimbrell** opened his practice at 328 Uluniu Street, Suite 103, Kailua. **Stephen De Nigris** became Kauai's first gastroenterologist.

Miscellany

A Scot lad met a Scot lass and offered to walk her home. "Shall we go through the woods instead of the village?" he suggested. "No!" she replied firmly. "Is it the gleam in my eyes?" "No, it is the tilt of your kilt," she said. (As told by our favorite humorist **Roger Brault**)

Laughter the best medicine

(Excerpts from *Readers Digest*)

A psychologist was giving a lecture at a men's club. "How many of you make love to your wife every night?" A few raised their hands. "Twice a week?" More hands. "Once a month?" Still more. "Only once a year?" A man in the back row jumped up and eagerly shouted, "Me!" "Why are you so cheerful?" the therapist asked. "Because tonight's the night!" (**Milton Berle**)

Psychiatrist's secretary: "There's a man in the waiting room who claims to be invisible." Psychiatrist: "Tell him I can't see him right now." (**Clifford Kuhu** MD)

Elected, appointed and honored

St. Francis Medical Center honored the following medical staff members: Distinguished Alumni Award **Richard Moore**; Accomplishment Award **William Dang Jr.**; Service Award **Herbert Y.H. Chinn**; Bioethics Award **S.Y. Tan**; Community Service Award **Ramon Sy**.

Hors de combat

In January, the AMA launched a $1.6 million print advertising campaign that asks, "Would you rather trust your life to an MD or an MBA?" AMA leaders fear that "giant profitseeking corporations" could come to dominate health care under the proposed Clinton Health Plan.

Physicians speak up

In a letter to the editor, retired thoracic surgeon **Paul Gebauer** pushes for legalized assisted death: "Suicide in any form is unwanted by doctors, legislators, everyone, and even by those who wish to or need to die. But it has been thrust upon them because it is the only way to circumvent a law which prohibits assisted death and compels doctors to do their duty furtively, or shirk it. There are times when a physician's job to relieve suffering and curtail useless living transcends life preservation. There are times when death should be provided, not abided."

Ronald J. Wong and **Vincent J. Nip**, in a letter to the editor, report that "the trauma service at the Queen's Medical Center admitted 85 gunshot injuries during a 2-year period Jan '92 to Dec '93. Excluding those treated and released from the ER, the average hospital cost of each admission, (minus surgeon and consultant fees) was more than $21,000 per patient. The opportunity for the Hawaii Legislature to enact tough gun control laws should not slip by. Private gun ownership carries substantial personal risk which far outweighs any benefits. There is growing medical evidence that restrictive gun legislation can reduce homicide and suicide rates." "In Washington DC, the enactment of a law barring the purchase, sale, transfer or possession of hand guns by civilians was followed by an abrupt decline in homicide and suicides." (*N Engl J Med,* Dec 91)

Potpourri

Larry Wong's repertoire:
Psychoceramics=crack pot
Honeymoon salad=Let us alone without dressing.

Health plans:

Kennedy Health Plan=Womb to tomb care
Clinton Health Plan=Erection to resurrection care.

Quotables

William Osler was the Leonardo Da Vinci of medicine. He's the last guy to know all you have to know. If he did not diagnose the condition, you didn't have it." (**John Towbridge,** associate clinical professor of medicine, U of Cal SF, Nov 5 '93, QMC Kam Auditorium)

Miscellany

One hot day, we were exploring the Scottish Highlands and stopped the car to let out our aging collie for fresh air. Tongue lolling, he lay panting on a grassy knoll, while my husband spread his map over the car's hood and, head in hands, proceeded to study it. Another car drove up. "Is he ill?" The driver asked in concern. "Can I help?" "Oh, no," I explained. "He's just getting old. He used to bound out of the car and jump all over me, ready for a romp in the grass." The stranger stared at me and hurriedly drove off. He hadn't seen our dog. (**Grace Parker,** *Readers Digest,* July '92)

National news

Abortion cost: The Clinton administration has decided that states must pay for abortions for low income women made pregnant by rape or incest. Medicaid had paid for such abortions for the last 12 years. But no longer.

Breast implants: In Jan. 1992, FDA Commissioner **David Kessler** had called for a moratorium on silicone breast implants. One year later, the AMA decided that there was no convincing evidence that breast implants posed

serious medical problems and declared that women ought to be able to get them for cosmetic purposes once informed of the risks.

Elderly in HMOs: In the Reagan and Bush administrations, Medicare officials insisted that HMOs would raise the quality of care of the elderly by coordinating services and save money for the government. A new study by Mathematics Policy Research (a private consulting group) said the government paid 5.7% more for Medicare patients in HMOs than in the regular Medicare program. Clinton officials are now saying they will not prod elderly Medicare patients to join HMOs.

Physician groups support Clinton plan

While the 296,000 member AMA has misgivings about requiring employers to pay for health insurance, 10 other groups with more than 300,000 members are supporting the plan. The groups are: The American Academy of Family Physicians, American Academy of Pediatrics, American College of Obstetricians and Gynecologists, American College of Physicians, American College of Preventive Medicine, American Medical Women's Association, American Society of Internal Medicine, American Thoracic Society, National Hispanic Medical Association and the National Medical Association.

The Clinton Plan would make upper income retirees—starting at $90,000 for an individual and $115,000 for a couple—pay 75% of the costs of their Medicare Part B coverage instead of the 25%.

Medicaid would save $51 billion from 1995 to 2000 by phasing out payments to hospitals serving large numbers of poor, uninsured people. The rationale is that under universal coverage, the hospitals no longer will have to provide so much charity care.

The government would raise $7.3 billion in extra Medicare payroll taxes by requiring all state and local government workers to pay the tax.

Three million disabled people would qualify for new home and community-based care. The state-run programs would be phased in over several years and provide services worth $11,000 a year on average. Severely mentally retarded persons living outside institutions could get help worth more than $31,000 each.

Research reports

Michael Aldous et al of the University of Washington studied 4,019 first-born infants of white women ages 35 to 39 and 410 first-born infants of white women age 40 and older. They found that white women age 40 and older were 2.3 times more likely to deliver infants weighing less than 5.6 lbs than women ages 20 to 24.

Researchers from UC at San Diego looked at the coffee and milk drinking habits of 980 menopausal women ages 50 to 98 and measured the bone density of their hips and spines.

Women who drank 2 or more cups of coffee

and a glass of milk a day had 6.5% higher bone density than women who drank no milk.

Depression and drug therapy
(Lecture by VP Daniel Casey, Prof of Neurology, Oregon Med School on 2/12/93 at KMC. Notes therefrom)

Depression: A common disorder afflicting 3.7% to 6.7% of the population and resulting in substantial morbidity and mortality.

Morbidity: a) diminished function at work and with family; b) resorts to self-medication with drugs and alcohol.

Mortality: 14/100,000 suicides. Most 2° depression.

Depression is a preventable disorder and is life threatening.

Three out of four prescriptions for antidepressants are written by non-psychiatrists ie family practitioners, internists and gynecologists.

Criteria for major depression: (5 out of 9 including 1 or 2) 1. Depressed mood 2. Loss of interest or pleasure 3. Weight loss or gain: more than 5% 4. Insomnia or hypersomnia 5. Psychotic agitation or retardation 6. Worthless or guilty feeling 7. Fatigue or loss of energy 8. Diminished mental concentration 9. Recurrent thoughts of death or suicide. Note: Most depressed patients will not say they are depressed.

Pathophysiology of depression: Deficiency of amine neurotransmitters
  a. Norepinephrine
  b. Serotonin

Drug	Serotonin	Norepinephrine
Paroxetine	4+	0
Sertaline	4+	0
Fluoxetine	3+	0
Amitryptyline	2+	+
Trazodone	+	0
Imipramine	+	+
Naprotyline	0	2+
Nortriptyline	+	3+
Desipramine	+	4+

• No evidence that combining drugs increases benefits, but it does increase the side effects.

Comparison of Drugs: Equal antidepressant efficacy. Equal onset of action (2 to 3 weeks). All drugs work equally well.

• SSRIs have more favorable side-effect and overdose-profiles as compared to tricyclics.

Tricyclic overdose: 10 day-plus dose is toxic (cardiac). 20 to 30x daily dose causes cardiac toxicity.

SSRIs: No toxicity even with 50 to 150x daily dose. Kinder to patients re side effects.

• Sertaline affinity to 5HT uptake sites versus binding to various receptors: 5HT=4+ Alpha NE=± 5HT$_2$=±

Prozac: Sexual dysfunction: 18%; soft stools and nausea 25%.

SSRIs lower serotonin uptake pump and thereby raise serotonin level.

Tricyclics lower: a. Serotonin uptake pump b. Norepinephrine pump c. Blocks choline and alpha receptors.

• Placebo has benefit: positive expectation of people works to peak at 2 weeks.

SSRIs and Tricyclics: 40% efficacy at 2 weeks; 80% efficacy at 8 weeks.

• Relapse rates lessened by staying on therapy.

Medicine's funny bone
(Excerpts from *Medical World News* July 1986)

An old psychiatrist and a young psychiatrist leave the office together at the end of a long day. The older man is dapper and has not a hair out of place. The younger doctor is totally unkempt and frazzled.

"How can you be in such great shape after a whole day of listening to people spill out their deepest, most gut-wrenching problems?" the young guy asks.

"So who listens?" replies the veteran.

★★★

"Surgeons do it.
Internists talk about it.
Radiologists just look at the pictures."

★★★

"Principles of dermatology:
If it's wet, dry it.
If it's dry, wet it.
If neither of these works, use steroids.
If steroids don't work, do a biopsy."

Condensed excerpts from "Stitches"
(The *Journal of Medical Humor*, January 1994)

When I was an intern rotating through urology, I remember the following conversation: I asked this Scottish lady: "Does your urine burn?" Lady: "I don't know, doctor, I've never tried to light it." (Dennis Gardiner, Nepean, Ont.)

A disgruntled 15 year old came into the emergency room having cut her finger on the meat-slicer at her part-time job at a delicatessen.

In order to take the young woman's mind off her plight, as I was sewing the wound, I asked her, "So, what were you making when you cut your finger?" "About $5.25 an hour," came the serious reply. (Chris O'Connor, Toronto)

This could take some time
"The identity of the headless corpse found in a tree in Woodland near Liskeard will not be positively known until dental records have been checked." *(Western Morning News)*

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Cardiac Transplantation in Hawaii

Carlos E. Moreno-Cabral MD, J. Haunani Nakaahiki RN

Clinical cardiac transplantation was successfully introduced 26 years ago, and from an initial experimental status, it has moved forward to become an accepted and well-established treatment modality for end-stage cardiac disease. The first cardiac transplant operation in Hawaii was performed in March 1987; the patient lived for 1 year. A total of 20 heart transplant operations have been performed in 19 patients at St. Francis Medical Center in Honolulu. There has been only one hospital death, and our current one-year survival is 77%, which is similar to national statistics. Our longest survivor is now more than 6 years following transplantation. The incidence of rejection episodes and infectious complications is comparable to other studies.

Introduction

Following successful animal experiments in the late 1950s, cardiac transplantation was applied clinically for the first time in 1967. This event led to an unwarranted rush of transplant operations worldwide with resulting poor outcomes. It was through the meticulous efforts of the Stanford group with steadily improving results in the 1970s that transplantation of the heart regained prominence as a valuable procedure in the treatment of end-stage cardiac disease. With the introduction of cyclosporine as part of the immunosuppressive regimen in 1980, a new higher level of success was achieved that produced the appearance of many new transplant programs. The surgical techniques and immunosuppression protocols have become standardized with expected good results. This report reviews the experience with heart transplantation in Hawaii since its inception in 1987.

Patients and methods

After months of preparation, the first cardiac transplant operation in Hawaii was performed in March 1987[1]. Since that time, a total of 20 operations have been performed in 19 patients. The selection of patients was based on standard criteria: All were in advanced cardiac failure and had no other alternative treat-

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ment. There were 17 men and 2 women who were aged 23 to 60 years old (mean 40). Seventy-four percent of these patients (14/19) had idiopathic dilated cardiomyopathy. Five patients had undergone previous cardiac surgery; one patient had 3 previous coronary bypass operations and the placement of an AICD. For patients who were discharged from the hospital, the length of stay varied between 14 and 74 days, with an average of 24 days. The operations were performed between March 1987 and May 1993, and the follow up was completed in December 1993. A profile of the recipient patients is seen in Table 1.

Our immunosuppression regimen has been modeled after the Stanford University protocol and consisted of triple drug oral therapy (cyclosporine, azathioprine and prednisone) plus induction with the monoclonal antibody OKT3 for 14 days. All patients had routine surveillance cardiac biopsies weekly after transplantation for the first 6 weeks, biweekly for 2 months, and monthly until 6 months following the operation. Thereafter, they were biopsied every 3 months for life. Once a year, full cardiac catheterization and coronary angiography were obtained.

Rejection was diagnosed in asymptomatic patients on routine biopsy using standard criteria and on symptomatic patients by clinical diagnosis plus echocardiogram and confirmed by urgent biopsy. Treatment of moderate or severe rejection consisted of 3 consecutive daily doses of 1 gram of methyl-prednisolone. If this failed to clear the episode, a second course of methyl-prednisolone or a repeat course of OKT3 was given. In the case of humoral rejection, characterized by the absence of cellular infiltrates and severe cardiac failure, plasmapheresis or immunoadsorption columns (ProSorba®) were used. This consisted of daily treatments for 3 days, followed by 3 more treatments every other day. In patients who rejected several months after transplantation, the episode was treated with high dose oral steroids (prednisone 50 mg twice a day for 3 days) with tapering over 2 weeks.

Infection surveillance was very strict. All patients (recipients and donors) were screened for CMV IgM and IgG, hepatitis, toxoplasmosis and HIV. After transplantation, routine cultures of sputum and urine were obtained twice a week. Weekly specimens of urine, throat secretions, and blood were obtained for CMV cultures. Appropriate cultures were repeated when clinically indicated.

Donor management was directed by the transplant surgeons.

Hemodynamic stability was emphasized with particular interest in maintaining adequate intravascular volume, minimal inoptropic support with no more than 5 mcg/Kg/min of dopamine and acceptable oxygenation.

Brain death in 14 of the 20 donors was caused by head trauma; 5 had spontaneous intracranial hemorrhage, and 1 had a malignant brain tumor (Table 2). Donor age varied from 14 to 50 years old with a mean of 28. There were 17 men and 3 women; adequate recipient=donor matching included blood type (Table 1) and body size, with discrepancies in body weight no larger than ± 20%, if possible. No prospective tissue typing or crossmatching was performed. Before final acceptance of a donor heart for transplantation, it was required to have had a stable hemodynamic course, a normal or acceptable LV function by echocardiogram, and satisfactory contractility by visual inspection after opening the chest. Pulmonary artery pressure and cardiac output measurements, via Swan Ganz catheter, were performed when clinically indicated. Cardiac catheterization and angiography were done if donors were older than 45 years of age, or if they had a history of hypertension, heavy smoking, or prior heart disease. Standard surgical techniques were used for organ procurement and graft implantation. All transplanted hearts were placed in an orthotopic position. None of the patients was mechanically assisted, either pulmonary or cardiac, at the time of transplantation. Three patients were hospitalized with moderate or severe congestive failure when donors became available. Another patient had been hospitalized for more than 2 months with refractory cardiac failure, requiring 3 weeks of intraaortic balloon (IABP) support, and complicated with a cerebrovascular accident. She recovered from this episode, was discharged home, and transplanted a few weeks later. All donors except 1 were from the Honolulu metropolitan area, and they were transferred to St. Francis Medical Center to decrease the ischemic time. One donor heart was procured in Maui and flown to Honolulu for transplantation.

Results

Survival/initial hospitalization. Operative mortality was 5%. Only 1 patient out of 19 died during the immediate postoperative period.

Long-term survival. The 1-year survival rate was 77%, at 3 years 70% of patients were alive, and 60% survived more than 5 years.

Functional results. All surviving patients except 1 became asymptomatic following transplantation. The patient who continued in failure was a very debilitated 60-year-old man who had 3 previous coronary bypass operations and was hospitalized with severe congestive heart failure and anasarca. He also had chronic pulmonary disease and following transplantation had a stormy course requiring re-exploration for bleeding, prolonged ventilatory support, and a tracheostomy. He was discharged after 73 days in functional class II. Currently more than 2 1/2 years following the operation, he still has moderate limitation in exercise tolerance. Ten of the 14 patients (71%) who survived more than 1 year were rehabilitated and went back to full- or part-time work, or full-time school. One patient retired voluntarily.

Cause of death. A total of 6 patients have died: One patient died during the initial hospitalization 4 days after the operation; 5 patients died 4 months to 26 months following transplantation. The only hospital death occurred in a 48-year-old woman who had early graft failure probably related to pulmonary hypertension (No. 2, Table 1).

Of the late deaths, 4 were due to rejection and 1 due to infection. The first transplant recipient died 12 months after transplantation from complications of rejection that resulted from non-compliance with the medical regimen. Severe rejection was the cause of death in 3 other patients; these occurred 7, 9, and 22 months following transplantation. The first of these patients (No. 13, Table 1) had an uncomplicated operation and was discharged after 21 days in the hospital. He subsequently had 3 episodes of rejection in the first 3 months, requiring intravenous methyl-prednisolone therapy. Seven months after the operation, he had an episode of upper respiratory infection and presented at another hospital with abdominal fullness and dyspnea. Work-up for intra-abdominal pathology delayed the diagnosis of rejection, and he presented to St. Francis Medical Center *in extremis* with cardiogenic shock. One gram of methyl-prednisolone was given at the other hospital before transfer. Total cardiopulmonary support (CPS ®) was provided, but it proved inadequate, with ongoing metabolic acidosis. The same day a donor heart became available and the patient was retransplanted, but could not be weaned from cardiopulmonary bypass and died. The second patient (No. 17, Table 1) had ongoing rejection since the transplant operation, and although clinically he did well for several weeks at a time, the protracted rejection which included alternating or combined humoral and cellular rejection, was never fully controlled despite multiple antirejection treatments. These included several courses of methyl-prednisolone, 3 courses of OKT3, 3 courses of plasmapheresis or immunoadsorption columns and a full course of total lymph node irradiation (80 cGy twice weekly for a total of 10 fractions or 800 cGy). He died 9 months after transplantation at home. The last of this group of patients (No. 11, Table 1) was admitted 26 months after transplantation with a severe episode of rejection and cardiogenic shock. He was placed on CPS 12 hours after admission, but continued deteriorating rapidly despite maximal support and died a few hours later. He is the only patient who has had documented severe 3-vessel coronary artery disease in the transplanted heart. This was known before death on his second-year routine coronary arteriogram, and confirmed at autopsy.

The patient who died of infection (No. 7, Table 1) had a prolonged re-admission to the hospital with disseminated CMV infection and an episode of severe rejection that was reversed with the help of CPS for 5 days. The ultimate cause of death was multiple organ failure from uncontrollable infection.

Morbidity

Infections. Infection episodes were relatively infrequent in our patients. Two episodes of successfully treated *pneumocystis carinii* pneumonia occurred in a patient 3 months and 11 months after transplant. One patient had disseminated CMV infection (previously discussed). Two other patients had systemic symp-

toms with elevated CMV titers and were treated with intravenous ganciclovir. Bacterial infections were seen infrequently and were never of life-threatening proportions. One episode of each of the following infections occurred at different occasions: Bacterial pneumonia, urinary tract infection, wound infection in a traumatic injury, and oral herpes. All of these episodes were adequately treated with the appropriate antibiotics.

Rejection. Of the 18 patients surviving the initial hospitalization, 13 patients (72%) suffered at least 1 episode of moderate acute cellular rejection requiring treatment during the first year. Of the remaining 5 patients, 2 rejected after 1 year, and 3 have never had episodes of rejection requiring therapy. As mentioned above, 3 patients had severe rejection that led to death, 2 within the first year, and 1 after 2 years. Humoral (vascular) rejection occurred in 3 patients at 2 weeks, 2 months, and 3 years following transplantation. These episodes were invariably severe and life-threatening with varying degrees of hemodynamic compromise. All 3 patients required admission to ICU and inotropic support, and 2 required IABP assistance. Treatment included high-dose methyl-prednisolone for 3 days and plasmapheresis and/or immunoadsorption columns. The initial episodes were reversed in all patients. One patient had recurrent rejection and eventually died of it (No. 17, Table 1. Discussed above). In the latest patient with humoral rejection, azathioprine was substituted with cyclophosphamide with good results. Graft atherosclerosis has been diagnosed by coronary angiography in 1 patient (2 years after transplantation) and confirmed as diffuse, severe 3-vessel involvement by autopsy after dying of rejection (See above). Another patient suffered an acute myocardial infarction several years after transplantation; there were EKG changes, but coronary angiography failed to reveal any obstructive lesions. Bradyarrhythmias occurred in 2 patients who responded adequately to oral theophylline. None of our patients has required implantation of a permanent pacemaker and none has developed malignant disease following transplantation.

Hospital cost

Information was available on the cost of the initial hospitalization of the last 9 transplant patients, all performed within the past 3 years. Excluding 2 patients, one with advanced debilitation who spent 2 1/2 months in the hospital following transplantation, and another patient who was hospitalized for 2 months before transplantation, the average hospital cost was $157,289. This reflects the expected current hospital cost for a relatively uncomplicated heart transplant operation excluding physician charges.

Discussion

Cardiac transplantation has achieved an important position in the therapy of incurable cardiac disease. Results have been consistently good since the advent of improved immunosuppressive methods. With the introduction of cyclosporine in 1980, the survival rates improved substantially from 63% to 80% at 1 year, and from 36% to 60% at 5 years.[2] The number of transplant centers and operations have increased remarkably in the past decade and the number of cardiac transplant operations worldwide increased from 700 in 1984 to 2,709 in 1992. A peak was reached in 1990 with a total of 3,289 operations.[3] Although the considerable increase in the number of operations is encouraging, the number of transplant operations remains limited by the availability of donors. Nearly 3,000 patients are waiting for donor hearts at any given time in the United States alone. Xenotransplantation will have to wait until greater advances in immunology take place, and it probably won't be a clinical reality within the next decade.

Selection criteria for recipients continue to evolve, however, the initial guidelines set by the Stanford group have remained mostly unchanged: The age limit is 60 years old, individualized consideration can be given to older patients if they are otherwise deemed good candidates. The oldest transplanted patient entered in the Registry of the International Society of Heart and Lung Transplantation was 75 years old[3] —newborns have been transplanted hours after birth. All candidates must have end-stage cardiac disease untreatable by other means with life expectancy measured in months, and a normal pulmonary vascular resistance (ideally < 3 Wood units). They should have normal or minimally affected kidney and liver function and have strong family support and good compliance, since the medication regimen, and infection and rejection surveillance are very stringent. Contraindications include any active infection, peptic ulcer disease, recent pulmonary embolism, current malignancy, insulin dependent diabetes mellitus and positive serology.

Operative mortality rates have remained steady at 8% to 10%[3]. We had a 5% mortality rate (1/19) and none of the last 17 patients has died during the initial hospitalization. Long-term survival rates are usually reported at yearly intervals with 1-, 5-, and 10-year survival rates used to compare results. Stanford reports an 80.7% and 59.7% 1- and 5-year survival rates for patients treated in the cyclosporine era (1980 to 1989)[2]. The same statistics are 79.1% and 67.8% reported by the Registry[3]. In the latter report, the 10-year survival rate was 55.8%. The survival rates at 1, 3, and 5-year intervals of 77%, 70%, and 60% in our program are similar to other reports.

It is unquestionable that cardiac transplantation has a profound effect in patients who are terminally ill and who would otherwise have a very limited life expectancy. Not only can this procedure add years to their lives, but, equally important, the majority of patients become fully rehabilitated and can enjoy productive lives. Seventy percent of our patients were able to go back to work or school. Similar functional results are reported from other institutions.[2]

In any organ transplantation, a narrow margin between infection and rejection is ever-present. Excessive immunosuppression will decrease the rejection rates, but it will increase the incidence and severity of infections. Deficient immunosuppression will result in fewer infection episodes, but the incidence of rejection will increase. Until better immunosuppressive drugs become available, we have to accept these potential complications and treat them with the best means available. Both infection and rejection remain the main causes of morbidity and mortality in transplant patients. As evidenced in our report, the majority of patients had at least one episode of rejection, and 5

Table 1 Characteristics of Transplant Recipients

No.	Age	Sex	Diagnosis	Blood Type Rec	Donor	Previous Surgery	Length of Stay	Outcome
1	50	M	IDCM	A	O	—	23	Died 1 year
2	38	M	IDCM	B	O	—	18	Alive 6 years 4 months
3	48	F	IDCM	O	O	—	4	Died 4 days
4	23	M	IDCM	A	A	—	35	Alive 5 years 6 months
5	42	M	IDCM	A	O	—	24	Alive 5 years
6	40	M	IDCM	O	O	—	41	Alive 4 years 6 months
7	25	M	LVA	O	O	Aneur resect	18	Died 4 months
8	34	M	IDCM	A	O	—	21	Alive 3 years 9 months
9	23	M	IDCM	A	O	—	18	Alive 3 years 6 months
10	56	M	CAD	A	O	CABG	16	Alive 3 years 3 months
11	34	M	IDCM	A	A	—	17	Died 2 years 2 months
12	60	M	CAD	O	O	3 CABGs	74	Alive 2 years 8 months
13	32	M	IDCM	A	O	—	21	Died 7 month after retransplantation
14	56	M	IDCM	O	O	—	19	Alive 1 year 10 months
15	56	F	IDCM	B	O	—	18	Alive 1 year 6 months
16	32	M	AR	O	O	AVR	19	Alive 1 year 4 months
17	31	M	IDCM	B	O	—	14	Died 9 months
18	54	M	AR	O	O	AVR	24	Alive 13 months
19	37	M	IDCM	AB	A	—	16	Alive 7 months

IDCM=Idiopathic Dilated Cardiomyopathy, **LVA**=Left Ventricular Aneurysm, **CAD**=Coronary Artery Disease, **CABG**=Coronary Artery Bypass Grafting, **AR**=Aortic Regurgitation, **AVR**=Aortic Valve Replacement

of 6 deaths were caused by or associated with rejection episodes. Typically, cellular rejection is discovered by routine biopsy in patients who are asymptomatic. Treatment with short-term enhanced immunosuppression with high-dose steroids aborts the episode and no long-lasting heart damage is seen. Recently, more serious rejection events have been seen. These are humorally mediated and typically present with sudden congestive failure symptoms which rapidly may advance to cardiogenic shock. These episodes are clearly life-threatening and a very aggressive approach is needed to reverse these events. Three of our patients have had such complications. Emergency biopsy has revealed little or no cellular infiltrates and may show vasculitis. Severe cardiac dysfunction is evident by clinical symptoms and signs and echocardiogram usually confirms the degree of impairment of left ventricular contractility. All 3 patients required inotropic medications to sustain cardiac function: 2 of the patients required mechanical assistance with IABP, 1 of them on 2 different occasions. The biopsy has not always been helpful, but when the combination of clinical findings is seen, immediate treatment is given. We have reversed all such episodes with the combination of high dose methyl-prednisolone and treatment with plasmapheresis or immunoadsorption columns. The immunoadsorption columns are used to remove circulating immunoglobulins in a selective manner rather than exchanging

Table 2 Donors. Cause of Brain Death		
Head Trauma	MVA	8
	GSW	5
	Fall	1
Intracranial Bleeding		5
Brain Tumor		1
MVA=Motor Vehicle accident		
GSW=Gunshot Wound		

the whole plasma volume as plasmapheresis does. This treatment modality has been used in the recent past, and there are no reports with large experiences available. We have shown that it is an effective way of treating this devastating complication. In one patient, we stopped the azathioprine and substituted it with cyclophosphamide which has more specific effect on the antibody production limb of the immune response. This change seems to have controlled the humoral rejection in a better way.

A serious problem in long-term survivors is the appearance of graft coronary atherosclerosis. Stanford reports a 25% incidence at 5 years,[2] and it seems to correlate with CMV infections. Currently, there is no effective way of preventing this complication. The only effective treatment once it is advanced is retransplantation. Fortunately, we have not seen this problem frequently in our patients. Only one patient has had significant coronary artery obstruction which had no clinical manifestations.

Infectious complications have not been a major problem in our patient population. It is well known that opportunistic infections, mostly fungal and viral, are prevalent in transplanted patients. With one exception, all infectious episodes have been adequately treated.

Cardiac transplantation is an expensive procedure. Nonetheless, studies have shown this operation to be cost-effective. It is clear that most patients with end-stage cardiac disease are disabled, many of them being unable to work with resultant loss of income, and others have repeated or prolonged hospitalizations with accumulating health care costs. A transplant operation often reverses this downhill trend and can return the patient to a functional status. The results are not optimal yet and further improvements are expected as more experience accumulates, but great advances have been made in the past 3 decades. This endeavor requires a monumental effort from different institutions and many individuals. The main reward that professionals involved in transplantation receive is seeing a patient recover from a devastating disease.

Addendum

Since the completion of this study, one more patient, our longest survivor (who lived more than 6 years) died in January 1994. The cause of death has not been determined, however his death does not alter the 1-year, 3-year or 5-year survival statistics.

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Allogenic and Autologous Bone Marrow Transplant Experiences in Hawaii

The Hawaii BMT program also has been investigated by NMDP. Approval has been given for St. Francis Medical Center as one of 72 hospitals capable of performing unrelated allogeneic BMT transplants from the world's pool of potential donors.

Summary

Allogeneic and autologous bone marrow transplantation has been performed in Hawaii since 1978 for leukemia, lymphoma, aplastic anemia, and advanced breast cancer. The numbers for each group are relatively small and the disease stages are diverse. Our program has been recognized and approved by the various national organizations, and we hope to continue to provide this treatment alternative to appropriate candidates.

Liver Transplantation in Hawaii

Linda L. Wong MD, Alan H.S. Cheung MD, Whitney M.L. Limm MD, Naoky C.S. Tsai MD*

The first liver transplant performed in Hawaii was on May 17, 1993 in a patient with end-stage liver disease caused by autoimmune hepatitis. Liver transplantation is a well-accepted treatment for end-stage liver disease with a 1-year patient survival of 80% to 85%. Early recognition of the appropriate candidate by primary care physicians and prompt referral to a liver transplant center are essential for optimal results. The indications, contraindications, organ procurement and allocation, complications, and results of liver transplantation are described. Finally, several controversial areas will be introduced, including liver transplant for alcoholic cirrhosis and hepatitis B, and use of transjugular intrahepatic portosystemic shunts (TIPS).

Case 1

In 1989 a 60-year-old woman who has a very distant history of breast cancer had a CT scan that noted a cirrhotic liver. A follow-up CT scan in 1990 showed the cirrhosis was unchanged. She had received no blood transfusions and was asymptomatic. In 1990, she developed intermittent mental slowness and fatigue. She was admitted in August 1992 for mental status changes, lethargy, and severe anemia. Her past medical history was significant only for a moderate amount of alcohol use, but none for more than a year.

Her physical examination was notable for mental slowness and encephalopathy, jaundice, scleral icterus, spider angiomata, and severe lower extremity edema. Her abdomen was distended with ascites and an umbilical hernia was present.

Her laboratory data was:

WBC: 5.2 x 10⁹cells/mm³ Hgb - 10.3 gm/dl; Hct 28.8%; Platelets 98K; Protime: 18.2 sec; PTT 41 sec; Albumin 2.5 gm/dl; Alk phos: 16.1 IU/l; Total Bilirubin: 7.6 mg/dl; AST: 91 IU/l; ALT: 37 IU/l; GGTP: 56 IU/l; Hep A,B,C; HIV: all negative; ANA titer 1:640; Antimitochondrial Ab<20; Alphafetoprotein 11.75.

Studies performed included CT scan and ultrasound of the abdomen which confirmed cirrhosis, splenomegaly, and patent vessels (portal vein, hepatic artery, hepatic veins, and vena cava).

In summary, she had end-stage liver disease probably from autoimmune hepatitis with manifestations of encephalopathy, ascites, malnutrition, and severe fatigue. She was evaluated by the members of the Liver Transplant Selection Committee at St. Francis Medical Center who agreed she was a suitable candidate for transplant; she was placed on the waiting list in April 1993.

On May 17, 1993, a suitable donor of identical blood type became available. The donor was hemodynamically stable and had good liver function prior to procurement. The donor procedure was done by the en-bloc technique, to include removal of the liver, pancreas and both kidneys. The donor organs were flushed with University of Wisconsin solution at 4°C. The pancreas was sent for use in Islet cell transplantation. The heart was procured by a separate heart team.

The liver recipient procedure began shortly thereafter. The cirrhotic liver was removed and the new liver was placed in the standard fashion using veno-venous bypass to maintain hemodynamic stability and prevent lower extremity swelling. The anastomoses included suprahepatic inferior vena cava (IVC), infrahepatic IVC, portal vein, hepatic artery, and bile duct. The entire procedure took 10 hours; cold ischemic time was 11 hours, and a total of 26 units of PRBCs were transfused.

Postoperatively, she maintained excellent liver allograft function. Her coagulopathy resolved (protime 11.3 sec., fibrinogen 458 mg/dl on the first post-operative day), she had no acidosis, and bile production was good. She also maintained good cardiovascular and renal function. She was given antilymphocyte globulin (ATGAM®) for induction therapy. Maintenance immunosuppression included prednisone, azathioprine, and cyclosporine. Her postoperative problems included febrile reactions to ATGAM®, and a mild rejection on the twelfth postoperative day which was treated with high-dose steroids. She was discharged on 21 days after the operation. She subsequently developed elevation of alkaline phosphatase and bilirubin, and cholangiograms suggested an extrinsic compression of the bile duct. She was found to have a mucocele of the cystic duct stump, which was drained intraoperatively. Her liver function tests returned to normal.

She is currently 6 months postop with continued good liver allograft function and no further rejection episodes. Her immunosuppression consists of prednisone and cyclosporine. She has gained weight (albumin 4.5 gm/dl), walks 3 miles each day, and performs household work.

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Discussion

Few medical discoveries have been as exciting as the development of liver transplantation. The first human liver transplant was performed in 1963 by Dr Thomas Starzl. His patient was a 3-year-old boy with liver failure caused by biliary atresia; he died intraoperatively from uncontrollable hemorrhage.[1] Liver transplantation has come a long way since then—with numerous advancements in preservation solutions, surgical techniques, and immunosuppression. Liver transplantation now has become an accepted treatment for end-stage liver disease—more than 2,900 liver transplants were performed in the United States in 1991, with one-year survival rates as high as 80% to 90%.

The above case illustrates the course of a fairly typical liver transplant. What follows is a discussion of liver transplantation to include indications/contraindications, the evaluation process, complications, and controversies.

Who needs a liver transplant?

There are 4 primary indications for liver transplant:
1. Irreversible advanced chronic liver disease
2. Neoplastic diseases
3. Metabolic liver diseases
4. Fulminant liver failure (usually from hepatitis B, autoimmune hepatitis or acetaminophen overdose)

Not all patients with the above-listed diseases will need a liver transplant; proper selection of patients and timing of surgery are essential. The patient should have advanced liver disease with complications such that liver transplant will improve survival and quality of life. General criteria for patient selection include:
1. Intractable ascites, not responsive to diuretic therapy
2. Uncontrolled variceal bleeding
3. Poorly controlled encephalopathy
4. Malnutrition
5. Fatigue, interfering with normal daily activities
6. Hepatorenal syndrome
7. Recurrent spontaneous bacterial peritonitis

Although the contraindications to liver transplant have become fewer with time, there are still 4 main contraindications:
1. Active sepsis outside the hepatobiliary tree
2. Malignancy outside the liver
3. Advanced cardiopulmonary disease
4. AIDS

Age, prior portacaval shunt, chronic alcoholism, and portal vein thrombosis are not absolute contraindications; however, these patients must be selected carefully. Advanced chronic renal failure may be a contraindication in certain scenarios, but a combined liver-kidney transplant can be performed.[2,3]

Who gets a liver transplant?

Before becoming a liver transplant candidate, the patient must be formally evaluated by a team of health professionals to include a transplant surgeon, hepatologist, anesthesiologist, nurses, and social workers. Multiple laboratory tests are obtained to assess the extent and etiology of liver failure. Serologic tests and tumor markers are also checked. An ultrasound examination and CT scan of the liver are used to look for tumors and determine vessel patency. All patients undergo cardiac evaluation with an EKG and echocardiogram and further testing is done for high risk patients. Psychosocial assessment is made to establish whether or not if the patient can adapt to the stresses of having a liver transplant, will be compliant with medications and postoperative care. Finally, the patient meets with a financial counselor. Members of the transplant selection committee will then meet to determine if a patient is an appropriate candidate.

How does a candidate get a liver?

When a patient is accepted as a candidate, he or she is placed on a waiting list. How a patient then gets a liver is largely regulated by a national organization called UNOS (United Network for Organ Sharing). It dictates the policies as to how donor organs are procured and distributed fairly. It oversees the actions of 261 transplant centers and 65 organ procurement organizations in order to distribute organs from nearly 4,300 cadaveric donors to the more than 22,000 patients waiting for transplants. This data includes all types of organs—most are waiting for kidneys and about 1,300 are waiting for liver transplants.

UNOS has divided the United States into 11 regions (Fig 1). When a donor liver becomes available, it is first used locally within the area of the organ procurement organization. If no suitable candidates are found, it is then offered within the region, and then nationally. The appropriate candidate for a donor liver is determined by the patient's size, blood type, time waiting on the list, and medical urgency status. Urgency status is the most important factor, and each patient is categorized into one of the 4 statuses listed.[3]

Status 1: Patient's level of functioning and overall health status are not yet affected by liver disease.

Status 2: Patient requires ongoing/frequent medical care, hospitalizations may be necessary.

Status 3: Patient is hospitalized and cannot be discharged.

Status 4: Patient is in the intensive care unit with liver failure and life expectancy is less than 7 days.

The entire system is continuously evaluated and improved by UNOS. Currently there is much debate as to whether major changes should be made in the allocation process. Some believe that giving priority to the sickest patients (Status 4) may not be practical because these patients already have many complications and are likely to have a higher mortality.

What is the hospital course of a liver transplant patient?

Performing the recipient operation of a liver transplant is probably the most complex and difficult of all abdominal surgical procedures. The procedure can take anywhere from 6 to 18 hours and requires meticulous technique and a tremendous amount of patience (Fig 2). Intraoperative problems can include hypothermia, coagulopathy, hypocalcemia due to multiple transfusions, and many hemodynamic changes caused by blood loss and reperfusion of the new liver.

Immunosuppression is started at the time of surgery and will continue throughout the patient's life. Each transplant center has
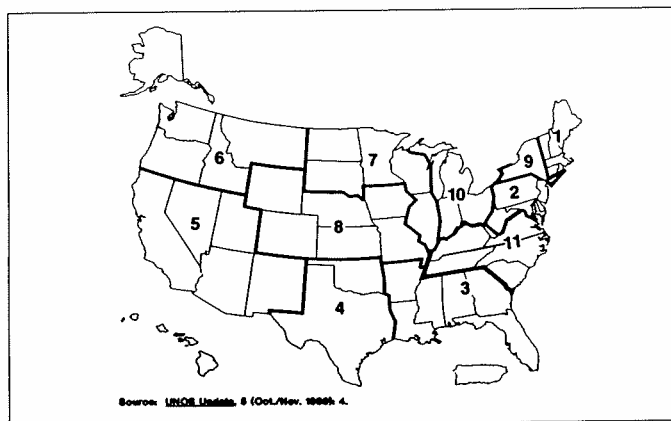
Figure 1.—Organs are distributed to local centers first, then within each of the 11 regions as determined by the UNOS map. (Courtesy of Thomas L. Fabry, MD and Franklin M. Klion, MD from the book *Guide to Liver Transplantation,* Ikagu-Shoin Medical Publishers, New York, New York; 1992)

Figure 2.—The completed liver transplant. Two methods of connecting the bile duct are depicted. (Courtesy of Thomas L. Fabry, MD and Franklin M. Klion, MD from the book *Guide to Liver Transplantation,* Igaku-Shoin Medical Publishers, New York, New York; 1992)

its own protocol and new drugs are continually introduced and tested. In general, maintenance immunosuppression is with a combination of steroids, azathioprine, and cyclosporine. Drugs such as antilymphocyte globulin and OKT3 (monoclonal antibody directed against CD3 molecule on T-cells) are used as induction therapy and to treat severe rejection episodes. FK506 is a drug with properties similar to cyclosporine and can be used as maintenance therapy in place of cyclosporine for those patients with refractory rejection or intolerance to cyclosporine. FDA approval of this drug is expected in early 1994.

What are the complications?

Because liver transplants are such complex procedures and the patient is wrought with portal hypertension and coagulopathy, complications are common. About 20% to 40% of all patients will have a surgical complication requiring re-operation. Most common indications for operative intervention include bleeding, infection, and bile duct problems.[4,5]

Medical complications usually are related to immunologic problems, infections, or the side effects of medications. Rejection is common, and histologically proven rejection has been shown in one study to occur in 73% of patients.[6] Primary graft nonfunction or dysfunction may be due to immunologic problems or problems during the organ procurement. Early infectious complications usually are related to surgery. Later infectious complications include viruses (cytomegalovirus, Epstein-Barr virus) or opportunistic pathogens (pneumocystis, listeria). Finally patients may be at risk for lymphoproliferative disorders (due to immunosuppression) or recurrence of their original disease (especially hepatitis B and neoplasms).

What are the results of liver transplantation?

When patients are carefully selected and managed, the 1-year survival rate is 80% to 90% and the 5-year survival rate is 60% to 65%; however, these numbers will vary depending on the patient's original disease. The most favorable survival is obtained when patients are transplanted for primary biliary cirrho-
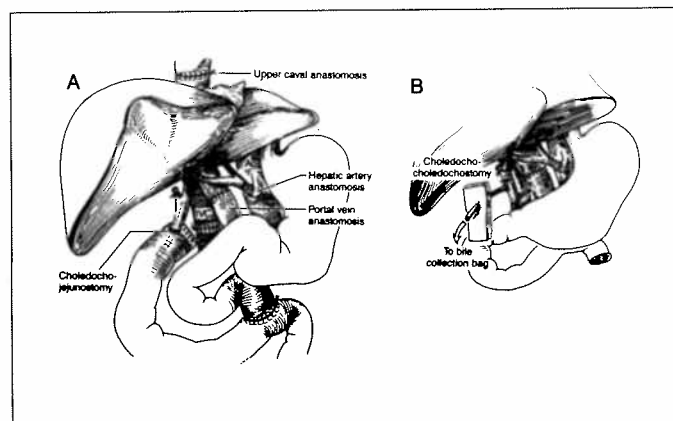
sis and sclerosing cholangitis. Results are less favorable for hepatic neoplasms and hepatitis B.

Should patients with alcoholic cirrhosis be transplanted?

Alcoholic liver disease is the single most-common cause for liver problems in the United States, but transplantation for this is somewhat controversial. The argument against transplantation is that these patients are "morally blameworthy", have associated medical problems, and are prone to recurrent disease. A number of studies have refuted this theory: The University of Pittsburgh demonstrated that 85.9% of the survivors remain abstinent post-transplant, and 74% return to some type of productive work. Factors that were predictive of abstinence include 1) support of a significant other, 2) acceptance of alcohol as the cause for liver disease, 3) active involvement in an alcohol treatment program, and 4) existing job or education allowing subsequent employment.[7] In general, patients with alcoholic liver disease can do well following liver transplant. Survival rates are comparable to patients with liver failure for nonalcoholic causes. Patient selection is absolutely essential, as only about 50% of all patients referred for transplant will be suitable candidates.[8]

Should patients with viral hepatitis B be transplanted?

An estimated 300,000 people will develop hepatitis B annually, with 15,000 having chronic hepatitis B and 300 progressing to fulminant liver failure.[7] Many of these patients will need liver transplants, however, there is concern over the significant rate of recurrence of hepatitis. We have learned a few things about the patterns of recurrent disease following transplant. It occurs more commonly in those with chronic Hepatitis B with cirrhosis, and less frequently in those with fulminant disease. High recurrence is thought to be due to extrahepatic replication of the viruses in such areas as bone marrow, spleen, and pancreas. Immunosuppression post-transplant also has been shown to enhance viral

replication; specifically steroids were found to increase hepatitis B surface antigen production. A number of centers are using hepatitis B immune globulin as prophylaxis with improved results. The 5-year survival is generally lower (60%) when compared to transplantation for other disease (80%).[9] Liver transplant for hepatitis B remains controversial; however, it is beneficial when performed in the proper setting. As we begin to understand immunoprophylaxis and develop new antiviral agents, perhaps we can learn to control recurrent disease.

What is TIPS?

The latest addition to the armamentarium of treatments for liver failure is the transjugular intrahepatic portosystemic shunt (TIPS). TIPS is a shunt that connects the portal venous system to the systemic circulation via the hepatic veins. It is essentially a portacaval shunt within the liver. These stents are placed by a skilled interventional radiologist with the assistance of high-resolution fluoroscopy, digital subtraction angiography, and ultrasound. Indications include portal hypertension with complications of bleeding varices, failed sclerotherapy, or ascites.[10] TIPS serves as a good bridge to liver transplant by decreasing the intraoperative and perioperative blood loss.[11]

Conclusions

The field of liver transplantation is exciting and dynamic. It is a well-accepted treatment for end-stage liver disease and when patients are carefully selected and managed, the 1-year survival rate is 80% to 90%. These are extraordinary results when it is considered this population of patients would not have survived their liver failure. With constant new developments in organ preservation, immunosuppression, immunoprophylaxis, and surgical techniques, results are likely only to improve.

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Pancreas Transplantation for Diabetic Patients in Hawaii

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Diabetes mellitus is a common disease affecting a large population in Hawaii. Over the past 20 years, pancreas transplantation has evolved into a viable therapeutic option for selected patients with diabetes mellitus. This report describes the first combined pancreas-kidney transplant performed in Hawaii on June 28, 1993 on a patient with juvenile-onset diabetes mellitus and diabetic nephropathy. The patient has remained off insulin and off dialysis since the transplant. The history, indications, techniques, and potential complications related to this procedure are discussed.

Case 1

The patient was a 38-year old woman from Maui who developed signs and symptoms of diabetes mellitus when she was 5 years old. Insulin was recommended at that time but her family refused. She was started on an oral agent, tolbutamide (Orinase®) in the 1980s. In 1986, she was started on insulin, and prior to surgery was administering 15 units of Humulin in morning and 5 units in the evening. On this schedule, her blood sugar ranged between 70 and 250 mg/dl on any given day. She had no history of seizures, coma or diabetic ketoacidosis, but developed progressive diabetic triopathy, including diabetic nephropathy, retinopathy, and neuropathy. She was started on hemodialysis on July 29, 1991. She had progressive retinopathy and has had bilateral laser photocoagulations as recently as March 1992. She had numbness and parasthesia of both lower extremities secondary to neuropathy; her other medical problems included a left heel ulcer, hypertension, and a history of asthma.

As part of her evaluation for a possible pancreas and kidney transplant, the patient underwent extensive ophthalmologic and cardiac evaluations, including a coronary angiogram; the results were normal. A duplex scan of the lower extremities revealed no evidence of significant atherosclerosis. Her creatinine level was 10.6 mg/dl and her hemoglobin A1C was 12% (normal range is 5.5% to 7.7%). She was deemed to be a good candidate, and was

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placed on the waiting list for a combined kidney/pancreas transplant on December 1992.

An 18-year old donor, who died of a severe intracerebral injury following a skateboard accident, was pronounced brain dead and consent was given for multiple organ procurement. The donor had a creatinine of 0.8 mg/dl, and normal glucose and amylase levels.

Our patient was hospitalized on the evening of June 27, 1993 and was found to have a serum glucose of 255 mg/dl. She was started on an intravenous insulin drip at 2 units an hour. Her BUN and creatinine levels on admission were 93 mg/dl and 10.6 mg/dl, respectively.

A combined cadaveric kidney and pancreas transplant was performed on June 28, 1993. The operation took approximately 7 hours: A midline incision was made and the kidney was placed intraperitoneally in the left iliac fossa, the renal artery and vein were anastomosed to the patient's left iliac artery and vein, respectively. The kidney graft functioned immediately, producing urine while the patient was still on the operating room table. The pancreas graft was reconstructed on the back table, since the liver was also procured. The donor splenic artery and superior mesenteric artery were reconstructed, using a Y-graft of donor iliac arteries. This Y-graft was then anastomosed to the patient's right common iliac artery; the donor portal vein was anastomosed to the patient's right external iliac vein; a segment of donor duodenum was left intact and was anastomosed to the urinary bladder (Fig 1). The ureter was then anastomosed using the posterior Leadbetter-Politano method.

Postoperatively, the patient was taken to the intensive care unit where she was continued on an insulin drip; her serum glucose had dropped immediately to 86 mg/dl. Intravenous insulin was continued for the first few days in order to maintain tight control of the serum glucose between 100 to 150 mg/dl. The insulin drip was stopped by post-operative day 5 and the patient's blood sugar remained stable while off insulin, ranging between 109 mg/dl to 150 mg/dl. (Fig 2). Immunosuppression was begun with ATGAM® for 10 days, followed prednisone, azathioprine, and cyclosporine A. Antibiotic prophylaxis was given with vancomycin and imipenem (Primaxin®) for 3 days. Fluconazole was given for 14 days, and CMV prophylaxis was instituted with ganciclovir for 10 days, followed by acyclovir for 3 months. The patient was discharged 17 days after the transplant, with a serum

amylase of 94 IU/l, serum glucose of 110 mg/dl without insulin, and a creatinine of 0.9 mg/dl.

The 6-month follow-up indicates the patient remains off dialysis and insulin. Her most recent serum creatinine was 1.1 mg/dl, and her blood sugar was 96 mg/dl. Her hemoglobin A1C level at 3 months was down to 8.0% (normal 5.5% to 7.7%). The patient did have an episode of acute rejection of both the pancreas and the kidney which was successfully reversed with OKT3®. She had complications related to her steroid immuno-suppression, including CMV infection, and a duodenal anasto-motic leak, which was successfully repaired. The patient is now at home on Maui.

Discussion

According to the local American Diabetes Association, diabe-tes mellitus affects about 78,000 residents of Hawaii. Since the discovery of insulin, Type 1 diabetes mellitus has been trans-formed from a lethal disease to a chronic illness, with many patients going on to develop secondary systemic complications. Since constant euglycemia is unachievable for diabetic patients by any practical mode of exogenous insulin administration, and since hypoglycemia is intolerable, chronic hyperglycemia (as documented by measurements of glycosylated hemoglobin) is the usual state in these patients.[1] After years of debate, the Diabetic Control and Complications Trial (DCCT) has now unequivocally shown that the development of neuropathy and retinopathy is related to the degree to which hyperglycemia is controlled.[2] Complications affecting the eyes, nerves and kidneys are present in more than 50% of patients who survive more than 20 years with diabetes. Even today, the average life span of people with diabetes is significantly shorter than that of the general population.[1]

As the DCCT study indicates,[2] only perfect glucose control for diabetic patients can prevent diabetic complications, but a perfect insulin delivery system has not been developed. An alternative to insulin injection is pancreas transplantation. It was originally thought that since diabetes is caused by insufficient production of insulin by the beta cells in the islets of Langerhans, transplanting these insulin-producing cells would allow perfect control of blood glucose.

The modern history of clinical pancreas transplantation was started on December 16, 1966, when the first human pancreas transplant was performed by Drs Kelly, Lillehei and associates at the University of Minnesota.[1,3] This case involved a uremic diabetic recipient on dialysis who had a simultaneous pancreas-kidney transplant. Since the initial transplant 27 years ago, more than 1,500 pancreases have been transplanted worldwide. The technique has evolved such that the 1-year patient survival is in excess of 90%, and the 1-year pancreas graft survival is approxi-mately 85%.[3] This is comparable to results attained in kidney and other solid organ transplants. Furthermore, successful pancreas transplants have been shown to stabilize or improve neuropathy and prevent recurrence of diabetic nephropathy in kidney grafts.

Diabetes mellitus

Diabetes mellitus (Type 1 and Type 2) affects approximately 5% of the U.S. population. It is the leading cause of blindness

each year. Compared with the normal population, patients with diabetes have a 25-fold increase in blindness, a 17-fold increase in risks of renal disease, a 25-fold increase risk of peripheral gangrene and a 2-fold increase in risk of heart disease and strokes[3]. Furthermore, diabetes accounts for 80% of major non-traumatic amputations each year. The late complications of diabetes include macroangiopathy, microangiopathy, retinopathy, nephropathy, cardiomyopathy, and neuropathy. Since the life expectancy of most diabetic patients is shorter than that of the normal population, the goals of the pancreas trans-plant are: 1) To maintain near normal glucose metabolism; 2) to improve the quality of life for these patients; and 3) to avoid the late complications and higher mortality. In 1990, more than 600 pancreas transplants had been performed worldwide.

Recipient selection

Unlike the heart or liver transplant, which are life-sustaining organs, the pancreas is non-vital in that exocrine and endocrine replacements currently are available. Therefore, the justifica-tion of the risk of surgery and life-long immunosuppression cannot be taken lightly. There are 3 categories of patients who could benefit from the pancreas transplant (Table 1).

The first are patients with end-stage diabetic nephropathy who are on dialysis. Many of these patients want to have a kidney transplant for an improved quality of life by being off dialysis. Since they will undergo surgery for the kidney transplant and will require life-long immunosuppression, performing a com-bined kidney and pancreas transplant in this group would not increase the surgical or immunosuppressive risks significantly. Our patient was in this category. Patients who have had a successful kidney transplant could ask to be candidates for a pancreas transplant, since they are already on life-long immuno-suppression. The only disadvantage is that they will have to undergo a second operation for the pancreas transplant.[4,5]

The second category is patients with pre-uremic diabetic nephropathy who have documented macro-albuminuria. The natural history in this group of patients is that they will ulti-mately require dialysis. Performing the pancreas transplant alone may prevent the diabetic damages to the kidney and ultimately avoid dialysis in these patients.

The final category is patients with severe diabetic manage-ment problems. These patients have hyperlabile diabetes or special problems associated with unawareness of hypoglycemia. Some of these patients have a profoundly poor quality of life with seizures and comas, and many of them are afraid to leave their homes. For these patients, a pancreas transplant alone could cure their diabetes and improve their quality of life.[6]

The detailed clinical criteria for candidates for pancreas transplantation or combined kidney/pancreas transplantation are listed in Table 2. Besides active infections or malignancies, other contraindications for pancreas transplantation are listed in Table 3.

Donor selection

Almost all transplant centers now rely exclusively on cadaver donors for their pancreas organs. The cadaveric donor should

Table 1 Possible indications for pancreas transplantation in diabetic patients

Patient's condition	Type of transplantation
End-stage diabetic nephropathy	Combined kidney and pancreas transplant, or pancreas after kidney transplant
Pre-uremic diabetic nephropathy	Pancreas transplant alone
Severe management problems: • Hyperlabile diabetes • Unawareness of hypoglycemia • Severe neuropathic pain	Pancreas transplant alone

Table 2 Clinical criteria for candidates for pancreas transplantation or combined kidney/pancreas transplantation

1. Adults, ages 18 to 50 years

2. Presence of insulin-dependent diabetes

3. Well-controlled blood pressure, with or without medication

4. No evidence of inoperable peripheral vascular disease—specifically, cerebrovascular disease or ischemic ulcers—or previous amputation necessitated by vascular disease

5. Not requiring narcotics or large amounts of analgesics

6. No recent retinal hemorrhage

7. No history of major or significant myocardial infarction

8. No insulin resistance—that is, insulin requirement of no more than 2u/kg.

9. No other contraindications to transplantation, including previous multiple operations, active infections, or malignant lesions

10. Ability to understand risks and benefits of the procedure and to cooperate and comply with the medical program

Table 3 Contraindications for pancreas transplant

• Ongoing peripheral gangrene

• Severe coronary insufficiency with angina or intractable cardiac decompensation

• Severely incapacitating peripheral neuropathy, ie, bedridden patients

• Severely incapacitating autonomic neuropathy, ie, gastroparesis

have no history of diabetes mellitus. Other absolute contra-indications include severe chronic pancreatitis and a history of pancreatic damage by trauma. Relative contraindications include alcoholism, recurring acute pancreatitis, and elevated levels of blood glucose or serum amylase levels. The usual

criteria for organ donation are noted in this issue in Dr Whitney Limm's article, "The Need for Organ Donation in Hawaii".

Operative technique

The procedure of pancreas transplantation has evolved to the current technique of transplanting the whole pancreas organ with a segment of duodenum for exocrine drainage into the urinary bladder (Fig 1). This approach allows external drainage of the pancreatic duct without the contamination involved with an enteric anastomosis. This also provides the opportunity to monitor urine pH and amylase as a measure of pancreas allograft function and to biopsy the pancreas if necessary via cystoscopy.[7,8]

Immunosuppression, rejection, and complications

The extensive experience at the University of Minnesota has suggested that a triple therapy of maintenance immunosuppression using cyclosporine, azathioprine, and prednisone in combination has the highest success rate. Antilymphocyte globulin, such as ATGAM®, usually is given in the immediate postoperative period.

Rejection of the pancreas allograft is mainly manifested in the deterioration of graft function; inflammatory signs may occur, although inconsistently. A gradual, progressive hyperglycemia with presumed etiology secondary to rejection may be noted. A decrease in urinary amylase output during rejection episodes may occur up to 4 days prior to clinical hyperglycemia. Urinary amylase has proven to be a sensitive indicator of early rejection; early treatment of rejection decreases graft loss. Furthermore, cystoscopically directed biopsy of the pancreas can confirm early rejection. Serum anodol trypsinogen also has been shown to be a marker for early acute rejection. Even with the triple therapy, rejection can occur in 50% to 70% of the cases,[1] as occurred in our patient. Fortunately, rejection can be reversed in over 95% of the cases by using OKT3® a monoclonal antibody directed against T-lymphocytes.

Surgical complications occur in 30% to 40% of cases: hyperamylacemia, graft pancreatitis, pancreatic pseudocysts and ascites, pancreatic fistula, anastomotic leaks with fistula, intra-abdominal abscess, graft thrombosis, bleeding, intestinal obstruction or perforation. Opportunistic infections and potential malignancies also can occur, as in any immunosuppressed patient.

Results

After a successful pancreas transplant, blood glucose normalizes within hours or days. Patients can maintain a normal or near normal fasting blood glucose and half develop normal glycosylated hemoglobin levels. Both were shown in our patient. Most individuals have a normal oral and intravenous glucose tolerance test. A successful pancreas transplant can prevent the occurrence of diabetic nephropathy or the progression of early diabetic lesions in grafts exposed to the diabetic milieu. Depending on the stage of the ophthalmic lesions, the probability of advanced retinopathy progression is not altered in the first few years after a pancreas transplant. However, the
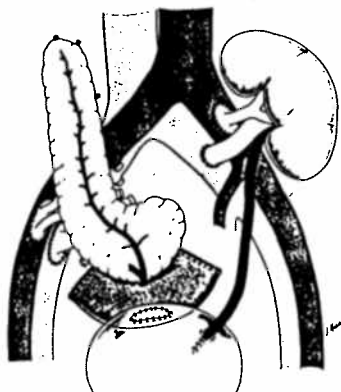
Fig 1.—Technique of combined pancreas-kidney transplantation with the duodenal segment technique. The kidney is placed in the left iliac fossa, and the pancreas in the right. The duodenum is drained into the bladder (Courtesy of WB Saunders Company.)[11]
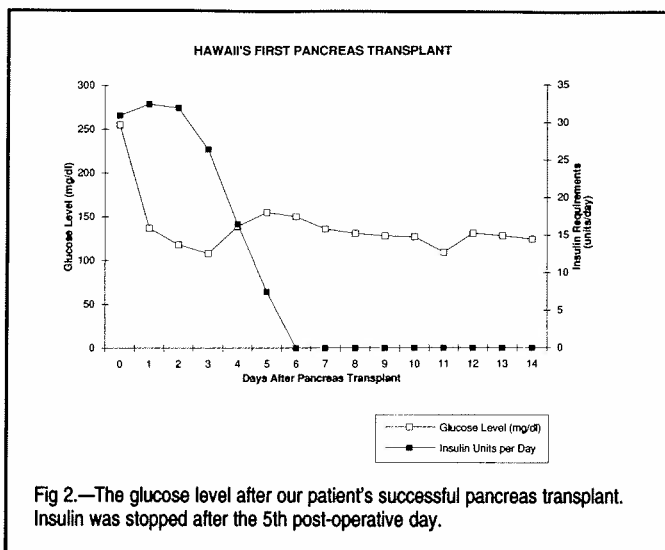

Fig 2.—The glucose level after our patient's successful pancreas transplant. Insulin was stopped after the 5th post-operative day.

retinopathy stabilizes after 3 years with a successful pancreas transplant. Neuropathy improves or stabilizes for most recipients. The nerve conduction velocity and evoked muscle action potentials increase. Patients with severe autonomic neuropathy have a significantly higher probability of survival than patients who did not undergo transplant.

Many studies have looked at the influence of a successful pancreas transplant on the quality of life and the effects of day-to-day living in these patients. The quality of life for many individuals improves simply with insulin independence. Ninety-two percent of patients thought that managing immunosuppression was easier than managing diabetes and insulin.[9] About two-thirds thought that diabetes was more demanding on their families' time and energy than the transplant.[9] All of the patients with successful graft function said they would encourage others with similar diabetic problems to consider a pancreas transplant.[10] Interestingly, even most of the patients with a failed pancreas graft opted for re-transplantation, and most with functioning grafts said that they would undergo a re-transplant if their current graft failed.[10] Since pancreas transplantation is a complicated procedure, it is natural to question whether the benefit is worth the price, and many pancreas transplant recipients have emphatically stated that it is.

The one year pancreas allograft survival rate is over 70% to 85% in diabetic recipients of a simultaneous kidney and pancreas transplant.[3,8] The one-year patient-survival rate is over 90%. This is similar to those achieved with other solid organ transplants.

Summary

Pancreas transplantation as a treatment for diabetes mellitus is the youngest area in the growing field of organ transplantation. Over the past 26 years, it has evolved into a viable therapeutic option for selected patients with diabetes mellitus. Until islet transplant or gene therapy for treatment of diabetes becomes a

reality, pancreas transplant remains the only proven cure for selected patients with diabetes mellitus in 1994.

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The Need for Organ Donation in Hawaii

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Donor organ availability is the primary limiting factor in organ transplantation. The number of patients on the national organ waitlist has increased to more than 32,000, while the number of donors has remained fairly constant at approximately 4,500 per year. In Hawaii, there are 98 patients awaiting organ transplants, and for the past 5 years, the average number of donors per year was 15. The criteria for organ donation, brain death, approaches to donation request, and the management of the multiple organ donor are discussed.

Introduction

The field of organ transplantation has made remarkable progress in recent years. Advancements in tissue typing, surgical techniques and immunosuppression have resulted in enhanced 1-year patient survival rates for kidney, heart, pancreas, and liver transplants. The advances in the field and resultant successes have led to a steady increase in the number of patients seeking transplants. The number of year-end registrations has been increasing since 1988, with annual increases ranging from 12% to 19%.[1] Overall registration on the United Organ Sharing Network (UNOS) waitlist has increased by 81% between 1988 and 1991.[1]

This increase in the number of patients on the waitlist has not been matched by an increase in the number of organ donors. From 1988 to 1991, the total number of cadaveric donors

ORGANS RECOVERED IN HAWAII

Fig 1.—A comparison of the number and type of organs recovered in Hawaii for the past 5 years.

increased by only 11%.[2] Because the number of organ donors has not increased in proportion to the waitlist, waitlist mortality is increasing. One estimate is that 38% of patients awaiting heart, lung, or liver transplantation die before an organ becomes available.[3]

In Hawaii there are 98 patients on the transplant waitlist (Table 1). Many patients have been on the list for several years as the state averages less than 20 donors a year.

Nationally, the reasons for the shortage of organ donors include: 1) The family is approached and declines permission, 2) organ donation is not considered after the diagnosis of brain death has been made, 3) a failure to identify brain death, and 4) poor organ perfusion through donor instability. When the family is approached and consent is declined, the following reasons have been given: Emotional, racial/ethnic and religious.[2]

The aim of this study was to examine the characteristics of the actual donors in Hawaii and compare them to national statistics. Discussion will be focused on the need to increase both the local and national donor pools, an explanation of brain death, approaches to donation request, and management of donors prior to organ procurement.
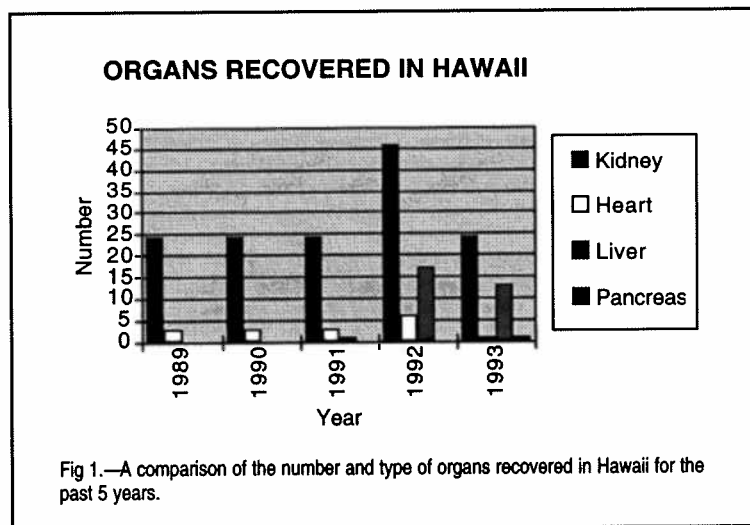
Methods

The Organ Donor Center of Hawaii is a non-profit organization devoted to coordination of organ donation in Hawaii. It also educates the medical community and the general public about the importance of organ donation. This organization, like the 65 other organ procurement organizations in the United States, is funded by Medicare and private insurance.

A retrospective analysis was performed on all organ donors in Hawaii using records from the Organ Donor Center of Hawaii.

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To develop a profile of the donors in Hawaii, the following information was obtained for each patient: Age, sex, cause of death, ethnicity, hospital where donation originated, and organs donated.

Results

Over a 5-year period from January 1, 1989 to December 31, 1993, 75 organ donors were recorded in Hawaii. Table 2 indicates the number and age distribution of donors per year. The average age was 31; local donors reflected the national statistics in that a majority were from the 19 to 35 age group. Seventy-five percent of local donors were male; this majority was consistent with the national data (61.5%).[2] Over 50% of the local donors were Caucasian, with Japanese, Chinese and Filipino minorities represented (Table 3).

For organ donors in Hawaii, motor vehicle accidents were the most common cause of death. Nationally, this cause is ranked behind cerebrovascular accidents, which is thought to be due to improvements in the care of trauma patients and passage of safety laws governing the use of seatbelts and motorcycle helmets;[2] perhaps the higher ranking locally reflected the absence of mandatory helmet laws for motorcycle riders. Locally, other causes of death included cerebrovascular accidents, gunshot wounds, asphyxiation and drowning (Table 4).

Thirty of the donors were hospitalized at The Queen's Medical Center, where a large number of trauma patients are treated. As a result of advances in organ procurement and storage, hospitals on Neighbor Islands contributed to the donor pool (Table 5).

In the early stages of this review, only kidneys and hearts were recovered for transplantation. In 1991 the first liver was recovered; the first liver recovered and transplanted in Hawaii occurred in 1993. Another landmark in local medical history also occurred 1993 when the first pancreas was recovered and successfully transplanted (Fig 1).

Discussion

The biggest obstacle facing organ transplantation is the limited number of organ donors. It is estimated there are between 4,992 and 28,954 potential cadaveric organ donors nationally each year.[4] The actual number of donors, however, has been fairly constant, with 4,516 donors in 1991.[2] Over the past 5 years, the state of Hawaii has averaged 15 donors per million of population a year. This is below the national average of 18 donors per million of population a year.

Criteria for organ donation

Organ donation should be considered when a patient is admitted with a life threatening or irreversible brain injury. The Organ Donor Center of Hawaii should be notified when a diagnosis of brain death is anticipated or has been made. Following declaration of brain death, consent for organ donation is obtained from the next of kin. Regardless of the patient's signature on a donor card or driver's license, no organs are removed without this consent. The involvement of the donation coordinator at this stage is crucial; these highly trained individu-

als can give families a clear and objective understanding of organ donation. Concerns regarding respect for the body and preservation of dignity, along with questions regarding funeral arrangements and viewing are of utmost importance to the grieving family. Donation coordinators are available 24-hours a day to assist the families, physicians and hospital staff throughout the donation process.

The ideal cadaveric donor is a previously healthy individual whose death is caused by an isolated, irreversible brain injury.[5] To be considered, adequate circulation and oxygenation to the organs must be maintained. Absolute contraindications to organ donation are: Non-CNS malignancy, active infection (bacterial, fungal, viral, parasitic), or seropositivity for hepatitis, HIV, and HTLV-1. The upper age limit for organ donation is increasing; in Hawaii, liver and kidneys from donors as old as 66 years of age with adequate physiologic function have been removed for transplantation. The generally accepted upper age limit for heart donation in Hawaii is 45 years of age.

Brain death

Brain death is required prior to cadaveric organ donation. The specific criteria for brain death was initially addressed by the Harvard Commission in 1968, with other studies following.[6] Currently, all 50 states have laws recognizing brain death.[5] The current guidelines for determination of brain death are summarized in Table 6. In Hawaii, declaration of brain death by 2 physicians is required; one of the physicians usually is a neurologist or a neurosurgeon and neither physician may be a member of the transplant team.

After metabolic factors have been corrected, tests are administered to determine cessation of cerebral and brain stem activity. While the law permits declaration of brain death by clinical examination alone, confirmatory tests such as an EEG or a nuclear medicine brain flow study may be performed.

A brain dead patient is legally dead. This concept may be difficult for the public to grasp and is important to consider when discussing the timing of the request for organ donation. Families should not be approached about organ donation until after they have been told their loved one is brain dead and all questions are answered about this diagnosis. This concept is known as *decoupling*. After the families have had the chance to accept brain death as final and to grieve over the loss of their loved one, then the option of organ donation can be presented. Research has shown that by using the decoupling process, the consent rate from families nearly doubled.[7]

Donor management

If there are no contraindications to organ donation after the medical history is reviewed, the functional status of the various organs is evaluated with blood tests and hemodynamic monitoring. The brain dead patient is often hemodynamically unstable during the evaluation process. To ensure adequate perfusion of the organs, a central venous catheter or Swan Ganz catheter and a Foley catheter often are necessary to guide fluid management. The goal is to maintain normal or near normal oxygenation and perfusion of the organs being considered for transplantation.

Table 1 Patients on Transplant Waitlist in Hawaii

As of November 24, 1993

Kidney	90	Heart	4	Liver	3	Pancreas	1

Total 98

Table 2 Donors by Age And Year in Hawaii

(1989 to 1993)

Age Bracket	1989	1990	1991	1992	1993
0 to 5				2	1
6 to 18	4	2	1	5	3
19 to 35	5	6	8	10	5
36 to 49	3	4	4	3	2
50 to 64				5	1
>65					1
Total Donors a year	12	12	13	25	13

Table 3 Donors by Ethnicity in Hawaii

(1989 to 1993)

Caucasian	44	(58%)
Japanese	8	(11%)
Chinese	4	(5%)
Filipino	3	(4%)
Local mix	5	(7%)
Other	11	(15%)
Total	75	(100%)

Table 4 Donors by Cause of Death in Hawaii

(1989 to 1993)

Motorcycle/Car	23	(31%)
Cerebrovascular	19	(25%)
Gunshot	9	(12%)
Other head trauma	11	(14%)
Asphyxiation	2	(3%)
Drowning	3	(4%)
Other	8	(11%)

Table 5 Donors by Hospital in Hawaii

(1989 to 1993)

Hospital	Number of Donors
The Queen's Medical Center	30
Kapiolani Medical Center	7
Straub Clinic and Hospital	7
Kaiser Permanente Medical Care Program	6
Tripler Army Medical Center	6
Maui Memorial Hospital	5
Castle Medical Center	4
Hilo Hospital	3
Kapiolani Medical Center at Pali Momi	3
St. Francis Medical Center	2
Kuakini Medical Center	1
Wilcox Memorial Hospital	1
Total	75

Table 6 Guidelines for Determination of Death

- Established in the absence of complicating metabolic factors, drug overdose, altered electrolyte, acid-base or glucose homeostasis, hypothermia (<32.2° C), or shock
- Etiology established, recovery excluded, persists on repeated examination

Neurologic Death
- Deep coma, cerebral unresponsiveness and unreceptivity
- Absence of brain stem functions
- No spontaneous respirations (apnea in the setting of hypercarbia)
- Reflexes are all absent: Pupillary light, oculocephalic (doll's eyes), oculovestibular (cold water calorics), oropharyngeal (gag), respiratory, and corneal

Cardiopulmonary Death
- Irreversible cessation of circulatory and respiratory functions

Over 70% of organ donors require treatment for diabetes insipidus and Pitressin is the most commonly used agent for this condition. Electrolytes are monitored frequently and corrected as needed.[7,8]

When the blood test results are deemed acceptable, the patient is then taken to the operating room. The organs are perfused with cold preservation solutions prior to surgical removal; this is referred to as core-cooling. This is done by placing catheters in the infrarenal aorta and vena cava.[5] Surgical removal of multiple organs follows this sequence: Heart, liver, pancreas, and kidneys.[5]

Once removed, the preservation of the organ can be prolonged using hypothermia either by means of simple cold storage or with a hypothermic pulsatile perfusion machine.[5] With the use of preservation solutions and either hypothermic technique, a heart can be preserved for 5 hours, liver and pancreas up to 24 hours, and a kidney up to 48 hours after removal.

Summary

Organ transplantation, both locally and nationally, is limited by the lack of organ donors. This review of the profile of local organ donors revealed similar demographic information when compared to national statistics. In an effort to alleviate the organ shortage in Hawaii, the past 5 years showed an increase in the types of organs obtained for transplantation. In addition, organs from older donors are being transplanted. Further study is needed to determine the barriers to organ donation. Once identified, and appropriate action initiated, it is hoped that the number of transplants will increase and the waitlist mortality can be minimized through maximizing organ recovery.

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The Weathervane — Russell T. Stodd, MD

For every action, there is an equal and opposite criticism.
At the December 1993 meeting of the AMA House of Delegates, the House wisely backed away from its previous policy of aggressive support of employer-mandated health insurance. Struggling for sugarcoating, Lonnie Bristow MD, Chair of the Board of Trustees, denied that the House was changing its policy, but rather was expanding it to allow for additional mechanisms, eg individual mandates, health IRAs. The president allowed as how he was "real disappointed" with the AMA. So to offset the AMA policy, the White House will seek the endorsement of the *cognitive* ACP and the AAFP. Clearly, the strategy is to divide the physician community and, foolishly, some segments of organized medicine seem bent on subscribing to federal control.

If an experiment works, something has gone wrong.
The health IRA is really a superb plan that would allow cost control, individual management, and a minimum of government intervention. The last point is the likely reason why the health IRA plan will lack administration support. And of course, our Hawaii Congressional delegation would not consider a plan that would escape from their constant socialistic agenda, irrespective of the benefits and freedom to both patients and providers.

Indolence is no way to practice medicine.
The defendant doctors, both eye surgeons, each accused the other of failing to provide care for a patient with acute glaucoma. The first physician was notified by the hospital ER physician by telephone at 10 pm that the patient was present with a working diagnosis of glaucoma or iritis. Without seeing the patient, the on-call ophthalmologist doubted the diagnosis and recommended sinus x-rays, and was off call at midnight. He directed that no further calls be made to him after that hour, and that any additional care should be provided by the ophthalmologist for the following day. That doctor was unavailable and the ER desperately called several eye surgeons before finally getting one to see the patient at 2:30 am, and he verified the diagnosis of angle closure glaucoma. The patient had numerous procedures on the eye, never regained vision, and ultimately the eye was removed. The jury returned a verdict in favor of the plaintiff amounting to $660,000—and assigned 75% fault to the first physician, 25% to the unavailable physician on call, and no judgment against the hospital. And the moral of the story is—some doctors immature with age.

The only imperfect thing in nature is the human race.
Surprise, surprise—a 4-year study of HMOs funded by HCFA, revealed that Medicare paid 5.7% more to HMOs than it would have expended if the care were provided under fee for service. "Our system for HMOs is just wildly inadequate," according to Bruce Vladeck PhD, head of the Health Care Financing Administration. The outcome of this enlightenment is that Medicare will not promote HMOs for its patients until HCFA finds a better way of paying for services, or at least that is what Vladeck is saying today. And, in addition, a nationwide study (published in *JAMA*) of 17,000 patients found widespread dissatisfaction with HMOs. Independent doctors were easier to reach, more apt to schedule appointments on short notice, and showed more interest in the patient's well-being.

Gatekeepers, HMOs, closed panels, please take note.
Another HMO item relates to rationing. Health Net, the second-largest health maintenance organization in California, denied a bone marrow transplant for a patient with breast cancer, claiming that the process was experimental. The patient's doctors said the procedure was her only hope, and an internal Health Net panel approved. However, the transplant was denied by an employee who was paid according to how much money he saved! The patient died, and the family's attorney sued claiming breach of contract. The jury ordered Health Net to pay $89 million total, $12 million in compensation, $77 million in punitive damages. To describe the hypocrisy in our system of justice, take note that a judge in Wisconsin denied a couple's similar suit to force the Blues (United of Wisconsin) to pay $120,000 for a bone marrow transplant for a 28 year-old woman with breast cancer. Go figure.

He's a fine friend. He stabs you in the front.
Doctors never sue doctors for malpractice, right? No, quite wrong. In fact physicians are just as likely, or perhaps more so than the general population, to seek damages for perceived injury. In New York state, a physician underwent blepharoplasty to remove excess skin from her eyelids, and subsequently had lagophthalmos with inadequate lid closure, burning, irritation and excessive dryness and infection. It was necessary to use lubricants and ointments to control symptoms, a not uncommon event in the plastic surgery world. A trial court directed a verdict for the patient,—but awarded no damage—but the court overruled the jury and said monetary damages should be awarded.

For every "10" there are ten "1s".
The frequently stuffy and tedious *New England Journal of Medicine* decided to inject some *Playboy*-type material by publishing a study of the sexual harassment of women doctors. Apparently it is a common occurrence when some men patients find themselves unable to accept a woman in a position of power, and express themselves by making sexual advances. While the aggressive behavior left the doctors angry or fearful, most of them did not find it a serious problem. Rather, the lady docs were considerably more intimidated by harassment from medical colleagues or supervisors.

Addenda
▲ 70% of the world's 15-million AIDS sufferers are in Africa.
▲ According to the National Institute on Alcohol Abuse and Alcoholism, per capita liquor consumption in Washington, DC is twice the national average.
▲ To paraphrase David Letterman, "Managed care sucks."
▲ "Merry Christmas from our family to yours." s/s The Clintons—but—but—but only Bill and Hillary were pictured!?!

Aloha and keep the faith
rts
■

Congratulations Hawaii

on

25 Years of Transplantation

"There is no medicine like hope,
no incentive so great,
and no tonic so powerful,
as expectation
of something tomorrow."

—O.S. Marden

In this country, there are more than 100 research-based
pharmaceutical companies working every day to turn hope into medicines,
and medicines into hope.

MILES /A

**Pharmaceutical
Division**

Biological Products Business Unit