Cover: *"Block Island II,"* oil on linen, 32" x 32". 2001, by Gretchen Dow Simpson, a Rhode Island artist. "Block Island II" and other new paintings may be seen at Axelle Fine Arts, 148 Spring Street, NYC, May 18 - June 19. Visit her website: www.gretchendowsimpson.com

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COMMENTARIES

An April Fool's Day Commentary

What a difference a scale makes!

It is not widely known that fava beans produce large amounts of L-diorthophenylalamine, L-Dopa, the percussor of dopamine, the neurotransmitter deficient in Parkinson's disease. To use fava beans to treat PD, however, requires ingestion of about one cup three times daily. While this did cure constipation in the few patients who completed the 1-month protocol, three dropped out and three suffered witnessed cases of spontaneous combustion. Improvement in motor symptoms was statistically significant ($p<.05$) but minor in degree. Smoking sun-dried fava beans also reportedly improved symptoms but the report was confounded by the subjects' use of inhaled gingko and oral mink milk.

We made the obvious leap, when we realized that oral intake of fava beans would be difficult, to using brain implants. Based on a two-decade experience of sticking all sorts of things into human brains, from human and pig brain cells, human adrenal glands, electrodes, catheters, drug wafers, we reasoned that an all natural, organically grown, free-range fava bean would be more likely to be well tolerated than any artificial material. Use of fava bean is supported by the entire group of Mediterranean farming associations and is opposed by only a handful of biotech companies who failed in their attempts to patent the fava bean. They requested a hold on NIH funding of fava bean research until a patentable bean can be "invented." This is under review by the Bush administration.

The particular subspecies chosen, "favora Parkinsonian," named by a descendant of the legendary physician, was, ironically, found to contain the highest percentage of L-Dopa among all species of the plant. It is found growing naturally in one of the uninhabited Greek islands. PD patients unable to tolerate L-Dopa or dopamine agonists by mouth who were incapacitated by their worsening motor symptoms were asked to volunteer for this project. The protocol had been approved by the Culinary Institute Review Board of Johnson & Wales University and co-sponsored by the Agriculture Department of the Interior Department of United States and the Institute of Alternative Medicine at the National Institutes of Health. Informed consent was obtained prior to study entry.

The patients received 15 fragments per side of $1mm^3$ of the heart of the bean 3 days after a sprout was identified. 5 fragments were implanted in the caudate and 10 to the putamen (4 anterior & 6 posterior). The procedure was well tolerated, with no major adverse events identified. All subjects received fava bean implants. There were no sham procedures. Subjects were evaluated at baseline, one week, four weeks and then every four weeks post-implant using standard measures of Parkinson motor function. Subjects were compared on the Unified Parkinson's Disease Rating Scale, motor section, at each evaluation to their baseline score. Subjects were advised to avoid prolonged sunlight to prevent the implants from excessive growth. Surprisingly, to the author, and the sponsors, no benefit was noted over the 25 weeks of the trial. To avoid overlooking a potentially helpful and much needed intervention, a re-analysis was undertaken by the Independent Safety and Efficacy Monitoring Committee, underwritten by grants from Enron, and by the Oversight Committee, sponsored by the Arthur Anderson company. Using a scale frequently employed in recent neurosurgical trials, The Universal Open Label Unbiased Assessment Tool. {See Figure} This simple global impression scale represents a realistic evaluation of the subject as if he was a real life patient in a private practice. On this scale patients are given 5 points for being alive, 5 points if better, 10 points if much better, 15 points if even better than that, 25 points if better than they've ever been but not actually mentally impaired.

Using this scale a very different outcome was documented. On this scale subjects improved by significant numbers ($p<10^{-6}$) and the treatment was an obvious success.

This brief description of a clinical research project illustrates the importance of choosing the best assessment instruments for a particular study. In many areas, PD research is a good example; a particular test becomes embedded as a "gold standard." In assessing side effects of antipsychotic drugs, for example, the Simpson Angus Scale has been the gold standard for measuring parkinsonism, although no study by PD experts has ever or would ever validate this scale which is quite obviously extremely poorly designed. Yet for 30 years it has been popular.

Open label studies are particularly easy to "under power," that is, use too few subjects to attain statistical significance, so sensitive scales need to be utilized.

We thank our Oversight Committee for forcing us to reassess our data. We would welcome readers' suggestion of other analyses but unfortunately when the NIH asked to review the data we discovered, much to our chagrin, that the records had been shredded.

– Joseph H. Friedman, MD

Open Label Assessment Tool

Better = 1; Much Better = 2; Even Better than that = 3

Item

- Tremor
- Rigidity
- Dexterity
- Balance
- Memory
- Gait
- Speech
- Thinking

•If score < 10 double

•If score is between 15 & 20 add (20-score)x2

•If score is > 25 convert to 30

The Arrival and Departure of a Baffling Disease

The world cowers as it now confronts a succession of unfamiliar infectious diseases, new forms of environmental poisoning and novel ways of inflicting harm upon the human body. Many have wondered in recent years what unspeakable sins must have been committed by people to justify the terror wrought by wave after wave of new contagions. In earlier years, people contend, there were no such calamities as HIV/AIDS, legionnaire's disease, Lyme disease, Ebola fever, toxic-shock syndrome, Hanta fever and yet other microbial terrors. These newly arrived burdens, they conclude, must represent the microbiological prelude to a global Armageddon.

Yes, there are some 35 million humans currently afflicted with the HIV pathogen; and other infectious ailments such as Ebola fever, while perhaps not totally new, now constitute a palpable threat to the health of humans living beyond the African rain forests. Yet in terms of infectious disease, men and women have never been healthier. Smallpox has been made extinct and will stay so unless man, in his infinite cleverness, uses it as a deliberate terrorist weapon; polio and measles, by virtue of effective vaccines, are close to global eradication; still other diseases of childhood, including diphtheria, pertussis and rubella, are a thing of the past, at least in those populations wealthy enough to immunize their children. And still other diseases, once major scourges, through no known medical intervention have disappeared from the face of the earth.

In the category of spontaneously retreating diseases, consider a devastating neurological disease which, from 1917 to 1925, afflicted about 250,000 people in Europe, Australia, Japan and the United States. The first cases, at least in the recent medical literature, were described in an article submitted by an Austrian neurologist named Constantine von Economo to the April, 1917, issue of Vienna's weekly medical newsletter.

Von Economo portrayed an ailment which began innocently enough with moderate malaise, some fever, and a headache often accompanied by pains in the muscles. But within a day or so these symptoms were complicated by confusion, paralysis of some of the eyeball muscles and a dramatic somnolence [sleepiness]. This latter finding prompted von Economo to call the disease *encephalitis lethargica*.

Close to half of his patients recovered with no further difficulties. But many, either immediately following the acute phase or after a symptom-free interval of months or more, went on to develop a progressively worsening rigidity of their limb muscles, rhythmic tremors of their hands, an expressionless face [despite the coexistence of a high measure of anxiety], restlessness, increased salivation and an inversion of sleep pattern [sleeping during the day while remaining awake at night].

The mask-like face, the restless, jerky movements, the tremors, the rigidity of the limbs exhibited by those patients in the chronic phase of *encephalitis lethargica* closely resembled another neurological disease described by Parkinson in 1817.

Indeed, many neurologists called this new disorder post-encephalitic parkinsonism. But there were notable differences. The disease described by Parkinson appeared, most commonly, in the elderly with no preceding episode of encephalitis. The biphasic disorder described by von Eonomo, on the other hand, arose at any age, including childhood.

The cases of this seemingly new disease, described in 1917, may not have been the first to be encountered by the medical profession. In 1675, Sydenham described something he called *febris comatosa* [sleeping fever]; in 1712, in the German city of Tubingen, there was a cluster of cases with brain involvement called *Schlafkrankheit* [sleeping sickness]; and in Italy in the 1890s there was an ill-defined disease, called *nona*, distinguished by excessive sleepiness and other nervous system symptoms. But the numbers of people involved in each of these instances was small. And because the clinical descriptions were so meager, it is difficult to determine whether these prior cases were of the same nature as the 1917 cases. But one thing is certain: they never reached the magnitude or gravity which characterized the 1917-1925 outbreak of *encephalitis lethargica*.

Before the epidemic had run its course, an estimated 40,000 cases had been identified in the United States, many dying during the acute phase; a moderate number recovering completely and about half going on to the protracted parkinsonian phase. Large numbers of these patients populated the nursing homes, particularly on the East coast. A motion picture, *The Awakening*, has described their plight.

The epidemic in the United States coincided with the great influenza pandemic of 1918-19; and while some at first thought that one caused the other, this view has not been accepted by pathologists [who demonstrated very different microscopic changes in each of the two diseases], by epidemoiologists [who showed that each disease had its own trajectory] or by neurologists [who distinguished the two diseases solely by clinical examination].

In England there were an estimated 10,000 cases and in western Europe an additional 120,000 cases. The pathologic findings were consistent with an infection of viral origin although no virus had ever been convincingly recovered; admittedly, the technics for viral isolation in those days were primitive.

Two curious epidemiologic features bear noting. First, most cases arose in the late winter months, thus suggesting that insects were not involved in its dissemination. Second, this epidemic was virtually confined to Europe, the United States, Canada, Australia and Japan.

Encephalitis lethargica remains a two-fold mystery. First, what caused it? And second, what factors, either ecological or man-made, accounted for its essential disappearance?

Answers to these questions are of more than academic interest. Medicine still has no inkling of the causative agent of this disease; therefore it has no way of preventing the disease or identifying its pathogen. And since the profession doesn't know what factor or factors caused it to wane in the 1920s, it has no intervention to employ as a preventive weapon should it reappear.

When virologists somberly reflect on diseases which may arise unbidden in the foreseeable future, *encephalitis lethargica* is always included in their list of possible candidates.

– Stanley M. Aronson, MD, MPH

The Evolution of Transplantation in Rhode Island

Reginald Y. Gohh, MD, and Angelito F. Yango, MD

Organ transplantation has established itself as effective therapy for end-stage renal, hepatic, cardiac and pulmonary disease, with more than 20,000 grafts performed annually in North America.[1] Similarly, successes of hematopoietic cell transplantation have resulted in a large number of patients becoming long-term survivors of diseases that previously were fatal. Before 1994, such programs did not exist in Rhode Island. Area residents who required transplantation travelled to Massachusetts, Connecticut or farther to obtain treatment. Such inconveniences not only added to the total cost of the transplant procedure, but also heightened the already considerable stress and anxiety of patients, who had to undergo the procedure away from home, removed from family and friends.

This issue of *Medicine & Health/Rhode Island* focuses on the transplant services that have become available in Rhode Island within the last decade, with particular emphasis on kidney transplantation. Dr. Gerald Elfenbein, the director of the **Roger Williams Medical Center's** (**RWMC**) Stem Cell Transplant Program, will also provide information regarding the innovative therapies now available at his center.

To evaluate Rhode Islanders' need for a kidney transplant program, an analysis was undertaken to estimate the number of local residents who might benefit. Although the actual number of kidney transplants performed on RI residents in transplant centers within New England increased from 12 in 1983 to 28 in 1991, this value was not an accurate representation of need, since it did not include the number of Rhode Islanders who would have undergone transplantation if there had existed a transplant center within the state. National utilization rates for renal transplantation expressed in relationship to the total number of U.S. residents maintained on dialysis yielded a more accurate measure of need. (Figure 1) Using this formula, it was estimated that 43 patients should have received a renal allograft in 1991, yielding an unmet need of 15 transplants in that year. This striking difference persisted even after adjusting for patient age (since an older patient population may not be as suitable for transplantation). Thus, although Rhode Island had one of the largest dialysis populations per capita in the country, Rhode Islanders received fewer kidney transplant procedures annually than U.S. citizens on average. In short, a substantial number of Rhode Islanders did not have adequate access to transplantation and would have benefited from the creation of a local site.

Although the lack of a local program was clearly a factor in limiting access to transplantation, such procedures are impossible without the availability of healthy donor grafts. The supply of donor grafts is the major factor affecting access to transplantation. However, these limitations can be greatest for residents of regions lacking transplantation programs, in large part due to the policies that govern regional allocation of donor grafts to specific institutions. These policies give regional priority for the use of grafts to those centers that also retrieve them. Although hospitals in Rhode Island could harvest cadaver kidneys, they could not take advantage of their regional priority for utilizing them because no area hospitals performed transplant procedures. This meant that organs harvested in Rhode Island were not, as a matter of priority, assigned to local residents, even when local residents may have been in need.

Given the demonstration of local need, the Kidney Transplant Program at Rhode Island Hospital was established in 1996. Since performing its first cadaver kidney transplant in March 1997, the program has grown, with more than 250 kidney transplants performed to date (Table 1). More importantly, the creation of a local program has resulted in a steady increase in the number of Rhode Island residents receiving kidney transplants (Table 2). Over the last three years, the average annual transplant rate locally now exceeds the national rate (6.2 vs. 5.1 transplants/100 dialysis patients), representing a diametrical change from previous results. This is a clear indicator that accessibility to transplant services has truly improved in Rhode Island.

Figure 1. Estimate Need of Kidney Transplantation in Rhode Island[2,3]

Step 1: U.S Rate of Transplantation per Dialysis Population (1991): (# Kidney transplants)/ U.S. Dialysis Prevalent Population = 10,026/ 142,488 =

7 Kidney Transplants per 100 Dialysis Patients

Step 2: Applying U.S. Rate of Transplantation to RI Dialysis Population (1991) 7/100 x 612 =

43 RI Residents Needed Kidney Transplants in 1991

Table 1. Rhode Island Transplant Rate4

Year	US Transplant Rate (per 100 dialysis pt.)	Expected Number of RI Transplant Recipients	Actual Number of RI Transplant Recipients (Tx Rate)
1993	6.3	43	30 (4.3)
1994	5.8	41	42 (5.5)
1995	5.6	42	37 (4.8)
1996	5.5	43	53 (6.6)
1997	5.2	41	59 (7.0)
1998	5.2	46	56 (5.7)
1999	4.9	44	48 (5.8)

Despite these encouraging results, a more somber observation is the stagnant rate of organ donation both nationally and locally. Simply put, the number of kidney transplants performed each year cannot keep pace with the number of candidates on the waiting list. Despite a 25% increase in the number of kidneys recovered nationally from cadaver donors between 1990 to 1999, the kidney waiting list has more than doubled in the same period.[1] When the transplant program was established at Rhode Island Hospital, it was hoped that organ donation would be spurred by increased public awareness and acceptance of the issue and, ultimately, more willingness to donate organs. Furthermore, clinicians would be more motivated to improve community education regarding organ donation. Unfortunately, efforts to increase the cadaver donor pool have been generally unsuccessful. Data from the New England Organ Bank, the local organ procurement organization, show that the potential organ donor pool has remained unchanged within the last decade, resulting in longer waiting times for those individuals seeking a cadaver kidney. The increasing demand for organs has increased the pressure to identify new sources of donor organs. These include the use of "marginal donors" (as determined by age, cause of death, or hemodynamic instability) and in particular, increased reliance on living related and living unrelated donors. As experience with the latter has accumulated, the results have been surprisingly superior to those after cadaver transplantation.[4] Thus for the first time, relative volume of living donor transplantation now exceeds 50% of total transplant activity at our center. Dr. Paul Morrissey and Bette Hopkins-Garcia discuss the efficacy and difficult ethics behind the use of living donors, both locally and worldwide. Nevertheless, the shortage of cadaver organs continues to pose the most severe limitation to the number of patients who could potentially benefit from transplantation.

....the number of kidney transplants performed each year simply cannot keep pace with the number of candidates placed on the waiting list.

The unprecedented success of patients undergoing organ replacement therapy is strongly correlated to the development and introduction of new immunosuppressive agents to the clinical armamentarium. Depending on the organ transplanted and the donor source, graft survival in the 85-95% range at 1 year has become commonplace,[1] with acute rejection rates reported at less than 10%. Because many of these recipients are living longer and ultimately returning to the care of their referring physicians, we have provided a review of the newer immunosuppressive drugs. Particular emphasis is placed on issues relevant to the primary care physician, such as drug interactions and side effect profiles. As the incidence of acute allograft rejection has decreased dramatically in the past several years, increasing attention has focused on the management of long-term complications in transplant recipients. Among these, infectious complications remain a major cause of morbidity and mortality for transplant recipients. Dr. Staci Fischer briefly reviews the epidemiology and clinical behavior of infection in the post-transplant recipient.

The participation of Dr. Fischer, an infectious disease specialist, in this forum highlights a generally unappreciated aspect of the transplant process: any transplant procedure is highly complex, requiring the active involvement of a wide range of health care specialists in a multidisciplinary approach. Furthermore, transplant recipients often have complex medical and social histories and complications arising from their primary illnesses. It is imperative, therefore, that the patient's primary physician be available nearby to take an active role in clinical decisions that arise during the patient's hospitalization for the transplant. Thus, the creation of local transplant centers has not only directly provided vitally needed services to a number of Rhode Island residents, but has also provided indirect benefits for the entire state. By enhancing the development of a local system of health services catered to these individuals, the "culture of transplantation" has become firmly entrenched in Rhode Island.

Table 2. Kidney Transplants at Rhode Island Hospital

Year	Cadaver Donor Transplants	Living Donor Transplants
1997	26	9
1998	27	25
1999	29	24
2000	31	32
2001*	29	33

*As of October 8, 2001

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Blood and Marrow Stem Cell Transplantation at the Roger Williams Medical Center, 1999-2001

Gerald J. Elfenbein, MD, FACP

Exactly three years to the day of the submission date of this manuscript, I became Director of the **Roger Williams Medical Center's (RWMC's)** Cancer Center and Director of the RWMC's Blood and Marrow Transplant Program. These three years have been invigorated with the acquisition of talented colleagues by recruitment and the performance and communication of groundbreaking clinical research. I will describe some of that work. For the next three years, our program has two major thrusts: an exciting and novel form of immunotherapy in the setting of minimal residual disease and our version of the non-myeloablative allogeneic stem cell transplant that has recently become popular. Finally, I will close with a basic research concept, tying everything together in a nice, even if futuristic, package.

Five Pilot Studies:

Following are five of the studies that we completed by what may be a novel method.

1. Conventional chemotherapy has little to offer in terms of long-term disease-free survival for patients with high-risk lymphomas. High-dose chemotherapy and autologous (self-donated) stem cell transplantation offer these patients an opportunity for long-term disease free survival. At RWMC[1], we explored the therapeutic value of a well-tolerated, high-dose chemotherapy regimen, used for many years in patients with breast cancer, the so-called **CTC** regimen, consisting of 6 g/m2 of **cyclophosphamide**, 500 mg/mz of **thio-TEPA** and 900 mg/m2 of **carboplatin**, in 17 patients. Patient characteristics included: age - range 21 to 63 (median 50) years; gender - 11 males and 6 females; disease - 7 with **Hodgkin's disease** (**HD**; 6 nodular sclerosis and 1 lymphocyte depleted) and 10 with **non-Hodgkin's lymphoma** (**NHL**; 4 large cell, 3 follicular mixed, 1 mantle cell, 1 immunoblastic, and 1 follicular small cell); disease status - 9 (3 HD and 6 NHL) in first relapse, 3 (1 HD and 2 NHL) in second relapse, 2 (HD) in third relapse, 1 (NHL) in first complete remission, and 2 (NHL) in first partial remission. All patients were induced with 4 cycles of quite aggressive chemotherapy, which consisted of courses of continuous infusion of **cyclophosphamide and etoposide** (**CE**; developed by Elfenbein's team in Gainesville, FL[2], alternating with courses of **dexamethasone, cytosine arabinoside, and cisplatin** (**DHAP**). **Peripheral blood stem cell** (**PBSC**) collection (to be reinfused after CTC) was performed by leukapheresis (in collaboration with the Rhode Island Blood Center)- during recovery from the last cycle of DHAP. With a maximum follow up of 46 months and a minimum follow up of 11 months (median of 24 months) for survivors, the Kaplan-Meier estimate for overall survival at 25 months is 52% and for disease-free survival at 25 months is 47%. Of the subset of 4 "better" but still high-risk patient (3 with HD in first relapse and 1 with NHL in first complete remission), 2 are alive and free of disease and 2 have died (1 of sepsis and 1 from recurrent disease). For the 7 patients who progressed, the median time was 3 months (range 1 to 7 months). CTC offers cyclophosphamide at a very high dose and two new alkylating drugs, thio-TEPA and carboplatin, for lymphomas. CTC appears to be quite active in a broad range of lymphomas, is deliverable in the outpatient setting, and should be of use in consolidating first complete remissions in high-risk NHL and second complete remission of high-risk HD. Finally, CTC is sufficiently well tolerated (there were two only toxic deaths [12%] in this group of high-risk patients) and has a quick enough recovery of granulocyte count (median time to reach an **absolute granulocyte count** (**AGC**) of 500/uL was day 12) and platelet count (median time to recovery of **platelet** (**PLT**) count of 20,000/uL was day 15) after PBSC infusion to permit relatively early introduction of a post-transplant treatment strategy to reduce the probability of relapse after high dose chemotherapy followed by autologous stem cell transplantation for high-risk lymphomas. Comment: This Phase II study establishes the well-tolerated CTC regimen as a safe and effective regimen for lymphomas making it a

Pt No	Pt Age	Gender	NHL Grade (gr.) or HD Status	Marrow Biopsy+ for NHL	Prior Fludarabine or Nitrogen Mustard	CD34+ PBSC after Chemo-growth Factor x 10^6/kg	CD34+ PBSC after G-CSF Alone x 10^6/kg	Expanded Marrow Cells from 80 ml x 10^7/kg	Day That AGC >500 per uL	Day That PLT >20K per uL
1	54	F	Intermediate gr.	Yes	Yes	0.28*	1.0	3.0	14	>120
2	69	M	Intermediate gr.	No	No	0.04*	2.3	2.6	10	16
3	69	F	Low gr.	Yes	Yes	0.42*	0.5	6.6	14	>120
4	64	M	Low gr.	Yes	No	N.D.	0.81*	1.0	13	20
5	34	M	Primary Refractory HD	No	Yes	0.62*	N.D.	1.0	10	16

{Table note: * indicates first mobilization attempt and identifies poor mobilizer for study entry.}

Pt.	Char.	CD34+Cells/Infusion	Day AGC>500/uL	Day PLT>20,000/uL
1	54 M	1.4 x 10^6/kg	+12, +12, +11	+19, +18, +17
2	57 M	0.7 – 1.3 x 10^6/kg	+12, +13, +10	+17, NR[1], +18
3	44 F	3.0 x 10^6/kg	NR[2], NR[3], +9[4]	NR[1], NR[1], 23[4]
4	66 M	1.3[5] or 7.6[6] x 10^6/kg	9[7], 9[7], 9[7]	16[7], 11[7], 11[7]

{Table notes: 1. NR = not reached before next cycle of L-PAM initiated; 2. AGC = 410/uL on day −21; 3. AGC = 212/uL on day −21; 4. Days after unselected, back-up PBSC were given does not include the 13 days since the selected BPSC were given; and 5. CD34+ cell concentration of selected cells; 6. CD34+ cell concentration of the unselected, back-up PBSC.}

platform onto which post-transplant consolidation therapy can be built (see below).

2. Many experts have preferred peripheral blood stem cells as a source of stem cells for autologous transplantation (see below). Failure to collect sufficient numbers of CD34 (the surface marker identifying hematopoietic stem cells) positive (+) PBSC after mobilization with chemotherapy and growth factors (chemogrowth factor mobilization) has, however, been seen in patients who are heavily pretreated or are older aged and/or have had prior fludarabine therapy. Failed attempts at remobilization often disqualify these patients as candidates for autologous transplantation. At RWMC and in collaboration with the **Hackensack University Medical Center (HUMC)** and **Progenitor Cell Therapy (PCT)** in New Jersey,[3] we studied four heavily pretreated patients with NHL and one patient with primary refractory HD for whom we could not collect at least 2 x 10^6 /kg CD34+ PBSC (the standard minimum collection required to ensure engraftment after high dose chemotherapy) after the first course of mobilization. Four were mobilized first with cyclophosphamide, prednisone and G-CSF (our best chemogrowth factor mobilization regimen for hematologic malignancies). One was mobilized first with high doses of the growth factor G-CSF alone (10ug/kg/day for 3+ days). Second mobilization attempts were made in three patients with G-CSF. Only in one patient did we collect more than 2 x 10^6/kg CD34+ PBSC in a single mobilization attempt let alone cumulatively. Subsequently, all 5 patients were primed with G-CSF at 10ug/kg/day for 2 days. On the day of a full bone marrow harvest as a back-up collection, the first 80ml of marrow aspirated (2 to 2.5 ml/site) were cultured in the AastromReplicell™ by PCT for 12 days. Expanded marrow cells were infused 48-96 hours after the completion of high dose chemotherapy with the CTC regimen (see above) for the 4 patients at RWMC and after BVAC (a different high dose chemotherapy regimen) for the patient at HUMC. The day of infusion of expanded marrow is called day 0 of transplant. On day +l after transplant, all cryopreserved, stored PBSC were thawed and reinfused. Expanded marrow cells were well tolerated. Patient characteristics, CD34+ PBSC numbers, and expanded marrow cell numbers plus AGC and PLT count recovery times after autologous transplant following high dose chemotherapy are shown in Table 1.

With the expectation of delayed engraftment as a result of poor first PBSC collection, these patients would not have been considered autologous transplant candidates. With the addition of expanded marrow cells to PBSC, autologous transplantation was made possible for these five patients whose first collections were inadequate. AGC recovery was prompt (median day to AGC >500/uL was day 13). PLT recovery was prompt (median day to PLT count >20,000/uL was day 20), as well, except in the two patients who had received prior fludaribine therapy. We concluded that ex vivo marrow expansion is effective in providing a suboptimal PBSC collection with enough of the right cells to produce rapid granulocyte and platelet recovery. At this point in time, we don't know exactly what the "right" cells are - stem cells or accessory cells. All 4 NHL patients responded to high dose chemotherapy and have tolerated rituximab (antiCD20 antibody) to reduce the probability of relapse. The HD patient refused interferon after completing his post-transplant irradiation therapy. Comment: This small study demonstrated clearly that bone marrow may be a valuable source of expandable stem (or other) cells (see below). The biggest problem is how long will it take Aastrom to bring the Replicell™ to market?

3. **L-phenylalanine mustard (L-PAM)** is one of the most active agents for **multiple myeloma (MM)** available. The maximum tolerable dose of L-PAM is 240 mg/m^2 in high-dose chemotherapy and less is used in combinations with busulfan or total body irradiation. The usual "transplant" dose of L-PAM is 200 mg/m^2 followed by an autologous PBSC infusion. This usually produces a lengthy hospitalization with significant enteritis and mucositis. At RWMC,[4] we performed a feasibility study to determine if 3 cycles of L-PAM (followed by autologous PBSC infusion each time on the day after L-PAM) could be delivered at 100 mg/m^2 at 3-week intervals for a total of 300 mg/m^2 and on an outpatient basis. Four patients with chemoresponsive, stage III MM had PBSC mobilized with cyclophosphamide, prednisone and G-CSF. After CD34+ cell selection, PBSC were frozen in 3 aliquots. A back-up, unselected, PBSC collection was also cryopreserved. G-CSF was started day +1 and trovafloxacin and fluconazole were started day +5 after PBSC infusion. Of the 12 cycles, 1 cycle was delayed 1 week because of a central venous access line infection and 1 cycle was delayed because of a death in the patient's family. There were 7 admissions: 5 for neutropenic fever (42%) and 1 each for mild enteritis and disseminated Herpes zoster. The data from the study are shown in Table 2.

For patient #3, delayed AGC re-

Site	Trial Type	Pts	PBSC	Pts	BMSC	P-Value
Seattle	Randomized	81	16 (11-29)	91	21 (13-36)	< 0.001
RWMC	Sequential	15	12 (9-16)	7	11 (8-14)	0.0278

coveries were seen despite acceptable numbers of CD34+ cells infused; for course #3, back-up PBSC were given when AGC recovery appeared to be late again and prompt engraftment ensued. When patient #4 experienced late AGC recovery during cycle #1 with selected cells, we immediately infused back-up PBSC for that and both subsequent cycles; prompt engraftment was observed from then on. All 4 patients showed reduction in their M-proteins. After recovery from the third transplant, patients #l, #3, and #4 received alpha-interferon and patient #2 received thalidomide because of prior exposure to interferon. These 4 patients demonstrate that 300 mg/m^2 L-PAM can be delivered within a space of 9 weeks with acceptable non-marrow toxicities and with rapid recovery of AGC and PLT counts after each cycle especially after the third cycle which is the cycle that is the prelude to post-transplant therapy. Comment: This feasibility study delivered 50% more L-PAM in the same period of time as a standard autologous transplant and recovery from transplant (63 days or 2 months) with much less toxicity. Moreover the patients were in good enough hematologic shape and general health to start post-transplant immune based therapy.

4. In 1998, we initiated a strategy to improve clinical disease-free survival for patients with hematologic malignancies. The strategy has five steps:

a. Increased intensity of disease specific, induction therapy (maximal cytoreduction; CE/DHAC [carboplatin switched for cisplatin to minimize nephrotoxicity developed by Elfenbein's team in Tampa] for NHL and HD and DCIE [dexamethasone, cyclophosphamide, idarubicin, and etoposide developed by Elfenbein's team in Tampa[5]] for MM).

b. Mobilization of blood stem cells with chemotherapy and growth factor for fastest recovery of granulocytes and platelets (cyclophosphamide, prednisone and G-CSF) instead of just G-CSF alone and to provide an antitumor effect as well.

c. Positive selection of CD34+ cells, i.e., stem cells (which, also, purges the PBSC collection of tumor cells, i.e., negative selection of tumor cells).

d. High dose chemotherapy with known effective regimens (disease specific but with lowest known toxicity; CTC for NHL and HD and L-PAM x 3 for MM).

e. Consolidation with disease-specific immunotherapy (treating minimal residual disease [see below]). At RWMC,[6] we evaluated the first 18 consecutive patients who were transplant eligible and are in or have already completed the 5th step. Among the patients were 10 with NHL, 1 with HD, and 7 with MM. Only 5 (28%) would be considered to be good prognosis patients (first complete remission of NHL or first partial remission of MM). Only 7 (39%) had sufficient CD34+ cells collected to allow positive selection. The 11 lymphoma patients (63%) received CTC (see above) and the 7 MM (37%) received 3 cycles of L-PAM (see above). AGC recovery to > 500/uL (see below) was prompt in 16 pts (89%). Lymphoma patients received involved field irradiation for residual masses or history of bulky disease. One patient (5.5%) refused immunoconsolidation therapy after completing irradiation for HD (see above). The 12 patients (67%) whose disease was CD20 positive (a surface marker for B cells, 2 with MM and 10 with NHL) received all four planned weekly doses of antiCD20 monoclonal antibody (rituximab). Five

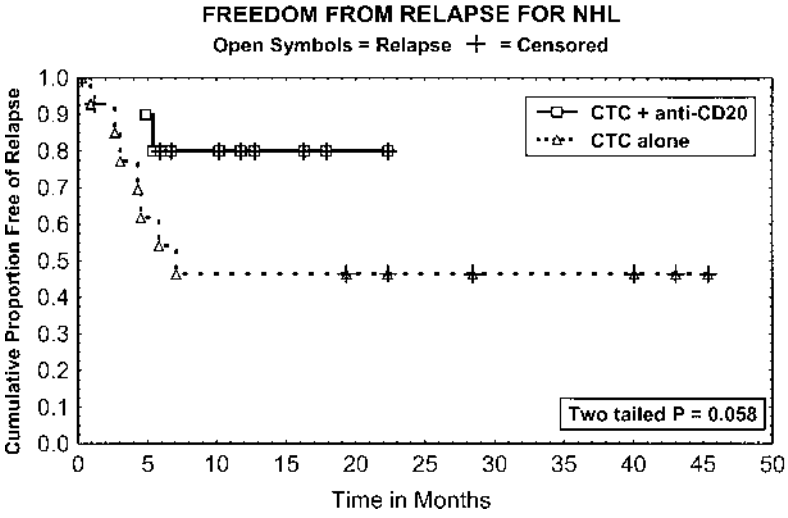

Figure 1.

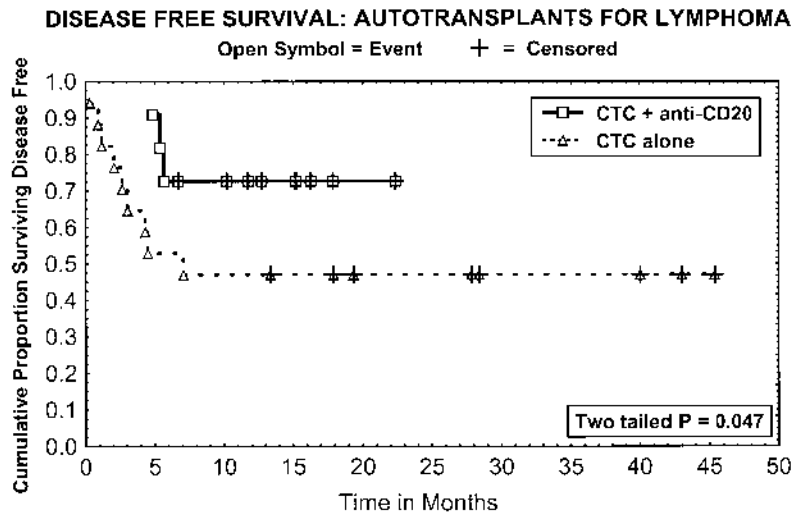

Figure 2.

of the 7 MM patients (71 %) were started on alpha-interferon but only 2 (40%) tolerated chronic administration of interferon. With a median follow-up of 15 months, there have only been 4 patients (22%) who developed disease progression. There have been 6 deaths (33%), 4 from progressive disease (22%) and 2 from late, trimethaprim-sulfamethoxazole resistant *Pneumocystis carinii pneumonia* (11%). We found it feasible to incorporate immunoconsolidation into the treatment after autologous transplant but it is too early to comment upon disease-free survival.[6] Comment: Now you can see where we were going all along with our strategy to improve disease-free and overall survival by better cytoreduction pre-transplant, less toxic transplant regimens, and immune based therapy post-transplant. We have compared the NHL patients in this study (#4) to the NHL patients in study #1. They (#4) are about as similar as you can get to historical controls (#1). They (#1) were treated nearly identically except for the post-transplant immunoconsolidation therapy (#4). With all the reservations intrinsic to comparing one small phase II study (#4) to another small phase II study (#1) performed at an earlier point in time, we did see a significant difference in freedom from relapse and disease-free survival for the patients who received the post-transplant anti-CD20 immunoconsolidation therapy (Figures 1 and 2).

5. There have been many debates whether blood and marrow derived stem cells engraft at significantly different rates after transplantation. Bensinger for the Seattle group (*NEJM* 2001;344:175-81) stated that their **randomized clinical trial (RCT)** "confirm(ed) that engraftment occurs more rapidly with peripheral-blood cells than with bone marrow" in allogeneic transplants. In 1995, Elfenbein's Tampa team published preliminary data[7] and, in 1999, they published the final report[8] "of the first prospective, stratified, randomized trial (also an

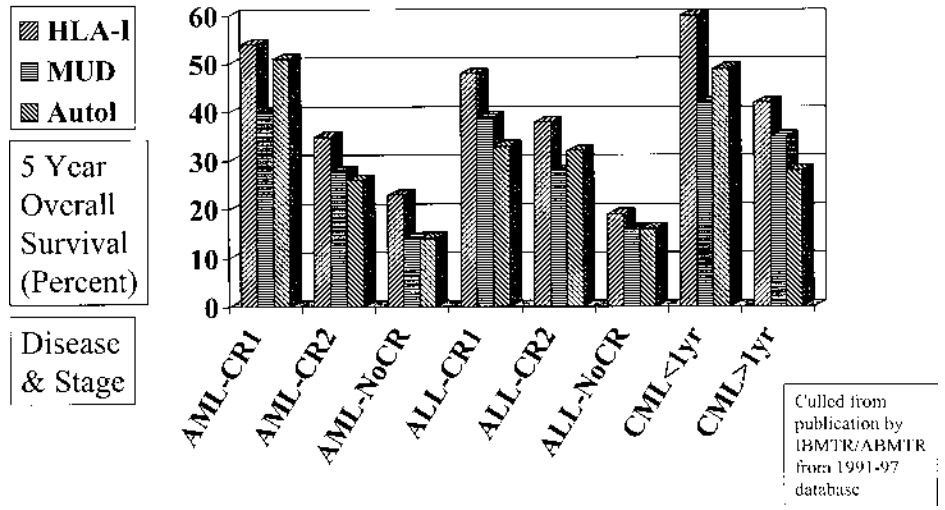

Figure 3.

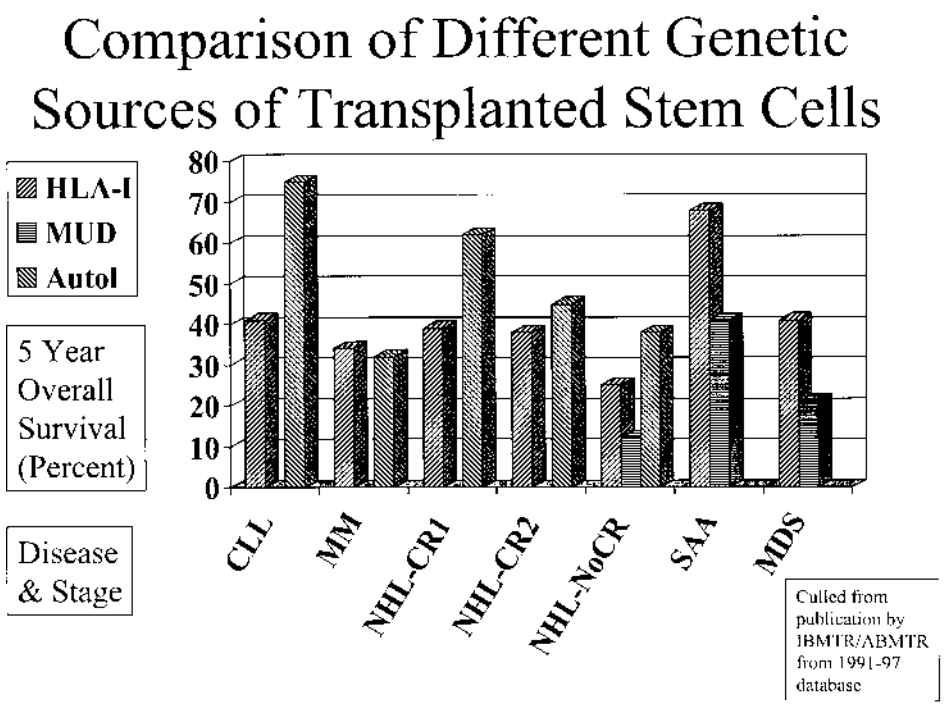

Figure 4.

RCT) comparing G-CSF primed bone marrow cells with G-CSF mobilized peripheral blood cells for pace of hematopoietic engraftment" demonstrating identical granulocyte and platelet recovery times for the two types of stem cells after autologous transplants. How could these two RCTs be in such stark contrast? The difference between the two RCTs is not whether the transplants were autologous or allogeneic, nor whether post-grafting therapy involved methotrexate or not. The difference is how the donor was treated prior to collection of the stem cells. In Bensinger, to collect PBSC the donor was pretreated with G-CSF at 16 ug/kg/day for 5 days whereas to collect stem cells from the bone marrow (BMSC) NO pretreatment was given. In Bensinger, cyclosporine and methotrexate were given as acute **graft versus host disease (GVHD)** prophylaxis. Myeloid engraftment was defined as the first of three consecutive days that the AGC was more than 500/uL. At RWMC,[9] we evaluated the results of our recent experience of 7 consecutive patients who had been transplanted with BMSC from healthy donors, all of whom had been pretreated with G-CSF at a dose of 10 ug/kg/day for 3 days. Only cyclosporine was utilized as GVHD prophylaxis. Prior to the return to BMSC, albeit G-CSF primed, we had performed a consecutive series of 15 G-CSF mobilized PBSC allotransplants that was rather novel in its time (starting June 1994). Table 3 summarizes the comparative study facts and presents engraftment results as the median day (range) for the AGC to exceed 500/uL.

We believe that large RCTs will confirm that G-CSF pretreated marrow will engraft just as rapidly as G-CSF mobilized peripheral blood and may, potentially, produce less GVHD. RCTs, no matter how large, may only be relied upon for interpretation within the bounds of their experimental design. Apparently, Bensinger et al. never anticipated that the confounding variable G-CSF was responsible for the effect they observed (difference in engraftment times) and not the anatomical site from which the stem cells were collected. Finally, these data demonstrate that post-grafting methotrexate delays the pace of granulocyte recovery considerably. Comment: The debate will rage on about bone marrow stem cells and blood-derived stem cells but I am convinced that the two are equivalent from the point of view of early engraftment. Bone marrow certainly offers advantages from the point of view of long-term engraftment while blood derived stem cells offer advantages from the point of view of antitumor activity. Both scenarios are dependent on the cells that contaminate the stem cell collections.

Two New Thrusts

I have been a "card carrying member" of two "brotherhoods", immunology and experimental hematology, since 1967 when I came under the tutorial wing of George Santos at Johns Hopkins. Therefore, I recruited Larry Lum from Wisconsin to develop a program in cellular immunotherapy but with an intriguing twist. Immunotherapy certainly has not been as successful as originally hoped. Why? What interested me so much in Larry's work is how low the effector-to-target ratios were in his *in vitro* cytotoxicity assays and that effectors could kill a second target cell in sequence. Potentially, this would help with the problem *in vivo* where the tumor vastly outnumbers the immune cell population. He does this by expanding and activating patient T cells *ex vivo* (call them activated T cells or ATC). But there is the problem of trafficking. How does he get the ATC to the tumor sites and, if they get there, why would they stay there? The answer to the first question is the cells arrive at the tumor sites in the blood at random unless they are directly injected into the tumor or are chemoattracted. Not easy to do, control, or ensure. The second question is more easily answered: "arm" the ATC with a bispecific antibody that, on the one hand, binds to the T cell and, on the other hand, binds to the tumor cell. Larry makes these "bi" antibodies in his own lab. His project is not only IRB-approved but also FDA-approved and looks at arming ATC with an antibody to HER2/neu found on some breast cancer cells and most prostate cancer cells. Patients with minimal residual disease are being treated now. There is also a project for metastatic breast cancer. In the not-too-distant future, we hope to have an antibody to EpCAM, which binds to a diverse number of carcinomas. Armed ATC may be considered the autologous ultimate in immunoconsolidation therapy.

Back to experimental hematology, I recruited Pete Quesenberry from Massachusetts, a world-class experimental hematologist whose success with low-dose total body irradiation and cellular immune therapy with HLA identical sibling donor cells in patients with hematologic malignancies made me take notice as this was the least toxic of all the "mini"-transplant regimens in the world. His goal was mixed chimerism (a state of co-existence of donor and host cells so that there would be no graft versus host disease and, because there was mixed chimerism, obviously there wasn't any rejection). But, even with mixed chimerism, there was an antitumor effect, the **graft versus tumor effect (GVT)**, else the diseases would not have gotten better. All this without major side effects. Simply marvelous pilot data. We activated this protocol at RWMC. Further, I have been struggling for many years with the problem of finding donors for patients when they don't have HLA-identical sibling donors, which happens more than 65% of the time. I have spent many years pursuing autologous transplants and study #4 is the ultimate expression of this research direction but it is limited by the number of antibodies that are currently available like rituximab for NHL. None yet for MM, for instance. HLA **matched, unrelated donor (MUD)** stem cells may now be obtained (about 65% of the time) from adults and from cord blood but the former transplants are very difficult to perform (read very toxic) and the latter are still rare in adults (because of low numbers of stored cord bloods and expansion problems). See Figures 3 and

4 for 5 year overall survival data after HLA-identical transplants, MUD transplants and autologous transplants for a variety of diseases. HLA-haplomatched (halfmatched) related donor allogeneic stem cell transplants have been performed in the new world as well as in the old world but in limited numbers. They are of the same difficulty as MUD transplants (read toxicity). The question, then, that Pete and I posed to each other was could mini-HLA-haplomatched allogeneic transplants be done using the same methodology as in his HLA identical sibling mini-transplants? If successful, there would be mixed chimerism, bi-directional tolerance, and dynamite GVT. At the time of this writing we have performed 13 of these HLA-haplomatched transplants. We are using a fixed number of CD34+ cells/kg and slowly escalating the number of T cells/kg in the graft after only 100 cGy of total body irradiation. Patients have tolerated the regimen very well so far. Patients with solid tumors and patients with hematologic diseases are both eligible. In the future, we will test donor ATC as opposed to quiescent donor T cells. GVT with quiescent donor T cells or donor ATC may be considered the allogeneic ultimate in the strategy of immunoconsolidation therapy.

The Closer

Now the closer, the ultimate in bringing the bench to the bedside, in combining immunology with experimental hematology, and in using adult stem cells to treat diseases other than those of the hematopoietic system or to attack cancer. We are working on a project in which adult stem cells will be targeted to ischemic myocardium with bispecific antibodies. If this troika of cardiology, stem cell biology, and immunobiology is successful, we'll be in the brave new world of treating ischemic heart disease and, potentially, congestive cardiomyopathies, in the future.

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Infections in the Transplant Recipient

Staci A. Fischer, MD

Despite advances in allograft matching, transplant surgical techniques, and immunosuppressive agents, infection remains a significant complication of renal transplantation. As recipients survive longer following transplantation, primary care physicians and nephrologists in the community must be aware of the epidemiology and clinical behavior of infection in the post-transplant patient.

Fever, considered a cardinal sign of infection in the immunocompetant host, is often absent in the transplant recipient, in whom corticosteroids attenuate the febrile response.[1,2] Leukocytosis may be absent as the result of azathioprine or mycophenolate mofetil therapy.[3] As a result, familiarity with the clinical presentation and timing of infections after transplantation are critical in reorganizing the presence of infection in these complex patients.

Presentation of Infection in the Post-transplant Patient

The clinical presentation of infections in renal transplant recipients may differ significantly from that in immunocompetant hosts.[4,5] Patients may present with vague symptoms such as fatigue, dyspnea, headache, malaise and/or chills, often without fever or leukocytosis. Notably, these symptoms are consistent with rejection as well as infection, so that aggressive diagnosis is warranted in evaluating these patients.

One of the most common focal complaints is that of nasal congestion. Azathioprine commonly causes this, and may increase the risk of upper respiratory infections such as sinusitis and otitis media in post-transplant patients. In addition to adenovirus, rhinovirus, *Streptococcus pneumoniae*, nontypable *Haemophilus influenzae* and other pathogens associated with such processes in normal hosts, more complex infections due to *Pseudomonas* species and fungi such as *Aspergillus* or the agents of mucormycosis may also be seen in the transplant patient. While empiric therapy for these and other infections may be necessary, antibiotics must be chosen carefully and patients followed closely for responses. If no response is seen in two to three days, or if symptoms progress, prompt referral to the transplant center should be obtained.

Diarrhea and other gastrointestinal symptoms (including nausea) pose another diagnostic dilemma in post-transplant patients. While taking numerous medications capable of producing gastrointestinal toxicity, these patients commonly present with cytomegalovirus and other infections with nausea or vague gastrointestinal complaints, often without significant fever. Early performance of stool studies (including examinations for white blood cells, enteric bacterial pathogens, ova and parasites, *Clostridium difficile* and *Cryptosporidium*) is indicated in the evaluation of diarrhea, with prompt endoscopic evaluation including biopsies in any patient with persistent gastrointestinal complaints.

Timing of Infections Following Transplantation

Because immunosuppressive therapy is most aggressive in the first year following transplantation, most patients are at greatest risk for opportunistic infection in the first twelve postoperative months.[5] Such pathogens include viruses such as **cytomegalovirus (CMV)**, **herpes simplex virus (HSV)** and **Epstein-Barr virus (EBV)**; fungi such as *Cryptococcus neoformans* and *Pneumocystis carinii*; higher-order bacteria such as *Nocardia asteroides*; and mycobacteria including *Mycobacterium tuberculosis*. Patients requiring additional immunosuppressive therapy or infected with certain immunomodulating pathogens such as CMV or hepatitis B or C are at greater and more prolonged risk for infection from these opportunists.

The time following transplantation has been divided into three periods: the early period (the first month post-transplant), when infections complicating the surgery itself, such as wound infections, urinary tract infection and pneumonia, occur; the middle period (1-6 months post-transplant), when more typical opportunists like CMV cause infection; and the late period (>6 months post-transplant), when opportunists such as *Pneumocystis carinii* and *Cryptococcus neoformans* typically cause disease.[5] (Table 1).

Renal transplant recipients are at particular risk for urinary tract infection, including pyelonephritis of the allograft.[6] In the immediate post-transplant period, infection may be the result of transmission of bacteria or fungi with the allograft itself. The presence of ureteral stents and bladder catheterization increases the risk of nosocomial urinary tract infections. Recipients of cadaver allografts with prolonged ischemic times are at particular risk for pyelonephritis as well as surgical wound infection.

Pathogens of Particular Concern in the Transplant Recipient

Legionella pneumophila is a fastidious gram-negative bacillus that is widely distributed in environmental waters and potable water systems and may cause sporadic or epidemic disease.[7] Patients typically present with fever, malaise and myalgias, followed by a dry cough which may be associated with pleuritic chest pain, abdominal pain, diarrhea and/or headache. Chest radiographs most commonly reveal unilobar alveolar infiltrates, although multilobar infiltrates and small pleural effusions may be seen. Hyponatremia may be a clue to the presence of *Legionella pneumonia*. Diagnosis requires growth on selective media. Direct fluorescent antibody staining of sputum or bronchoalveolar lavage specimens may be useful while cultures are pending. Treatment consists of 21 days of azithromycin or quinolone therapy. Due to significant interactions with erythromycin, this antibacterial drug should generally be avoided in the transplant setting.

Listeria monocytogenes colonizes the gastrointestinal tract and may produce bacteremia, meningitis or meningoencephalitis, typically in the middle or late periods.[8] Patients usually present with fever, headache and/or altered mental status. **Cerebrospinal fluid (CSF)** examination typically reveals a neutrophilic pleocytosis and hypoglycorrhachia; gram

staining generally fails to demonstrate the characteristic gram-positive organisms. Culture of blood and/or CSF remains the cornerstone of diagnosis. Penicillin or ampicillin (or trimethoprim-sulfamethoxazole in the penicillin-allergic patient) is recommended for 21 days.[9] Third generation cephalosporins, commonly employed as the empiric therapy of acute bacterial meningitis, are ineffective against Listeria.

Nocardia asteroides may cause pneumonia and/or brain abscess, usually in the middle period.[10,11] Fever and cough are common with nodular or cavitary infiltrates on chest roentgenogram. Metastatic abscesses may develop in the brain, skin, bone, liver, kidney or joints. Modified acid-fast staining of tissue specimens may reveal the characteristic beaded, branching filaments; culture is diagnostic. Trimethoprim-sulfamethoxazole is the antimicrobial of choice for *Nocardia* infection, typically administered for 12 months.

Cytomegalovirus **(CMV)** is the most common infection following transplantation, and usually develops in the middle period.[12,13,14] Disease is most common and severe in patients seronegative for CMV pretransplant who receive a CMV seropositive kidney. Patients may present with flu-like symptoms (CMV syndrome), nonproductive cough associated with bilateral interstitial and alveolar infiltrates (pneumonitis), nausea and bloating (gastritis), diarrhea or gastrointestinal bleeding (colitis), visual acuity changes (chorioretinitis), or more uncommonly, with hepatitis, pancreatitis, myocarditis or encephalitis. Prolonged fever or malaise may be symptoms of CMV infection of the transplanted kidney itself. Diagnosis generally requires histologic evidence of CMV, with the presence of characteristic intranuclear inclusions in tissue specimens; culture may be helpful. Treatment consists of intravenous ganciclovir administered for 14 to 21 days.

Epstein-Barr Virus (EBV) may cause a febrile mononucleosis-like syndrome, although splenomegaly and pharyngitis are uncommon and the heterophile antibody test is often negative.[15] Diagnosis requires culture of EBV from normally sterile body sites and/or positive immunofluorescence studies on tissue samples. Although acyclovir is commonly prescribed, its clinical utility has not been demonstrated in this setting. The most feared complication of EBV infection is **post-transplant lymphoproliferative disorder (PTLD)**, a proliferation of previously infected, transformed B lymphocytes that may be malignant. Most PTLD patients present with fever and lymphadenopathy, sometimes with pulmonary or hepatic involvement. As this entity often requires withdrawal of immunosuppression, patients with suspicion of PTLD should be referred to the transplant center for definitive diagnosis and therapy.

Patients may present with vague symptoms such as fatigue, dyspnea, headache, malaise and/or chills, often without fever or leukocytosis.

Pneumocystis carinii, now classified as a fungus, may present with fever, dyspnea and nonproductive cough of subacute onset, most commonly in the first year post-transplant.[16] Chest radiographs typically reveal diffuse interstitial infiltrates, and hypoxemia may be present. Bronchoalveolar lavage fluid or tissue specimens reveal the characteristic cysts upon silver staining. As fewer organisms are generally present in transplant patients than in those with HIV infection, examination of expectorated sputum is insensitive. Treatment consists of high dose trimethoprim-sulfamethoxazole for at least 14 days.

Aspergillus species may cause pneumonia in the early or middle periods.[17,18] Patients typically present with fever and a dry cough, although with vascular invasion, hemoptysis and pleuritic chest discomfort may develop. Hematogenous spread to the brain may result in confusion and/or focal neurological deficits. Computed tomography scans reveal low-density lesions with minimal contrast enhancement, and cerebrospinal fluid cultures are generally negative. Amphotericin B should be instituted immediately in these patients, as the mortality rate remains high (>90%).

Candida albicans and other candidal species, common gastrointestinal tract and skin colonizers in post-transplant patients, may cause wound infection, pyelonephritis, fungemia, esophagitis, or other serious infections. Amphotericin B should be used in acutely ill patients, or fluconazole in the patient with non-life threatening disease involving susceptible species.

Prophylactic Antibiotics

Some of the opportunistic infections discussed above are preventable. Patients are generally placed on daily or thrice weekly **trimethoprim-sulfamethoxazole (TMP-SMX)** for prophylaxis of *P. carinii* and *Toxoplasma gondii* in the first year following renal transplantation.

As mucocutaneous fungal infections, most notably oral candidiasis, are common in the early period, topical antifungal therapy with nystatin solution or clotrimazole troches is commonplace.

Patients may also receive prophylaxis against CMV and/or HSV infection. There are dozens of published trials of a variety of agents, often used sequentially or in combination, to prevent CMV disease. In general, recipients without prior evidence of CMV infection who receive a kidney from a similarly CMV-naïve donor do not require specific CMV prophylaxis, although any blood products administered to them should be CMV seronegative, irradiated or filtered to remove the white blood cells which latently carry the virus. Other kidney transplant recipients should be prophylaxed against CMV using antiviral agents such as ganciclovir, valganciclovir or valacyclovir for 3 to 6 months after transplantation.[19] Because the prevention and early diagnosis of CMV infection and disease is of utmost importance in the care of the transplant patient and represents an area of constantly changing diagnostic and therapeutic modalities, these aspects of the patient's care should be dictated by the transplant center.

Immunizations, important elements of infection prevention in all patients, are less effective and sometimes contraindicated in the transplant recipient.[20,21] While the influenza vaccine is typically administered to transplant recipients annually, their seroconversion rate is substantially lower than that of the healthy adult population. Live virus vaccines (i.e., the measles-mumps-rubella, yellow fever, Bacille-

Calmette-Guerin or BCG, and oral polio virus vaccines) are contraindicated in all immunosuppressed patients, as they have been associated with the development of disseminated infection in these settings. Studies of the Varicella vaccine are underway to evaluate its use in susceptible transplant recipients; many transplant centers are administering this vaccine to seronegative patients pretransplant.

Guidelines for the Care of the Post-transplant Patient

Care of the renal transplant recipient inevitably involves monitoring his or her household contacts — looking for signs of potentially transmissible infections from humans and pets alike. In general, frequent hand washing by all household members (especially children) is the most important intervention to be made. A veterinarian should evaluate pets regularly, and the transplant recipient should avoid direct contact with animal excrement, the source of many pet-transmitted opportunistic infections. Significant animal scratches and bites, including those from healthy-appearing cats or dogs, should be evaluated quickly in the post-transplant patient, as a number of serious infections (most notably those from *Capnocytophaga* species and *Pasturella multocida*) may result.

Children living with or in frequent contact with the renal transplant recipient should not receive the oral polio vaccine, which is associated with fecal shedding of live viral particles for weeks to months following administration. In these children, the parenteral, inactivated polio vaccine should be administered instead.

Transplant recipients should avoid ingestion of undercooked meats, unpasteurized milk products and raw seafood, and should seek infectious disease consultation prior to any trips outside the continental United States for specific infection prevention instructions.

Antibiotic Selection in the Post-transplant Patient

While antimicrobial spectrum is the primary consideration in choosing empiric therapy in this patient population, it is critical to recognize the potential drug interactions that may occur when some common antibiotics are used.[22]

Some macrolides, including erythromycin and clarithromycin, are metabolized via the cytochrome p450 system and may dramatically increase cyclosporine and FK-506 serum levels, resulting in nephrotoxicity. Azithromycin and clindamycin, which utilize alternate routes of metabolism, are considered safe to use. The use of itraconazole and ketoconazole may have similar effects.

The use of doxycycline, isoniazid and rifampin may accelerate cyclosporine and FK-506 metabolism, resulting in subtherapeutic serum concentrations. The use of nephrotoxic agents such as the aminoglycosides and amphotericin B should be approached with great caution in patients on cyclosporine or FK-506. With the increasing number of cephalosporins, quinolones and liposomal amphotericin B products available, avoiding more toxic antimicrobial drugs is becoming easier with time.

Conclusion

The care of the renal transplant recipient requires a team approach, with thorough patient education, aggressive surveillance and effective prophylaxis and treatment of the inevitable infections which develop. The primary care physician serves as a critical link between the patient and the transplant center. Armed with a general background in post-transplant opportunistic infections and a commitment to detailed evaluation, nephrologists and general internists may contribute more effectively to the life and care of these complicated patients.

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Live Donor Renal Transplantation

Paul Morrissey, MD, and Bette Hopkins-Garcia, RN, MS, CCTC

Kidneys can be purchased for live donor renal transplantation in Turkey, India, Iraq and other nations.[1] These "donations" are legal in some countries, overlooked in others and unfortunately often managed in a "black market" where the middleman (facilitator) takes a cut of the procurement fee. While this practice can be viewed from many sides (ethical, medical, social justice, utilitarian) it highlights the fact that most patients are not thriving on dialysis, the majority favor transplantation as an alternative, that there is a worldwide shortage of cadaver organs and that live donor transplantation is the best therapy for **end-stage renal disease (ESRD)**. I will explore these issues with reference to the state of renal transplantation in Rhode Island.

Historical Perspective

Prior to 1954 nobody survived ESRD. The successful identical twin kidney transplant performed at the Peter Bent Brigham Hospital on December 24, 1954, offered hope to those in need of renal replacement. Identical twin transplantation remained the only viable option for treating ESRD until 1960 when the first immunosuppressive therapies were added. Hemodialysis was introduced in the 1960s; by the end of that decade centers were established in many major medical centers throughout the United States.

Dialysis did not become widely available until Congress amended the Social Security Act in 1972 to provide Medicare coverage to people with ESRD. A patient was dialyzed on the floor of Congress to demonstrate this new therapy. Joseph Chazan, MD, established the first public hemodialysis unit in Rhode Island at the Rhode Island Hospital in 1970. Less than three years later the first "free-standing" unit opened in East Providence. **Continuous ambulatory peritoneal dialysis (CAPD)** was introduced shortly thereafter. Since that time patients with ESRD have had three treatment options: hemodialysis, CAPD and renal transplantation.

Steady progress has been made in the safety and efficacy of all renal replacement therapies. With the advent of new immunosuppressive agents, renal transplantation has become safer and more successful. One-year allograft survival rates of 50%, common in the 1970s, improved to 80% in the 1980s and are now >85% for cadaver renal transplants and >94% for live donor renal transplantation. In 1999, 12,485 renal transplants were performed of which 8011 were from cadaver donors and 4474 from living sources.[1]

ESRD affects persons of all ages. The average age of persons starting dialysis is 61 years old. The incidence of ESRD is increasing most rapidly in the older age groups with 35% of all new patients older than age 65. An increasingly difficult task is choosing the appropriate ESRD modality for older persons with hypertensive nephrosclerosis, type II diabetes mellitus and advanced arteriosclerosis. The prevalence of ESRD (1997) according to Medicare records was 1,105 per million. In Rhode Island, a state of 1,053,000 persons, approximately 900 persons are on dialysis and 400 have functioning renal transplants.

Living Donors

Live donor renal transplantation (LDRT) is the optimal therapy for most patients with ESRD.[3] Some patients are excluded due to comorbid illness, advanced age with limited life expectancy and social instability (noncompliance). Over 50,000 patients are on the national waiting list for a renal transplant, including 2000 patients in New England where we typically recover organs from 170 brain-dead organ donors per year. The typical wait for cadaver renal transplantation in New England is 2 years for ABO=A or AB and 3 - 4 years for ABO=O or B. Recent data suggest that the less time spent on dialysis the better the patient's outcome.[3] Given the long waits in New England, this can only be achieved by securing a live donor.

Nationally, living donors provide 36% of all kidneys transplanted and the number is steadily increasing. (Table 1) However, this pattern is not seen worldwide with the number of LDRT per million population reported in 1997 as: USA (14.1), Canada (9.5), UK (2.8), France (1.2) and Spain (0.5). At RIH, 119/256 (46 %) transplants have come from a living donor and LDRT comprised more than half of the transplants in the past two years.

Kidneys from live donors provide superior results to cadaver sources. (Table 2) Both one-year and long-term success rates are excellent. Immediate function of the kidney occurs in 19/20 cases and 98% of transplanted patients have a functioning allograft at one month. Initial immunosuppressive requirements are less than for cadaver renal transplants, as is the risk of early acute rejection. As a result, the attendant infectious complications and the predictable side effects of chronic immunosuppression are decreased. In

Table 1. Growth in Live Donor Renal Transplants (LDRT) in the U.S. and Outcomes

	Number of Transplants		One-Year Graft Survival	
YEAR	LDRT	CRT	LDRT	CRT
1991	2393	7281	90	81
1993	2851	7510	91	83
1995	3359	7689	93	85
1997	3907	7767	94	87
1999	4474	8011	95	89

Table 2. Live Donor (LDRT) versus Cadaveric (CRT) Renal Transplantation.

Item	LDRT	CRT
Allograft half-life	16-19 years	10-12 years
Waiting time	2 - 4 months	24 - 48 months
Donor Age	18 - 60	4 - 80
Quality of kidney	Excellent	Good to excellent
Immediate function	95 %	50 %
Average hospital stay	5 - 7 days	7 - 14 days
Immunosuppression	Lower doses	Standard
Risk of acute rejection	5 - 10 %	15 - 20%

contrast to cadaver renal transplantation, a live donor transplant can be scheduled electively, typically within 2-3 months of initiating evaluation, and is more likely to be an early or even the initial ("preemptive") treatment for ESRD.

The Living Donor

The benefits of LDRT must be balanced with the risk of major surgery in an entirely healthy person. The donor's benefit is slightly less tangible - derived from the satisfaction of helping a loved one. Potential living kidney donors must meet five basic requirements: (1) good to excellent health, (2) ABO-compatible with the recipient, (3) two kidneys with normal function, (4) crossmatch negative (nonreactive) - no lysis of donor lymphocytes by recipient's serum and (5) properly motivated without evidence of financial remuneration or coercion. In short, a potential donor for an unsensitized (lacking preformed antibodies) recipient must be a healthy, willing, and ABO-compatible individual with normal renal function.

In our experience, the donor source has been sibling (46), child (25), parent (15), spouse (9), distant relative or in-law (9), friend (11) and stranger (4). Thirty-three of the donors were unrelated to the recipient. The four "stranger" donors included a Buddhist priestess from Vermont who contacted our program in 1998 wishing to donate a kidney to anybody on our list.[5] After proceeding with a psychological evaluation and the routine medical work-up the New England Organ Bank was contacted to assist in selecting the appropriate recipient. On May 22, 1998 the live donor transplant occurred from an "anonymous" donor who never crossed paths with the fortunate recipient of her good will. Two other "strangers" were part of a two-way swap agreed upon to match ABO incompatibilities. Two children, each unable to donate to his mother, donated a kidney to the other family in a series of simultaneous surgeries. A fourth stranger donation took place under a novel program, "Hope Through Sharing", which allows persons waiting for a kidney transplant to move to the top of the list when a relative, with an incompatible kidney, donates to a stranger on the list. On August 27, 2001, a woman donated her kidney to the top ABO-compatible patient at Rhode Island Hospital and her ABO-incompatible husband became the top listed person in his blood group for all of New England. This gentleman, listed for only four months, received a cadaver kidney 11 days later. As a result of this living donor, two persons were transplanted - the donor's husband and a fortunate second patient who received a living donor allograft.

Kidneys from live donors provide superior results to cadaver sources.

Morbidity and Mortality of LDRT

Although widely accepted as standard practice in the U.S., some centers continue to be reluctant about the use of live donors for transplantation. This is a truly unique circumstance in medical practice - placing an individual "at risk" for the benefit of another. While our society accepts individuals taking risks and occasionally losing their lives for an overall good (fire fighters, soldiers and police officers), some believe that the medical profession should operate under a different standard. Major concerns for the donor include the potential morbidity and mortality of the donor nephrectomy, long-term function of the remaining kidney and the psychological well being of the donor. Donor mortality, typically from pulmonary embolism or a peri-operative cardiac event, is about 0.03 - 0.05%.[6] Previous studies have reported morbidity rates of 8 - 24%. Long-term follow-up (20 - 30 years) demonstrates that renal function remains stable. Occasionally the donor will develop insignificant microscopic proteinuria years after nephrectomy. Quality of life studies and psychological assessments after kidney donation reveal that most (> 93%) were happy to have donated and > 95% would or probably would donate again given the same circumstances. Quality of life studies show that kidney donors surpass the national norms even years after donation. One recent study also reveals that the life expectancy for kidney donors is greater than average.

Experience with LDRT at RIH

Our overall experience at RIH with LDRT has been excellent. The donor and recipient operations are performed simultaneously in adjoining

operating rooms. The kidney is recovered from a flank incision between the 11th and 12th ribs. Immediate function occurred in 113/119 transplants with two cases each of slow graft function, delayed graft function (one dialysis session required after surgery), and primary graft nonfunction. The overall initial success rate was 98% and graft survival at one year was 93%. The primary reason for graft failure was recipient death with a functioning renal transplant (6 cases). Two grafts never functioned and two were lost to recurrent acute rejection.

Of primary concern in this venture is the wellbeing of the healthy donor. Operative complications following 119 donor nephrectomies were limited to one wound infection, one UTI, two cases of pneumothorax and one blood transfusion. Five cases were performed laparoscopically with the kidney removed intact through a 3-inch incision in the pubic hairline. This procedure provides a quicker postoperative recovery, better cosmesis and has encouraged some people to donate who would not have agreed to an open procedure. In our hands, laparoscopic donor nephrectomy has been performed with a level of safety that mirrors the open procedure. Following donor nephrectomy the average patient uses parenteral narcotics for 2 - 3 days and oral narcotics for one week. Donors have been discharged home in 3.85 ± 0.67 days and typically return to work in 2 - 6 weeks. In Rhode Island most donors qualify for **Temporary Disability Insurance (TDI)**. Although the entire cost of kidney donation is covered by the recipient's insurance, many donors lose vacation time and wages.

Efforts to Increase the Rate of Transplantation

For most persons with ESRD kidney transplantation and in particular kidney transplantation from a live donor represents the best option for long-term survival, a high quality of life and reduced complications. We are limited by the availability of kidneys to transplant. Cadaver donors are increasing in age and many kidneys considered unacceptable five years ago are being transplanted into appropriately matched recipients as "marginal" organs or even as dual renal transplants (two marginal kidneys transplanted into a single recipient). Efforts continue to increase the availability of live donor kidneys as we extend the social acceptability of unrelated and stranger organ donation. Interestingly, in a Gallup poll this year 80% of respondents supported stranger kidney donation. Furthermore, respondents answered that they would (24%) or probably would (21%) donate a kidney to a stranger in need for free. This remarkable response has not been realized in practice (only a few hundred altruistic donations have occurred), but it implies an untapped resource. At RIH, we have formed a committee of hospital staff and social workers to review potential altruistic donors. More information is available at our website www.lifespan.org/transplant/donor/altruistic.

Future Consideration

Despite the generosity of the public and their good intentions expressed in the Gallup poll, we have a critical shortage of organs for transplantation. Innovative practices have led to increased rates of donation, but the supply does not match the need. We may be entering a time where economic reimbursement for the donor is a practical, safe and fair means to solve this problem. In the current system the donor often pays travel expenses and then loses wages and vacation time while recovering from the surgery. Even paying $20 for analgesics upon hospital discharge is a burden for some donors. Such disincentives need to be removed to encourage this act of heroism (donating an organ). Regulating payments to donors or their families offers the best opportunity to eliminate current injustices and abuses in the system. The suggestion that rewarding their gift reduces these persons to commodities supposes that the transplant team can be removed from their obligation to "care about the patient". It has been suggested that all organ donors (cadaver and living) be awarded a Gold Medal from the government. The worth of this medal may be $3000 (less than 1/6 of the current kidney acquisition fee). This money could be used to defray funeral costs for cadaver donor families or used by the living donor to supplement lost wages. The reward may encourage some to donate who would not. For others, not desiring financial compensation, the medal could be saved and cherished as a reminder of their heroism. Careful oversight of this program would protect donors from exploitation and increase the availability of living donors - the optimal therapy for ESRD.

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An Update In Transplant Immunosuppressive Therapy

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As we enter the millennium, the most widely acknowledged advancement in transplantation has been the development of more selective and potent immunosuppressive agents. In the early period of transplantation, the selection of maintenance immunosuppression was limited to the combination of azathioprine and corticosteroids. Unfortunately, these agents were relatively non-specific and ineffective and carried the risk of a multitude of side effects. The major clinical concerns at that time were the prevention of acute rejection and improvement in patient and graft outcomes, since expected patient survival post-transplant was low. The development of cyclosporine in the 1970s marked the first application of T-cell selective immunosuppressive therapy. The widespread clinical application of this agent in the 1980s significantly improved transplant outcomes and, depending on the specific organ and donor source, graft survival in the order of 85-90% at one year became commonplace.[1]

The last decade has built on the foundations of T-cell targeted immunosuppression with the introduction of tacrolimus, mycophenolate mofetil, rapamycin and new polyclonal and monoclonal antibodies directed at specific receptors (IL-2 receptor) on activated lymphocytes. (Table 1) These agents have been used in various combinations with the goal of achieving maximal immunosuppressive potency with minimal side effects. It is now commonplace to have rates of acute rejection less than 10% (Table 2), verifying the synergistic interactions of these agents. The outstanding results that are achievable with these newer medications makes it difficult to select a protocol based solely on efficacy data. The goals that define immunosuppressive therapy have shifted toward reducing maintenance immunosuppression and minimizing side effects. Furthermore, more emphasis is now placed on choosing immunosuppressive regimens tailored to fit the unique characteristics of the individual transplant recipient. The purpose of this article is to review these newer agents, their mechanisms of action and side effects, examine the choices that currently exist for immunosuppression, and finally discuss the potential hazards of their long-term use.

Tacrolimus

Tacrolimus (FK506) is a macrolide compound that possesses similar but more potent (approximately 100 times more) immunosuppressive properties compared to cyclosporine. Initially, the **Food and Drug Administration (FDA)** approved this agent for use in liver transplantation because of its superiority in preventing acute rejection, but it has since gained increasing popularity in renal transplantation as well. Despite having radically different chemical structures, tacrolimus shares a similar mechanism of action to cyclosporine; therefore both agents have been placed in the same category of immunosuppressive agents known as calcineurin inhibitors. Both drugs form a complex with a specific cytoplasmic receptor protein (cyclophilin or FK-binding protein respectively), which then target specific signal transduction pathways downstream. The net effect is the downstream inhibition of IL-2 signaling and IL-2 receptor elaboration, thereby inhibiting clonal expansion of cytotoxic T-cells and other cell lines involved with the acute rejection process.[2] In randomized clinical trials, tacrolimus produced similar patient and graft survival in renal transplantation compared to modern versions of cyclosporine (microemulsified form).[3] Be-

TABLE 1
CLASSES OF IMMUNOSUPPRESSION

CLASS OF AGENT	OPTIONS	SIDE EFFECTS
CALCINEURIN INHIBITOR	CYCLOSPORINE	Nephrotoxicity Hypertension Hirsutism Hypercholesterolemia
	TACROLIMUS	Nephrotoxicity Islet cell toxicity Neurotoxicity Mild hypertension
ANTI-METABOLITE	AZATHIOPRINE	Leukopenia Thrombocytopenia Hepatits Cholestasis
	MYCOPHENOLATE MOFETIL	GI upset Leukopenia Thrombocytopenia Anemia
OTHERS	CORTICOSTEROIDS	Hypertension Glucose intolerance Obesity Avasculer necrosis Oseteoporosis Cataracts
	RAPAMYCIN	Hypercholesterolemia Thrombocytopenia Leukopenia Anemia
ANTIBODY INDUCTION	THYMOGLOBULIN ATGAM	Fever/chills Thrombocytopenia Leukopenia Serum sickness Increased CMV risk
ANTI-CD25 MONOCLONAL ANTIBODY	BASILIXIMAB DACLIZUMAB	Virtually none

TABLE 2
IMMUNOSUPPRESSIVE REGIMEN EFFICACY RESULTS AT 1 YEAR

REGIMEN	ACUTE REJECTION (%)	GRAFT SURVIVAL (%)
CsA/pred (AZA)	40-50%	85-90%
CsA/MMF/pred	15-20%	90-95%
Tacrolimus/MMF/pred	10-15%	90-95%
CsA/Sirolimus/pred	10-20%	90-95%

Abbreviations are: CsA, cyclosporine: AZA, azathioprine: MMF, mycophenolate mofetil; pred, prednisone
Adopted from reference 2.

cause their mechanisms of action are similar, cyclosporine and tacrolimus cannot be used synergistically or additively; rather, immunosuppressive protocols must employ either one or the other, not both.

Since both cyclosporine and tacrolimus are useful in maintenance immunosuppression, the choice between the two medications must be based primarily on the side effect profile of these agents. However, the toxicities are relatively similar, except that tacrolimus produces more hyperglycemia and neurotoxicity. Tacrolimus is associated with less hirsutism, gingival hypertrophy and gynecomastia. In addition, there are improved lipid profiles. Hence, the development of one or more of these toxicities is reason enough to convert from one agent to another.

Both cyclosporine and tacrolimus are hepatically metabolized by cytochrome P4503A4, and therefore have similar drug interactions with agents that affect this metabolic pathway. (Table 3) Many of these interactions involve commonly used medications and consequently, any new agents must be introduced with the recognition of potential interactions. Patients should be warned to consult physicians experienced with the use of either cyclosporine or tacrolimus before considering the introduction of new pharmacologic therapy. Even over-the counter preparations such as St. John's wart may induce P450 metabolism, resulting in acute rejection because of subtherapeutic cyclosporine levels.[4]

Clinically, the most important drawback of either of the calcineurin inhibitors is the development of nephrotoxicity. Both agents enhance the production of TGF-beta, which has been implicated in the development of interstitial fibrosis and ultimately graft failure. Thus, although the calcineurin inhibitors have resulted in dramatic reduction in acute rejection rates and improvement in short-term outcomes, they have not been as successful in

The goals that now define immunosuppressive therapy have shifted toward reducing maintenance immunosuppression and minimizing side effects.

increasing long-term survival. The impact of calcineurin-inhibitors on the renal allograft is clearly demonstrated in the recent histologic study of protocol kidney biopsies obtained at 2 years in the phase III tacrolimus versus cyclosporine trial. An alarming 66% of biopsy specimens in both groups have evidence of chronic transplant nephropathy.[5] Multivariate analysis showed that acute cyclosporine or tacrolimus nephrotoxicity in the first year had a strong correlation with the development of chronic transplant nephropathy. This is the genesis of a number of clinical studies designed to either completely eliminate or spare the use of calcineurin inhibitors to minimize nephrotoxicity. Although early results are encouraging, there is still no compelling data to support the notion that these agents can be safely removed from the immunosuppressive armamentarium without adversely affecting graft outcomes.

Mycophenolate Mofetil

Mycophenolate mofetil (MMF) was introduced into clinical transplantation in 1995 following a series of large clinical trials in cadaver renal transplantation showing improved efficacy over azathioprine for the prevention of acute rejection when used in combination with cyclosporine and prednisone.[6,7] Similar to azathioprine, it has an effect on purine biosynthesis, but acts differently in that it does not act as a false substrate for enzymes. Rather, MMF noncompetitively inhibits inosine monophosphate dehydrogenase, thereby inhibiting the synthesis of guanosine nucleotides and disrupting nucleic acid synthesis. The mechanism of action of MMF is more selective in that it inhibits the "de novo" pathway of purine synthesis while allowing the "salvage pathway" to continue its function unabated. T- and B-lymphocytes have an obligate need for purine biosynthesis via the de novo pathway, while other mammalian cells (particularly the brain) are more dependent on the salvage pathway. Because of its improved efficacy and specificity, MMF has largely replaced azathioprine either as initial immunosuppression or after an episode of acute rejection. Although the cost differential between the two agents is substantial, shorter hospitalizations for rejection offset the initial cost differential.

The most common adverse events reported with MMF are related to the GI tract and appear to be dose-related. Diarrhea has been reported to occur in up to one third of patients with varying degrees of nausea, bloating and vomiting occurring in up to 20% of patients. Although MMF targets lymphocytes relatively specifically, leukopenia, anemia, and thrombocytopenia occur with a similar frequency to that of azathioprine, but generally respond to dose reduction. Most importantly, MMF has not been shown to have any nephrotoxicity, making it a useful adjunctive therapy to the calcineurin-inhibitors.

Sirolimus

Sirolimus, also known as rapamycin, is a macrolide antibiotic compound that was introduced into clinical transplantation in 1999. It is structurally similar to tacrolimus and binds intracellularly to the same cytoplasmic-binding protein (FK binding protein). However, its immunosuppressive activity is distinct from that of the calcineurin inhibitors. Like cyclosporine and tacrolimus, sirolimus interferes with the antigen-driven transduction of signals from the cell membrane to the nucleus. However, this agent also interrupts the signaling machinery which commits T cells to divide, leading to cell cycle arrest in the G1 phase.[9] Additionally, sirolimus inhibits B-cell production of immunoglobulins much more effectively than either cyclosporine or tacrolimus.

The clinical efficacy of sirolimus has been verified in a number of clinical trials. These have demonstrated a significant reduction in the incidence of acute rejection

TABLE 3
DRUG INTERACTIONS WITH CALCINEURIN INHIBITORS

DRUGS THAT DECREASE CALCINEURIN INHIBITOR CONCENTRATION

Phenytoin
Carbamazepime
Barbiturates
Intravenous Bactrim
Nafcillin
Isoniazid
Rifampin and Rifabutin
St. John's Wart (Hypercum Perforatum)
Omeprazole

DRUGS THAT INCREASE CALCINEURIN INHIBITOR CONCENTRATION

Calcium channel blockers (verapamil, diltiazem, nicardipine)
Macrolide antibiotics
Doxycycline
Ticarcillin
Antifungal agents (ketoconazole, fluconazole)
Amiodarone
Carvedilol
Metoclopramide
Colchicines
Sex hormones
Alcohol

when combined with cyclosporine and prednisone, compared with either azathioprine or placebo.[2] Since then, it has been used in a number of different drug combinations, including calcineurin-inhibitor free regimens where patients were randomized to receive either rapamycin or cyclosporine, with all individuals receiving corticosteroids or azathioprine.

The major side effects of rapamycin are myelosuppression and hyperlipidemia. The dyslipidemia is characterized by severe hypertriglyceridemia, suggesting a possible role in the inhibition of lipoprotein lipase activity. However, treatment with HMG CoA reductase inhibitors is effective in improving lipid profiles. Rapamycin is not nephrotoxic when used alone. However, the combination of rapamycin and cyclosporine has been suggested to cause synergistic nephrotoxicity in animal studies.[10] Rapamycin is also metabolized hepatically through the cytochrome p450 pathway and therefore is subject to the same drug interactions that complicate the use of cyclosporine and tacrolimus.

Trends In Immunosuppressive Therapy

The new millennium has brought a gradual shift in immunosuppression in renal transplantation from consistent dependence on calcineurin inhibitors and corticosteroids to increasingly bold experimentation with the sparing or elimination of immunosuppressive drugs. With the range of agents available today, immunosuppression that is based on relative patient risk is an achievable goal. Although optimal approaches have not yet been established, a number of risk factors relative to acute rejection and long-term outcomes have been established. Cadaver donor source, African-American race, history of previous poor transplant outcomes and, to some extent, the etiology of underlying renal failure, might all be considered risks favoring the occurrence of acute rejection and may warrant enhanced immunosuppression. On the other hand, older recipients, recipients of HLA-identical cadaver grafts, as well as recipients of living related grafts, may be less likely to develop acute rejection. These are the individuals who should be targeted for dose reduction or drug elimination. Also, use of nephrotoxic agents might be avoided in those patients with "marginal" graft function. Immunosuppression-associated metabolic disturbances (e.g. hypertension, bone loss) should be reduced and managed as much as possible in all patients, but especially in those patients with pre-existing disorders such as cardiovascular disease, diabetes or osteoporosis. This has spurred particular interest in the use of steroid sparing regimens. Lastly, patient compliance may improve outcomes, and simplifying regimens and minimizing unpleasant side effects can achieve this goal. The ultimate ambition, short of the promise of drug-free immunosuppression, is to reduce mortality in the long-term and to improve the quality of life for all patients.

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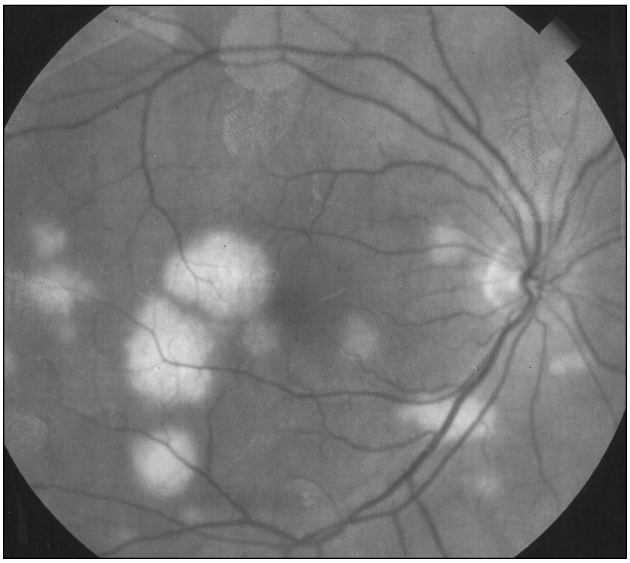

Figure 1. Fundus photographs demonstrating multifocal, round, yellowish choroidal lesions in both eyes.

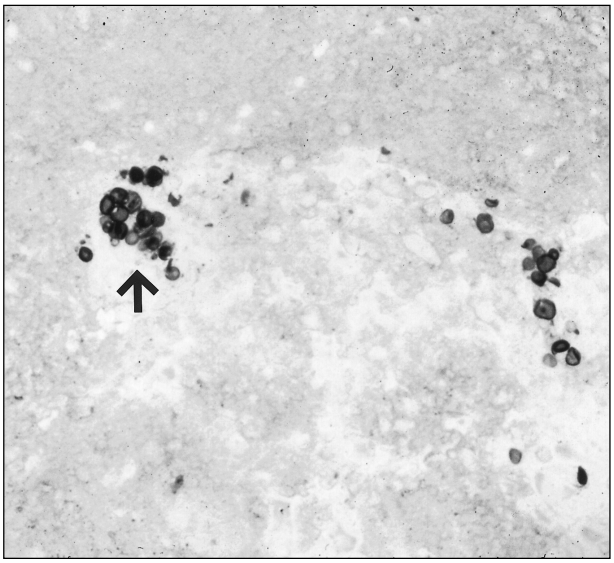

Figure 2. The bronchial biopsy is shown with Gomori methenamine silver stain demonstrating the thin-walled Pneumocystis organisms (arrow). (Original magnification x240).

Pneumocystis Carinii Choroiditis

Ophthalmologic consultation was requested in a 34 year-old AIDS patient admitted to the hospital with pneumonia, who complained of decreased visual acuity. On fundus examination, he was noted to have multiple slightly elevated, oval, yellow-white choroidal lesions bilaterally (Figure 1). While in the hospital, a chest and abdominal CT scan demonstrated multiple hypodense lesions in the spleen, and diffuse, nodular pulmonary infiltrates. Gomori methenamine silver stain of a bronchial aspirate (Figure 2) demonstrated the thin walled *Pneumocystis carinii* organisms (arrow).

Pneumocystis carinii choroiditis is a rare complication of infection with *P. carinii*. Most cases have occurred in AIDS patients receiving aerosolized pentamidine for pneumonia prophylaxis, as in this case. Ocular infection produces bilateral, multifocal, plaque-like choroidal lesions concentrated in the posterior pole. There is little inflammation both clinically and histopathologically, and the lesions cause a modest decrease in visual acuity. The choroidal lesions and visual deficits usually improve after treatment with systemic antibiotics. As antiviral therapies continue to improve, the incidence of *P. carinii* choroiditis in patients receiving inhaled pentamidine is likely to rise. The ophthalmologist can play an integral role in screening and treating these patients.

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Images in Medicine: We encourage submission to the Images in Medicine section from all medical disciplines. Image(s) should capture the essence of how a diagnosis is established, and include a brief discussion of the disease process. The manuscript should be less than 250 words and include one reference. The manuscript and one or two cropped 5 by 7 inch prints should be submitted with the author's name, degree, institution and e-mail address to: John Pezzullo, MD, Department of Radiology, Rhode Island Hospital, 593 Eddy St., Providence, RI 02903. An electronic version of the text should be sent to the editor at jpezzullo@lifespan.org.

Rhode Island Quality Partners, Inc.

Diabetes and Heart Disease

Raymond Maxim, MD

Despite a strong correlation between diabetes and heart disease, and the well-documented effectiveness of available treatments, few patients are adequately monitored and treated. In 1999, diabetes affected more than 10.5 million Americans.[1] Almost 8% of the entire population[2] and more than 12% of those over the age of 65 were diagnosed with diabetes. And, as it stands now, approximately 65% of those individuals with Type 2 diabetes will die from heart disease.

Three areas where significant gains can be made to lower the risk of heart disease in individuals with diabetes are the treatment of lipids, lowering blood pressure and addressing other patient-modifiable patient cardiovascular risk factors.

Lipids in Heart Disease

The typical lipid pattern in diabetic individuals is an elevated triglyceride level and decreased HDL level. LDL levels do not usually differ from those who do not have diabetes. However, the LDL in diabetics may be smaller, denser and more atherogenic. The single, strongest predictor of cardiovascular risk is the decreased HDL level.

HMG CoA reductase inhibitors and fibric acid derivatives are effective in reducing cardiovascular disease in diabetics. The Scandinavian Simvastatin Survival Study[3] reduced cardiovascular disease in diabetics with elevated LDL. Other studies have supported the effectiveness in reducing CHD by statin drugs. In the Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial,[4] gemfibrozil lowered risk for cardiovascular events in those with existing cardiovascular disease by 24%.

Treatment recommendations for dyslipidemia from the American Diabetes Association[5] are much more aggressive than currently practiced by physicians in most communities. In the 2002 Clinical Practice Recommendations, those individuals with existing heart disease and LDL levels $\geq$ 100 mg/dl should have both pharmacological and **medical nutritional therapy** (MNT) initiated concurrently. The combined MNT and pharmacological therapy recommendations are the same for diabetics without existing CHD and LDL levels $\geq$ 130 mg/dl. For those patients with no preexisting CHD and LDL levels < 130 mg/dl, MNT can be started alone or in concert with pharmacological therapy for three months. If goals of LDL <150 mg/dl is not reached then pharmacological therapy should be introduced.

Options for pharmacological therapy to raise HDL are limited. Nicotinic acid is the most effective agent available but is relatively contraindicated due to its negative effect on glycemic control. Fibric acid derivatives are effective and are the first line choice after, or in conjunction with, weight loss, exercise and smoking cessation.

Hypertriglyceridemia is positively affected by improved glycemic control. Therefore, efforts to lower triglyceride levels should begin after optimizing glycemic control. Fibric acid derivatives and high dose statins are effective second line therapies. Combination therapies with statins, fibrinates, or nicotinic acid can be used with appropriate precautions. The level of triglyceride at which to initiate pharmacological therapy is less clear-cut, but is strongly recommended after 400 mg/dl.[5]

Hypertension

One of the more dramatic findings in the **United Kingdom Prospective Diabetes Study (UKPDS)**[6] was the effect that treating hypertension had on the complications from diabetes. For each decrease of 10 mmHg in systolic blood pressure, there was an 11% decrease in risk for myocardial infarction independent of glycemic control or initial blood pressure.

Despite overwhelming evidence that treating hypertension reduces risk for cardiovascular disease and stroke, only 25% of patients are adequately controlled. In an observational study published in the February issue of *The Archives of Internal Medicine*, only 38% of patients with poorly controlled hypertension for at least six months had a change in pharmacological therapy.[7] Contrary to available evidence, the physicians surveyed were willing to accept a higher blood pressure.[8]

Current recommendations for patients with diabetes and hypertension are to initiate pharmacological therapy for a **systolic blood pressure (SBP)** $\geq$ 140 mm/Hg or a diastolic blood pressure (DBP) of $\geq$ 90 mmHg. For patients with SBP between 130-139 mmHg or DBP, between 80-89 mmHg treatment should begin with lifestyle changes and behavioral therapy for 3 months. Those patients not meeting SBP <130 and DBP <80 should begin pharmacological therapy.

Patient Modifiable Risk Factors

In addition to the above modifiable risk factors, patients can effect change in their smoking status, physical activity, weight loss and fat consumption. Evidence suggests that physician counseling is effective in producing behavior change in these areas. The 1999 **Behavioral Risk Factor Surveillance System**[1] (**BRFSS,** a national bienially administered survey) data looked at four counseling topics crucial to good diabetes care. Survey respondents with diabetes were asked if they had received counseling about weight loss, smoking cessation, exercise and low-fat diets. Respondents were advised to lose weight in only 48% of physician visits. Additionally, patients were counseled to exercise only 67% of the time, to eat less fat 78% of the time, and to quit smoking 78% of the time. Some of the reasons primary care physicians gave for the low prevalence of counseling included lack of time, minimal training in counseling techniques and uncertainty that they can effect change in patient behavior.

Conclusion

In Rhode Island, only 75% of Medicare beneficiaries with diabetes had at least one lipid profile evaluation in the last two years (unpublished Medicare fee-for-service claims data 1999-2000). It is clear that physicians need to become more aggressive in their treatment of lipid disorders and hypertension if our patients are to realize the gains evidence demonstrates are obtainable. It is equally clear that despite a lack of confidence in our counseling skills, patients depend upon their physicians to provide that counseling. We should actively seek out additional training in counseling techniques and behavior change to improve our skills and increase our confidence in our counseling abilities. After all, we are still the most powerful voice when it comes to changing our patients behavior.

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Advances in Pharmacology
Drug Product Expiration Dates: Practice Implications

Celia P. MacDonnell, PharmD, RPh, and Norman A. Campbell, JD, PhD, RPh

Are expired drugs still safe and effective? Health care professionals have been grappling with this question since 1979, when the **Food and Drug Administration (FDA)** began to require prescription drug dating. The FDA initially intended to set uniform stability testing and reporting guidelines. With the ever-rising cost of prescription drugs it is crucial that the expiration dates of both prescription and non-prescription drugs are determined for a maximum period of time while maintaining optimal efficacy.

The expiration date of a drug product is normally determined by estimating the time at which 95% one-sided lower confidence interval of a quantitative drug characteristic (e.g. assay) intercepts the lower specification limit.[1] Stability data on test batches are generated for a period of 12 months prior to submission of the regulatory dossier. If statistical analysis then demonstrates that the batches are similar, the data are pooled, to yield an overall estimate of expiration date. If the stability data from all of the batches cannot be pooled, an overall expiration date will be defined using the data from the least stable batch tested.[1]

Statistical analysis is not the only factor germane to the determination of drug stability. Dr. C. Rhodes from the Applied Pharmaceutical Sciences Department at the University of Rhode Island notes that the stability of pharmaceutical products "encompasses many potential routes of degradation." The conventional classifications of degradation of pharmaceutical products are chemical, physical, or biological. Degradation of these products may additionally be classified by the adverse effects of the instability of a pharmaceutical product as modifying efficacy, safety or ease of use or patient acceptability. In terms of efficacy the most obvious effect is loss of potency of the drug.[2]

Environmental conditions and proper storage are key to the determination of safety and efficacy of any drug product. The shelf life of a drug is defined as the time during which the drug product will maintain greater than 90% of the label claim

potency. The estimation on the time that will elapse before potency is less than 90% of the label claim includes specific limits of storage conditions. Although shelf lives may be estimated by accelerated stability testing protocols, real-time product stability testing is necessary to validate stability claims.[2] Additionally, the manufacturer's determined product expiration dates only apply if specific storage requirements are met from the time the product leaves the manufacturer until it is supplied to the user.[3]

The shelf life of a drug is defined as the time during which the drug product will maintain greater than 90% of the label claim potency.

In 1985 the FDA began a partnership with the **Department of Defense (DOD)**. This collaboration was initiated by a **Government Accounting Office (GAO)** audit of U.S. Air Force contingency hospitals in Western Europe. The audit identified stockpiles of medical supplies near the manufacturers' expiration dates. The imminent replacement of these materials represented a significant monetary impact to the Air Force. As a result, the idea of extending the shelf lives of these products began to be explored. The FDA developed an approach for controlled accelerated aging, coupled with computer modeling and laboratory testing, to predict the continued stability of the active components of the products.[4]

On March 28, 2000, *The Wall Street Journal* featured an article addressing the FDA's Shelf Life Extension Program and the issue of medication potency past expiration dates. *The Journal* reported that after 15 years of testing, about 90% of the drugs tested in this military program were safe and effective far past their original expiration date.[5]

Although under the FDA's guidance drug shelf life extensions are occurring in the military sector, these recommendations cannot be extrapolated to the private sector at this time. In a recent telephone interview, Ms. Donna Porter, from the FDA's Office of Regulatory Affairs, issued a strong warning against such conclusions. Ms Porter, who has also been involved with the Military Shelf Life Extension Program for the past 15 years, warns that the drugs largely being tested for stability do not necessarily apply to the private sector. Included in the products being tested on a yearly basis are items such as antidotes for biological warfare. She also calls attention to the fact that military personnel are a young, healthy group. Their medical needs as well as their pharmaceutical needs are not representative of the general population. Medications common to an elderly population such as nitroglycerin, insulin and digoxin were not part of the testing.

Ms Porter also emphasized the fact that the medications being tested by the FDA for the military are continuously stored under controlled conditions. It is well known that storage in high humidity may interfere with the dissolution characteristics of some oral formulations. Carbamazepine tablets, for example, when stored under humid conditions have failed to dissolve and have been associated with clinical failure.[6]

Whether or not outdated drugs are harmful is a question that requires further research. However, the potency they maintain varies with the drug, and the storage conditions, particularly humidity. Health care professionals who prescribe, administer and/or dispense prescription-only drugs should factor this information into their decisions.

It is important to note the use or distribution of a drug product after its FDA-mandated expiration date may have legal consequences which should be discussed with institutional or person legal counsel. Under provisions of the **Federal Food Drug and Cosmetic Act (FDCA)** such distribution may constitute the prohibited act of ..."misbranding..."[7] by mislabeling, subjecting violators to criminal and civil sanctions. In addition these expired drug products may be considered contraband and therefore subject to seizure by federal and/or state authorities.

Licensing boards may look to distribution or administration of drug products beyond their labeled expiration dates as unprofessional conduct or substandard practice with concomitant sanctions. In Rhode Island, statutory and regulatory provisions require dispensed prescriptions to bear a "beyond use date" determined as not later than six months if the manufacturer's date is less than one year or 12 months from the date of dispensing if the labeled date exceeds a year.[8]

Should a patient be harmed by a subpotent or superpotent drug or its degradation products, a plaintiff could allege negligent malfeasance or substandard practice. In either case, a practitioner-defendant could be in danger.

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Health by Numbers

Rhode Island Department of Health
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Diabetes: An Epidemic of a Chronic Disease

Barbara Kondilis, MSW, MPH, Joann Lindenmayer, DVM, MPH, and Dona Goldman, RN, MPH

Diabetes is the seventh leading cause of death in the United States and often leads to heart disease, stroke, blindness, or amputation of the leg or foot.[1] In Rhode Island, diabetes was the underlying cause of death for 266 deaths during 1996 and was a contributing cause through its complications for another 693 deaths.[2]

The prevalence of diabetes has been increasing in recent decades at near epidemic rates. Nationally approximately 8.5 million persons (3.2% of the population) were diagnosed with diabetes in 1996. Between 1980 and 1996 the prevalence of diagnosed diabetes increased by 2.7 million persons, representing an increase of 19% in the age-adjusted prevalence rate.[3] For every two cases of diabetes that are diagnosed, there is an additional case that has not been diagnosed. As of the year 2000, an estimated 70,000 Rhode Islanders ages 18 and older had diabetes (with 46,000 cases diagnosed).

Type 2 diabetes represents 95% of all cases of diabetes. There is a strong association between obesity and the development of Type 2 diabetes.[4] Obesity has been increasing both nationally and in Rhode Island, and research has shown that lifestyle change, including weight loss and physical activity, can reduce the incidence of diabetes in high-risk populations.[5]

Methods

Rhode Island utilizes the **Behavioral Risk Factor Surveillance System (BRFSS)** to track population information on diabetes. The BRFSS is a statewide telephone survey of randomly selected adults (ages 18 and older) who live in households with telephones. It asks respondents questions about a variety of health-related behaviors. During 1994-1997, the number of interviews performed was about 1,800 per year (150 per month); during 1998-2000 it increased to approximately 3,600 per year (300 per month). Fifty states and four territories perform the BRFSS with funding and methodological standards provided by the **Centers for Disease Control and Prevention (CDC)**.[6]

The BRFSS question used to measure diabetes prevalence for the years 1994-2000 is: "Have you ever been told by a doctor that you have diabetes?" The survey also asks height and weight of each respondent, from which the **body mass index (BMI)**, defined as weight in kilograms divided by the square of height in meters, is calculated. A BMI of 25 to 29.9 is considered overweight, and a BMI of 30 or above is considered obese.

Results

The prevalence of diagnosed diabetes has been increasing in Rhode Island over the period examined, 1994-2000. (Figure 1) In 2000, the prevalence rate among adults, 6.0%, was nearly one-third higher than the rate in 1994, 4.6%.

Diabetes is far more commonly diagnosed among older adults than younger adults. (Figure 2) The prevalence rate is highest among adults ages 65 years or older, followed by ages 45-64 years, and ages 18-44 years. The rate increases nearly five-fold from the 18-44 age group to the 45-64 age group, then by another 44% among those 65 years and older.

Over the period 1994-2000, the proportion of people who are obese among adult Rhode Islanders increased from 13.4%

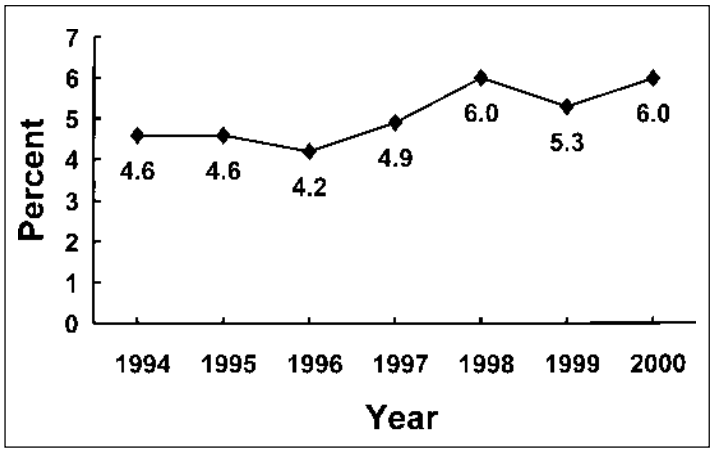

Figure 1. Prevalence of Diagnosed Diabetes among Rhode Island Residents Ages 18 and Older, by Year, 1994-2000.

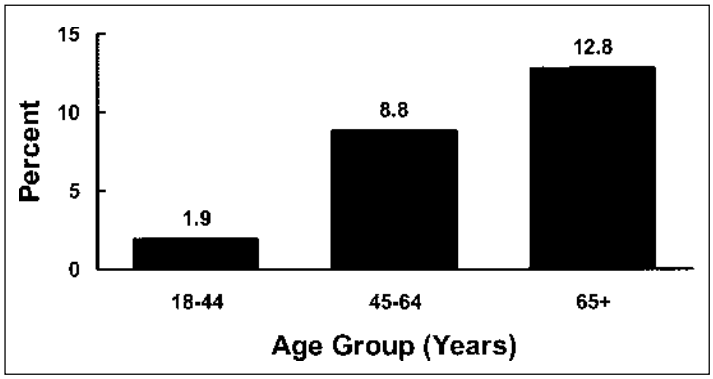

Figure 2. Prevalence of Diagnosed Diabetes among Rhode Island Residents Ages 18 and Older, by Age Group, 2000.

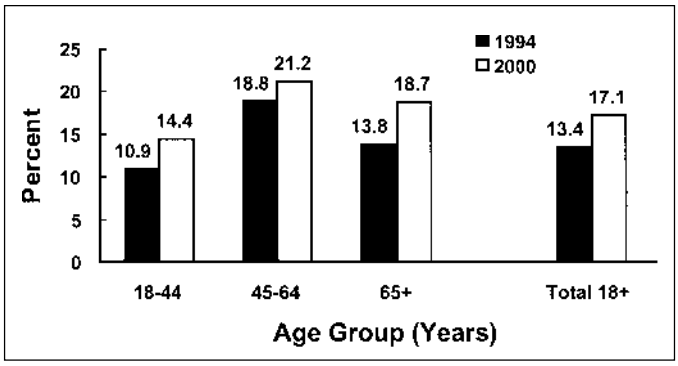

Figure 3. Prevalence of Obesity among Rhode Island Residents Ages 18 and Older,

to 17.1%, or by more than one-quarter. (Figure 3) Increases in obesity were seen among all age groups, but the increases among the elderly (up 36%) and younger adults (up 32%) were noticeably greater than the increase among those ages 45-64 (up 11%).

Discussion

The **Diabetes Control Program** (**DCP**) at the Rhode Island Department of Health is dedicated to integrating health systems for improved provider and patient support for better diabetes control. The DCP is working towards fulfilling the diabetes-related objectives of Healthy People 2010 on reducing mortality, reducing the disease burden, reducing disease complications, and increasing health services and patient protection, including diabetes education.[4] The DCP primarily focuses on secondary prevention and is moving to include primary prevention with community collaborations and guidance from national experts such as the CDC.

National and international studies such as the **Diabetes Prevention Program** (**DPP**) study and the Finnish Diabetes Prevention Study have shown that primary prevention of type 2 diabetes is possible through weight control and physical activity, particularly in persons with impaired glucose tolerance and other high-risk characteristics.[7] Local and national health initiatives face more than programmatic challenges. The ultimate challenge is to support individuals to modify their behavior to prevent obesity and to better manage their diabetes. This includes larger systemic changes such as environmental modifications (i.e. safer walking areas, modest food portions in restaurants, healthier food and beverage choices in schools), and municipal, state, and national policies that encourage people to make better dietary choices and that encourage physical activity.

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Asthma, Particulates, and Diesel Exhaust

Leanne Chiaverini

Asthma exacerbations are caused by irritants known as "triggers." Common triggers include particulate matter and other substances in tobacco smoke and vehicular exhaust, dust mites, pet dander, cockroach feces, mold spores, pollen, and strong odors. Activity, respiratory infections, and climate (temperature and humidity) can also precipitate asthma attacks.

Particulate matter (PM), one of several major air pollutants, is considered an important asthma trigger in urban locations because of the public's heavy reliance on cars, trucks, and buses. The U.S. **Environmental Protection Agency (EPA)** defines PM as a mixture of solid and liquid particles in the air. The EPA and several other federal agencies have labeled it a primary air pollutant and a probable human carcinogen.[1,2] PM less than 2.5 micrometers in diameter ($PM_{2.5}$), a common component of exhaust from vehicles, power plants, and industrial facilities,[2] is of particular concern because its small size allows it to bypass the body's defenses and easily reach the deepest recesses of the lungs where it is more likely to be retained. Because PM can act as an asthma trigger, causing a decrease in lung function and inflammation of the airways, asthmatics are at a considerable risk of experiencing adverse effects from exposure to it.[2-4] Dozens of studies worldwide confirm that PM (often from diesel fuel) can aggravate or produce symptoms of asthma and other respiratory illnesses, retard lung development, and cause premature death, especially among people with cardiopulmonary diseases. A study conducted by the National Health and Environmental Effects Research Laboratory found that exposure to PM promotes airway inflammation and hyperresponsiveness.[5] High levels of PM have been linked with high levels of medication use, hospital and emergency room admissions, and work and school absences.[2-4]

The EPA estimates that diesel exhaust is the source of more than 20% of the fine PM in New England air.[6] Diesel exhaust is comprised of hundreds of constituent chemicals, many of which are harmful to both humans and the environment. Under the Clean Air Act, forty of these chemicals are classified as "hazardous pollutants;" some of them have been designated probable human carcinogens.[3] The major pollutants in diesel exhaust include:

Diesel particulate matter (DPM)
Polynuclear aromatic hydrocarbons (PAH)
Nitrogen oxides (NOx)
Volatile organic compounds (VOC), which include hydrocarbons (HC)
Sulfur dioxide (SO2)
Carbon monoxide (CO)[7]

PM is a significant ingredient in diesel exhaust. Composed of more than 98% $PM_{2.5}$, these particulates are very small.[4] The release of DPM into the atmosphere is caused by poor refinement of diesel fuel and incomplete fuel combustion, and

Table 1. Encapsulated History of Diesel Exhaust Policy in the United States

1970:	Congress revised the Clean Air Act, requiring 90% CO, HC and NOx reductions from light-duty diesel vehicles by 1976. Authority to regulate motor vehicle pollution was given to the United States EPA.[18]
1977:	Congress amended the Clean Air Act, requiring heavy-duty vehicles to make 90% CO and HC reductions by 1984, and a 75% NOx reduction by 1985.[18]
1982:	Air Resources Board regulates PM_{10}[4]
1985:	EPA, under the Clean Air Act, set emissions standards for new diesel-powered trucks and buses.[18]
1987:	EPA regulates PM_{10}[4]
1990:	Congress amended the Clean Air Act, including more stringent control over PM from diesel engines. EPA placed restrictions on the sulfur content of diesel fuel.[18]
1993:	EPA put forth regulations for 80% reduction of sulfur content in fuel, and 60% reduction in particulate emissions from urban buses.[18]
1993:	EPS initiated the Urban Bus Retrofit/Rebuild Program. Required that urban buses operating under certain conditions use EPA certified retrofit pollution control technology or be rebuilt using certified low emission components during engine rebuilds.[1]
1994:	EPA reduced PM standards for new diesel-powered truck and bus engines.[18]
1996:	EPA further reduced PM standards for new diesel-powered truck and bus engines.[18]
1997:	EPA adopted new National Ambient Air Quality Standards for particles under 2.5 microns in size.[4]
2000:	EPA adopted new diesel regulations requiring reduced emissions from new engines, along with the use of ultra low sulfur fuel. Expected to be fully implemented in 2010.[18]

Adapted from: Massachusetts Enhanced Emissions and Safety Test. Diesel Background. http://vehicletest.state.ma.us/dieselbg.html

is directly related to the sulfur and PAH content of the fuel.[8] NOx and VOC combine in the atmosphere to create ozone.[9] Ozone is the prime ingredient in smog, which is annually responsible for an estimated 6 million asthma attacks and 150,000 emergency room visits.[10]

Children, with airways that are small in diameter and not fully developed, are especially sensitive to diesel exhaust. "There is no known safe level of exposure to diesel exhaust for children, especially those with respiratory illness."[3] Diesel exhaust may cause difficulty in breathing, especially if airways are already inflamed or constricted by asthma. Children riding on school buses may be exposed to unusually high concentrations of DPM. In 2001, the National Resource Defense Council found this exposure to be as much as four times that of someone riding in a car in front of the bus.[11] More recently, an **Environment and Human Health, Inc. (EHHI)** research team found that concentrations of $PM_{2.5}$ in school buses were often 5-10 times higher than average levels measured at fixed-site monitoring stations.[3] Concentrations increased when buses were idling with windows open (especially when queued to load or unload students), when driving on routes with their windows closed, and when moving through heavy traffic.[3] In the United States, 24 million children make nearly 10 billion school bus rides on 600,000 school buses.[3] More than 99% of school buses in the U.S. are powered by diesel fuel.[3]

Adults are also susceptible to diesel exhaust. Occupational exposures put more than one million workers at risk for adverse health effects ranging from headaches and nausea to cancer and respiratory diseases.[12] Those occupations at increased risk include but are not limited to: workers of railroads, mines, loading docks, farms, toll booths, and bridges and tunnels; truck drivers; and auto, truck and bus mechanics/garage workers.[12]

Sources of diesel exhaust may be categorized into three groups: mobile sources (cars, trucks, tractors, lawnmowers), stationary point sources (factories, refineries, power plants), and smaller stationary area sources (dry cleaners, gas stations).[13] Heavy-duty diesel trucks and buses are a major contributor to air pollution. In the United States, heavy-duty vehicles (such as semi-trucks, buses, and waste-haulers) account for a mere 2% of all on-road vehicles, but produce one third of all nitrogen oxide emissions and almost two-thirds of all particulates from on-road vehicles.[8] Heavy-duty vehicles in Rhode Island emit 347 tons of PM per year and are responsible for 52% of the total PM emitted by all Rhode Island vehicles.[8]

The United States has been cognizant of improving air quality since the creation of the Air Pollution Control Act in 1955.[14] Major actions taken in the past three decades to reduce pollution from diesel exhaust are summarized in Table 1. The Urban Bus Retrofit Program, organized in 1993, has retrofitted or rebuilt approximately 10,000 of 42,000 eligible urban buses.[1] New diesel regulations adopted by the EPA in 2000 are expected to prevent annually an estimated 8,300 premature deaths, 360,000 asthma attacks, 386,000 cases of respiratory symptoms in asthmatic children, 1.5 million lost work days, 7100 hospital admissions, and 2400 emergency room visits for asthma.[15]

Despite these accomplishments and the development of more stringent air quality standards, the matters surrounding diesel exhaust are far from resolved. There are numerous ways to limit emissions of and exposures to diesel exhaust.

- Create and implement anti-idling programs and laws. Anti-idling campaigns, programs, and laws are an inexpensive and efficient approach to reducing diesel exhaust. Idling engines emit unnecessary toxins into the air, adding to the levels of diesel exhaust. For example, idling school buses expose children to high levels of diesel exhaust. In addition to the health impact, vehicle idling is an environmental hazard and an expensive practice. Truck drivers often leave their engines running during 6-hour sleep periods, burning approximately one gallon of diesel fuel each hour.[6] At this rate, a vehicle in operation for 300 days will idle away 1,800 gallons of fuel per year.[6] Each truck releases an annual ten pounds of particulate matter into the air, and at $1.25 per gallon, pays an idling fee of $2,250.[6] With an estimated 1.3 million large trucks and 4.2 million tractor-trailer rigs on US highways, the costs mount.[16] Companies accept this cost because it is convenient (diesels are hard to start when cold) and because running the engines keeps heaters or refrigerators running. Small generators or auxillary power units that supply heat, air conditioning and power, provide efficient alternatives to idling.[6]
- Require, promote or provide incentives to increase the use of cleaner diesel fuels and non-diesel alternatives. Pollution control devices in engines are destroyed by the sulfur in diesel fuel.[8] The use of **ultra-low sulfur diesel fuel (ULSD)**, which contains less than 15 parts of sulfur per million, can reduce PM by 20-25%.[6] To support these efforts, ULSD should be made available nationwide. Emulsified diesel fuel, which has been mixed with water and other additives, is an option for vehicles that do not remain dormant for long periods. Emulsified diesel fuel can reduce PM by 50%.[6] Other alternatives include battery electric vehicles, hybrid electric vehicles, compressed gases, and fuel cells.[8] Buses that run on natural gas emit 60-98% less carbon than diesel-powered buses.[3]
- Retrofit diesel vehicles with pollution control equipment. Heavy-duty vehicles may be retrofitted with interior air filters, oxidation catalysts, and particulate traps.[3] Use of the latter in combination with ULSD can reduce PM emissions by 90%.[6]
- Replace existing Heavy Duty Engines with newer vehicles. "Require and provide financial support for eventual replacement of existing diesel fleets with low emission vehicles, especially in areas of the country beyond compliance with current federal pollution standards."[3]
- Require routine maintenance and implement routine emissions testing. Require on-board equipment and in-use emissions testing to prevent cheating.[8]
- Federal, state and local governments, and school districts should work together to implement the following changes in school bus emissions:
  - Prohibit school bus idling.
  - Plan and implement a school bus retrofit program.
  - Require routine maintenance and periodic tailpipe

emissions testing.

Require the design and installation of air filtration equipment capable of removing vehicle exhaust from air entering bus passenger cabins.

Limit ride duration.

Allocate buses with the lowest emissions to the longest routes, giving priority to communities with the poorest outdoor air quality and to routes that have the highest traffic intensity.

Reconsider location of bus parking lots.

Adjust contract provisions to lease retrofit buses and require clean fuels.[3]

- Account for other exposures to air pollutants. Develop air quality monitoring programs that consider indoor and within-vehicle exposure to air pollution, and establish health protective standards accordingly. Create additional stationary monitoring networks and use personal monitoring devices to collect data. Efforts to better understand the variability in exposure should begin by focusing on susceptible populations.[3]

Commentary on Public Health Briefing

Charles Sherman, MD

The increased prevalence and incidence of asthma are alarming. Although newer medications have helped in managing symptoms, only through environmental control can we expect to greatly lessen the severity of disease.

Leanne Chiaverini has written an excellent briefing on the adverse health effects of particulate matter, especially diesel exhaust particulates, for both asthmatics and non-asthmatics. She clearly summarizes the significant morbidity and mortality resulting from exposure to small particles. Of great concern is the recent association between diesel exhaust particulates and lung cancer.

Ms. Chiaverini has also outlined several interventions that can limit diesel exhaust particulates. The medical community must support these measures and become more vocal in advocating for tougher air pollution standards.

Physicians can get involved in several ways. They can testify at legislative hearings. They can write letters to local and state representatives, voicing their concerns and those of their patients. Physicians can also work directly with school administrators to devise a plan to reduce school bus emissions (before those emissions drive kids to your office). Contact Molly Clark of the American Lung Association of Rhode Island (MClark@ lungri.org or 401-421-6487) to find out how to get involved.

I often tell my patients that they would do best to live in a bubble, where all respiratory triggers could be eliminated. Given that this solution is not viable, we must control all harmful environmental exposures as a first step.

- Create safer work environments. Use safe work practices, ventilation, and personal protective equipment to protect workers who are exposed to diesel exhaust.
- Promote recycling. The burning of diesel fuel is a significant source of carbon and other greenhouse gas emissions. Recycling reduces the amount of energy used in industrial processes and transportation, thus reducing greenhouse gas emissions. Rhode Island recycling efforts in 1995 reduced greenhouse gas emissions by approximately 30,000 tons of carbon equivalent per year, an amount equal to nearly 5% of all industrial carbon dioxide emissions.[17]

As Rhode Island develops policy to manage PM in the air, the medical and public health communities must work together to assure that health concerns are given appropriate weight. In addition to formal representation at official policy forums, physicians are well-positioned as credible advocates for improved air quality.

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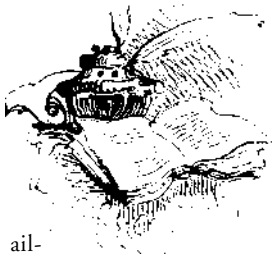
– A Physician's Lexicon –



Hands on Medicine

Mainstream medicine, sometimes called allopathic medicine, has never claimed that it possessed a monopoly over the broad field of health care therapeutics. There had always been competing, alternative health care systems, each with its own premises, operating philosophy and history.

Homeopathic medicine seeks out drugs which produce effects simulating the visible symptoms of the disease in question. It then treats the disease in question with extremely small [homeopathic] doses of the same drug in the hopes of achieving a cure. This doctrine was first enunciated by a German physician, Samuel Hahnemann, in 1795 and was called homeopathy [Greek, *homos*, meaning similar and *pathos*, suffering.] It may have been based on an earlier view of Parcelsus, *similia similibus curantur* [like things are cured by like things].

Hahnemann, in 1824, also coined the descriptive word, allopathic [Greek, *allos*, meaning other, and *pathos*, meaning suffering] to describe the field of conventional medicine.

There have been still other schools of health care such as hydropathy [Gree, *idro-* , meaning water]; naturopathy [Latin, *natura,* meaning an untouched existence]; and balneopathy [Greek, *balneon*, meaning bath] which have emphasized the curative role of bathing, exercise and prudent diet. Many of these schools have diminished in popularity or have been absorbed by still other schools of therapy.

Chiropodist, a word coined in 1785, defines those practitioners who are concerned with ailments of the hand [Gree, *cheiro-* , meaning hand] or feet [Greek, *podos*, the foot]. Currently these practitioners refer to their art as podiatry since virtually all of their skills are now applied to diseases of the foot.

Osteopathy [Greek, *osteon*, meaning bone] was first described by Andrew Taylor Still, a midwestern practitioner who advocated vertebral manipulation or massage to alleviate various neuromuscular disorders. Current osteopathic thinking is gradually merging with allopathic teaching.

Another advocate of spinal manipulation to counteract alleged derangement of the neuromuscular system was an American, David Daniel Palmer, who constructed a system of care called chiropractic [Gree, *cheiro-* , meaning hand and *prakticos*, meaning fit for action]. The Greek, root, *cheir*o- [sometimes spelled *chiro-*] crops up in words such as chiromancy [the reading of palms], chirography [handwriting] and chiroptera [the order of hand-winged mammals, the bats]; and, of course, cheirurgery, the ancient predecessor of the word, surgery.

And then there is the ancient art of acupuncture [Latin, *acus*, meaning needle or sharpness; and *punctura*, meaning to perforate or prick]. The Latin root, *acus*, appears in such words as acute, ague [a corruption of *febris acuta*] and acumen [Latin, *mens*, meaning reason or understanding; thus sharpness of intellect].

– Stanley M. Aronson, MD, MPH

Vital Statistics

Rhode Island Department of Health
Patricia A. Nolan, MD, MPH, Director of Health

Edited by Roberta A. Chevoya

Rhode Island Monthly Vital Statistics Report

Provisional Occurrence Data from the Division of Vital Records

Underlying Cause of Death	Reporting Period			
	April 2001	12 Months Ending with April 2001		
	Number (a)	Number (a)	Rates (b)	YPLL (c)
Diseases of the Heart	261	3,106	296.3	4,385.5 **
Malignant Neoplasms	206	2,391	228.1	6,694.0
Cerebrovascular Diseases	45	504	48.1	660.0
Injuries (Accident/Suicide/Homicide)	38	380	36.2	6,736.0
COPD	45	512	48.8	452.5

Vital Events	Reporting Period		
	October 2001	12 Months Ending with October 2001	
	Number	Number	Rates
Live Births	1249	13,463	12.8*
Deaths	795	10,142	9.7*
Infant Deaths	(8)	(103)	7.7#
Neonatal deaths	(6)	(89)	6.6#
Marriages	820	8,472	8.1*
Divorces	404	3,371	3.2*
Induced Terminations	408	5,478	406.9#
Spontaneous Fetal Deaths	103	1,018	75.6#
Under 20 weeks gestation	(98)	(935)	69.4#
20+ weeks gestation	(5)	(83)	6.2#

(a) Cause of death statistics were derived from the underlying cause of death reported by physicians on death certificates.

(b) Rates per 100,000 estimated population of 1,048,319

(c) Years of Potential Life Lost (YPLL)

Note: Totals represent vital events which occurred in Rhode Island for the reporting periods listed above. Monthly provisional totals should be analyzed with caution because the numbers may be small and subject to seasonal variation.

* Rates per 1,000 estimated population # Rates per 1,000 live births
** Excludes two deaths of unknown age.

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Ninety Years Ago

[April, 1912]

In "The Relation of Sociology to Law and Medicine," J. W. Dealey, Professor of Social and Political Science," noted the rapprochement of the disciplines (law, medicine, political science) - a change from the view of Plato: "Plato...assumed that the presence of lawyers and physicians denoted a decadent, or at any rate, an imperfect civilization, since neither a natural nor a perfect civilization would have use for members of either profession."

Frederick N. Brown, MD, in "As to the Advent of Babies," described the doctor's entrance into the mise en scène of childbirth: "What a sympathetic and worrying mother, an anguished and terrified patient who immediately hails one's presence as the end of her suffering, often a repellent and obtrusively retiring aunt or sister - who never thought much of the match, anyway - to the good old nurse who has long been a friend of the family, who has watched the case closely and has already deduced by infallible signs that it is to be a girl, and who already has the burnt rag, the cotton twine and the kitchen scissors at hand; who is also recognized as the master of ceremonies, and as a matter of entertainment, at once - in the presence of the patient and family - launches off into a long, detailed description of the harrowing scenes she has witnessed - one of which presented much the same symptoms as the patient, and winds up describing the delivery of each of her own seven children - and this dear little friend of hers is sick just as she when her little boy was born with the club feet. Either cowering in a corner is the culprit who is responsible for all this present trouble, or else he is careening over the house in a condition of nervous and uncertain flippancy."

Fifty Years Ago

[February, 1952]

Janis Gailitis, MD, and Anthony Caputi, MD, contributed "Auricular Fibrillation with Complete Heart Block and Adam-Stoke Syncope." This case report discussed a 70 year-old woman admitted to Newport Hospital. She had suffered 5 episodes of dizziness, followed by fainting, in the year before admission. After treatment (epinephrine hydrochloride 1:1,000, with oxygen atrophine with ephedrine), she recovered.

In "Acute Myocardial Infarction: Some Observations," Frank B. Cutts, MD, discussed 216 cases admitted over five years to Rhode Island Hospital. "In general patients were kept at bed rest from 2 to 6 weeks....Mild sedation was prescribed as needed to help promote a placid outlook."

In "Doctors and Scholars," Dennis P. McCarthy, OP, PhD, vice president and head, Department of English, Providence College), discussed the physician-authors Oliver Goldsmith, Thomas Linacre, and Sir Thomas Browne.

An Editorial congratulated Woonsocket Hospital on its new building.

A second Editorial, contributed by the Department of Defense, offered "Explanations of its Policies and Procedures Regarding the Doctor Draft Act."

Twenty Five Years Ago

[February, 1977]

Stanley M. Aronson, MD, introduced this issue on the "Future of Visual Services in Rhode Island." The articles included: "Ophthalmology in Medical Student Education: Philosophy, Control of Process," by Bruce E. Spivey, MD; "Relationship of Ophthalmology to other Science Modalities," by Arthur H. Keeney, MD, DSci; "A Department of Ophthalmology: A Personal View," by Steven M. Podus, MD; "Future of Ophthalmology," by Carl Kupfer, MD; "Visual Sciences at Brown University: One Possible Approach," by Harold F. Spalter, MD; "Another Possible Approach," by A. Robert Bellows, MD; and "Draft Version of the Final Report to the Dean of Medicine from the Committee on Ophthalmology, September 21, 1976."

John E. Farley, Jr., MD, Chair, Drug Abuse Committee Report, contributed an editorial that voiced concern over the misuse of prescribing practices by physicians - a misuse that increased the illegal supplies of controlled substances. Recently the AMA had published guidelines on barbituates; the Rhode Island Medical Society had published guidelines on amphetamines in hyperkineses. The Medical Society opposed use of amphetamines in treatment of intractable obesity.

An editorial, "Glaucoma: A Primer," mentioned possible benefits of marijuana.