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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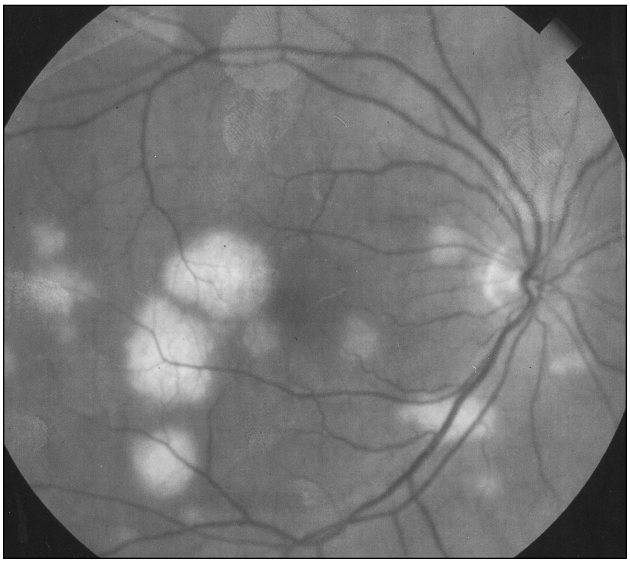

Figure 1. Fundus photographs demonstrating multifocal, round, yellowish choroidal lesions in both eyes.

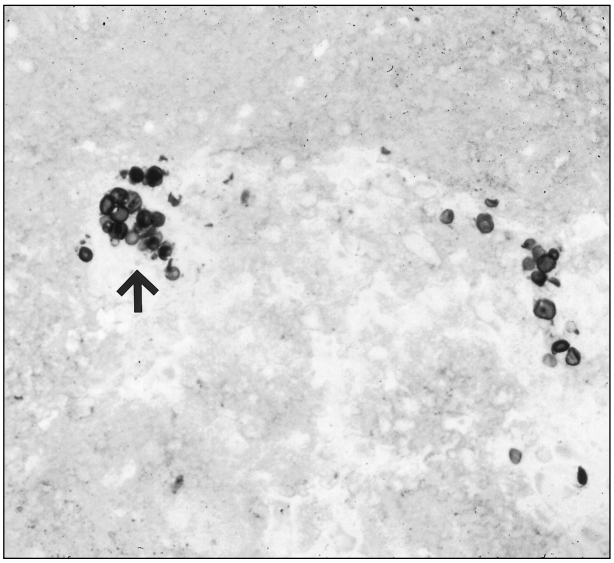

Figure 2. The bronchial biopsy is shown with Gomori methenamine silver stain demonstrating the thin-walled Pneumocystis organisms (arrow). (Original magnification x240).

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

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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

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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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