sMATTerings

Midwest Association for Toxicology and Therapeutic Drug Monitoring

Volume 8 Issue 1 March 2002

From the Editor's Desk

It's time for another edition of sMATTerings. In this issue, Suzanne White takes us out of the laboratory and shows us the implications and sequelae of acidosis in the clinical setting.

John Wilson and C.E. Pippenger enjoin those who are involved in TDM to wrap their minds around and in-depth discussion about what could, and should, be done in that arena.

We also have an Annual Meeting coming up in Madison. Chris Goodall has spear-headed what promises to be an excellent meeting – hope you can be there.

In closing, you may have noticed an effort on our part to increase membership. In keeping with that project, I would like to introduce two of the newest members of MATT … two old lab rats named ralpH and pHrank. Thanks to the artistry of Trooper Sarah Krebs, these two have been given life. Sarah was a cartoonist for The State News while at Michigan State University during her undergraduate days. We look forward to seeing more of the guys in the future.

There when it sMATTers most!

Fred

IN THIS ISSUE

President's Korner

Chris Goodall

Yesterday I watched the closing ceremony of the Winter Olympic Games. The Olympics are one of very few reasons I will set aside some of my responsibilities and chores to view the television for hours and days on end. I enjoyed every minute. Like many girls, I grew up with Peggy and Dorothy, so of course I was thrilled with the excitement of the figure skating program. I was touched by the gracious attitude and the incredible display of sportsmanship that was exhibited by the Canadian skaters. I saw several American medallists that were thrilled when winning silver or bronze. I heard interviews that spoke of the joy of the sport, the team and the chance to participate, medal or none. It was pure pleasure to see such wonderful representation of our country. For the second time in less than six months, I am reminded how lucky we are.

And now, it is on to those responsibilities that were set aside. First and foremost, the plans for the annual meeting are progressing well. The slate of speakers will be mixed with clinical and forensic topics. Topics include new diagnostic tests, analytical techniques, and recent advances in the forensic testing arena. A few of the speakers will provide some food for thought as well. It appears a record number of vendors will be on site and we have commitments for a few poster presentations. There is still time to submit an abstract. We are an informal group and do not publish our proceedings. If you have a poster from a previous meeting that would be informative for our group, please contact me about displaying again at MATT in Madison. The preliminary program agenda and registration materials are included in this issue. I hope to see you all in Madison, April 25 and 26.

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MATT is an association focused on advancing the scientific, clinical, professional, and educational aspects of Toxicology and TDM. MATT provides a network for interested individuals in the Midwest.

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I am excited to tell you that the executive committee has approved the development of a new and updated Web Page for MATT. The page will be set-up with an Internet Service Provider and maintained by a member of the executive committee after development is complete. The officers are pleased with the new look. The welcome page will feature the logo that was approved at last years annual meeting. The page should be up and available for viewing by late March of this year. If you have any information on the history of MATT, that you would like to share, please send it to me via email at cr.goodall@hosp.wisc.edu

Thanks to all of you that have sent in membership renewals. Options for membership cards are being investigated. The cards will be ready in time for the annual meeting. If you do not attend the meeting, the cards will be sent out by mail in May. The membership renewal is vital to maintaining communication within the organization. The bylaws for MATT indicate renewal is to be done in December. We did not use that date in the recent drive but will do so in the future. I am warning you all now so you are not surprised when we set a deadline the next time around.

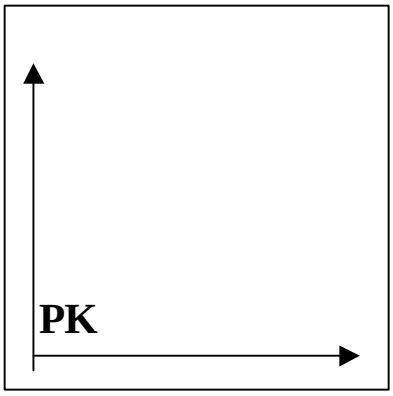
The laboratory is changing as fast as the world around us. We must go beyond accepting the change; we must embrace it and help plan for it. It is through my involvement in AACC, SOFT and MATT that I find continuous education and new ideas for laboratory development. The shortage of qualified personal and the never-ending budget crisis will not disappear. Together we can work toward the development of laboratories that maintain the professional integrity valued by all. I urge you to remain active in your professional life. As the Olympic games have progressed to extreme sports, the laboratory must reach to its extreme as well. ***Please join us in our pursuit of science, education and friendship!***

Annual Report of the MATT Treasury for 2001 and Financial Update for 2002

	1/1/00 to 12/31/00	1/1/01 to 12/31/01	1/1/02 to 2/26/02
Starting Balances:			
Checking Account	$7,451.28	$11,434.24	$11,465.68
Certificate Account	$1,078.96	$1,136.36	$1,167.97
Total Starting Balance	$8,530.26	$12,570.60	$12,633.65
Expenses:			
Office Support	($800.00)	($847.25)	($57.50)
SMATTerings	($679.90)	($320.15)	($531.50)
Office Expenses	($183.00		
Annual Meeting	($3,645.11)	?????	($500.00)
MATT logo			($75.00)
Total Expenses	($5,308.01	($1488.56)	($1164.00)
Income:			
Membership Dues	$1800.00	$1000.00	$340.00
Annual Meeting	$6,970.97	?????	
Other Income	$520.00	$520.00	
Certificate Interest	$57.38	$31.61	
Total Income	$9,348.35	$1551.61	$340.00
Total Starting Balance	$8,530.26	$12,570.21	$12,633.65
Total Expenses	($5,308.01)	($1488.56)	($1164.00)
Total Income	$9,348.35	$1551.61	$340.00
Total Ending Balance	$12,570.60	$12.633.65	$11,809.65
Checking Account	$11,434.24	$11,465.68	$10.641.68
Certificate Account	$1,136.36	$1,167.97	$1,167.97
Account Ending Balance	$12,570.60	$12,633.65	$11,809.65

The treasury has slightly increased over the past year. The net income or loss from the Annual Meeting is not known because an official report of the meeting has not been filed. However, John Wilson states that the Annual Meeting held in Detroit will show less than a $10 surplus. Membership dues declined by $800, which is the second straight year of reduced members.

Submitted by Timothy E. Caragher, Treasurer



Pharmacokinetics Korner

By John M. Wilson and C. E. Pippenger

This issue of PK Korner is co-authored by C. E. Pippenger. Dr. Pippenger, among many other things, is the founding editor of Therapeutic Drug Monitoring, a journal dedicated to "accelerating an exchange of knowledge between clinical and laboratory workers who share a common interest in therapeutic drug monitoring."[1] Together we share the concern that TDM is not making the progress that must be made given its important early successes and that a renewed commitment and a focused action plan is necessary to insure that the potential of TDM to affect and enhance human life is fulfilled.

AN ACTION PLAN FOR TDM RENAISSANCE

Introduction

The value of therapeutic drug monitoring (TDM) in the clinical management of numerous diseases is clearly established. Historically, the last 35 years witnessed the development of TDM as a new discipline whose technology and theory were on the frontiers of science. The measurement of drug concentrations in biological fluids was accepted by the medical community as a valuable tool in the clinical management of patients, essential in the development of therapeutic regimens, and as a routine laboratory test procedure. The major goals of those involved in the birth and early TDM development during the late Sixties and throughout TDM's infancy in the Seventies were to improve patient care and make TDM a routine laboratory procedure readily available to all patients anywhere any time. To reach these goals development of new technologies, new markets, and education of both the medical and lay communities were essential requirements. By the early Eighties TDM had achieved these goals!!

Unfortunately, the TDM successes came with a high price. As the TDM technologies evolved into routine procedures they were no longer on the frontiers of science. Consequently, young people were not attracted to enter the discipline. Perhaps more importantly, the commercial manufacturers went from a market development mode into the "protect our market" mode. Consequently only a few new TDM assays (FK 506, Topiramate, Mycophenolate Mofetil) have been introduced into the market place in the last 17 years!! Although many new drugs have been introduced into clinical practice, no TDM assays for these drugs are readily available to the practicing clinician.

Lack of TDM assays has resulted in tragic consequences for clinical medicine that significantly impacts all patients. The absence of TDM methodologies denies the patient access to rational therapeutics. Instead, appropriate therapeutic regimens are determined by dosing to pharmacodynamic effectiveness, which in truth means dosing by trial and error. Initially, TDM was a defensive tool employed to avert the many, varied, sometimes very serious, toxicities that followed from conventional practices. The mark of its success is that management evolved into monitoring and to prediction. Not only was it possible to decrease the incidence of toxicity and generate cost avoidance, but, changes in patient status could be recognized faster, and regimens could be adjusted prospectively for direct savings. As much as we would like to say that times have changed and conditions have improved, it is only partly true. New drugs also demonstrate significant toxicities and it will always be a better practice to prevent their occurrence than experience them before backing off a toxic dose. The failure of the analytical tool to keep pace with medical practices represents a backward step and assures the unnecessary deterioration of the patient's quality of life while they wait for the right drug combination or regimen.

The following list is a compilation of some of the issues we believe need to be addressed by the TDM Renaissance and a plan of action to achieve those ends. The opinions expressed are solely the authors' perceptions. Those of you engaged in TDM may not agree with some observations or with our proposed actions, but you are all responsible for the consequences of doing nothing. Now is always the best time for any action, and we urge you to read and form your own conclusions, to act in the best interests of your profession and the patients who will become your beneficiaries, and to react, by writing to us at jwilson@beaumont.edu or pippengc@gvsu.edu to let us know what you think.

1.TDM Automation – The movement of single assay systems to multiple assay platforms and the consolidation of testing to reduce costs has been a natural progression in many areas of the modern clinical chemistry laboratory. Unfortunately, this has produced important negative features. In the infancy of TDM an assay would be developed using spectroscopic or chromatographic equipment. Growth in demand created a commercial market for rapid, automation-based tests that would reduce the cost of labor and provide broad availability to hospitals large or small. When the TDM test was transferred to the new platform the replaced chromatographic equipment was frequently considered unnecessary and obsolete and was abandoned along with the skills necessary to keep it operable. Without a flexible and creative testing capability, pathologists, chemists, and clinicians had to wait for a commercial entity to provide an immunoassay in order to introduce a new test. The laboratory capability stagnated. Clinicians found the laboratory more responsive in test turnaround but less responsive for test creation. Opportunities were lost, treatment modalities went unsupported and medicine learned to live without. Outside the routine clinical laboratory in forensic toxicology labs, in crime labs, in environmental labs and in large commercial laboratories the challenge was perceived and progress continued. These laboratories took advantage of new technologies in GC, GC/MS, HPLC, LC/MS, and in spectroscopy and demonstrated that new test development could be made practical, affordable, and efficient.

Action: At the least every hospital greater than 250 beds should ensure that its laboratory have at least 1 gas chromatograph and 1 HPLC. The use to which they are put will vary with each institution, but we believe that if they exist they will be used and used for an important purpose. Further, every laboratory in a hospital in an urban environment should do more than minimal toxicology screening and should possess a GC/MS.

2. Pharmaceutical Marketing – The Pharmaceutical Industry dictates product development strategy by what marketing departments perceive and dictate as appropriate to sell the greatest amount of product not by what the medical community needs to ensure the best possible patient care. Many companies who have introduced a new antiepileptic drug into the market have opposed routine TDM of their product. They believe the myth that physicians will not prescribe and consumers will not buy a drug with TDM requirements, because monitoring emphasizes potential toxicity and brands a drug as unsafe. For years, the pharmaceutical industry's archaic marketing practices have denied both clinicians and patients a valuable tool to control the patient's disease.

Action: It is not enough to educate clinicians; we must make a major effort to educate the management component of the pharmaceutical industry. Until they understand the realities of TDM in relation to its ability to increase sales by enhancing their products reputation for efficacy and safety they will continue to oppose TDM. We must conduct those studies and publish the results that show there are benefits to monitor such drugs.

3. Diagnostic Manufacturers – Abbott, Bayer, Dade-Behring, Microgenics, and Roche have not introduced a new TDM assay other than immunosuppressant drugs in the last 17 years. They will not develop a new assay unless they are guaranteed a market. The truth is the diagnostics industry either forgot or chose to ignore the fundamental lessons learned during TDM's evolution. A market does not exist until the assay is available which allows the market to be developed. When an assay or product is available the market will rapidly develop. (Even Syva lost sight of this concept.)

Action: It is not simply to say "if you build it, they will come". But, if laboratories maintain the capability to respond to local needs and then make their accomplishments known, the market will respond, because that is the nature of markets, to accept risk and to expand.

4. The Federal Government – The implementation of the Medical Devices Act and the assumption by the FDA of required clearance for new medical devices has had an inhibitory effect on the introduction of new tests by manufacturers. The introduction of DRGs by the federal government, acting in its role as prime payer, attempted to address increases in medical costs by limiting what could be charged for laboratory testing by placing price controls on the marketplace. The FDA has a similar role in the oversight of new drug applications and has been uniformly criticized for the slow pace of drug introduction into the United States. The introduction of new medical diagnostic tests has repeated the experience.

Action: The new drug application process was improved when important drugs were introduced in other countries years before US approval and American citizens were forced to go abroad for treatment. Studies demonstrated the accumulation of New Drug Applications.[3] The realization that fast track approaches are essential and the implementation of users fees made the FDA more responsive. The same could be applied to the introduction of new tests. There is also room for a stronger view. In a democracy the things that count are ideas, speech, votes and money. We believe that it is time for the oversight role of the FDA in test evaluation to end. The benefit of FDA review is minimal because, even after FDA approval, a user will undertake evaluation and validation at the local level. But, the delays imposed by the FDA are costly and redundant. It would be better to give the FDA disapproval authority rather than approval authority and greatly reduce its impact on the new test market. Price controls through DRGs have placed artificial barriers on the implementation of new testing strategies. Delays and inconsistencies in the introduction of CPT codes has made recovering investment time more difficult. The market is unlikely to innovate when the returns from innovation are controlled. It is time for those affected to speak out. We won't tell you how to exercise your rights as citizens, just that what you do matters and if you think the FDA has had a negative impact on your profession you should make yourselves heard.

5. Clinical Pharmacists – Over the past two decades pharmacists (PharmDs) in Clinical Pharmacy have claimed and taken pharmacokinetics and the interpretation of TDM concentration as their turf. Most only practice in a hospital environment. (Most hospitals do not have formal Clinical Pharmacokinetics services because they are too expensive to operate.) The vast majority of their efforts are usually spent regulating antibiotic or antineoplastic therapy while other areas of need tend to be neglected.

Action: We invite every Clinical Pharmacokinetics Service in the U.S. to do an internal audit. Ask yourself if you are doing all that you could do. There are many opportunities for the employment of pharmacokinetic principles in routine management. Here are some suggestions: Cancer management, Immunosuppressant dose prediction, optimization of AIDS therapies, and utilization of antidepressant and antipsychotic medications.

6. Clinical Laboratories – PharmDs took over what chemists abdicated. TDM was the domain of clinical chemistry laboratories. They provided the insights and tools to the medical community. The PharmDs were smart enough to walk out of the pharmacy on to the floors and work with the physicians. Chemists wouldn't leave the laboratory to talk to the physicians on the floors nor would the physicians leave the floors and go to the laboratory. TDM is an interactive discipline that requires many skills and constant communication. Clinical laboratorians must understand the needs of clinicians and the practices of the consult services. They must listen and accommodate these clinical needs by establishing analytical services that provide the correct concentration at the right time and assure that that result goes to the individual who can provide the most optimal care for the patient as soon as possible.

Action: If there is no formal communication between the Pharmacy and the Laboratory establish it immediately. Listen, respond and act in the best interests of patient care

7. Clinical Laboratory Role – Even if a Pharmacokinetic service exists in your institution clinical laboratories must take a proactive TDM role. The wealth of information available to clinical chemistry laboratories will only enhance TDM services and patient care. The classic studies of Les Shaw et al.[2] clearly demonstrated the importance of drawing digoxin levels at the appropriate time. Of the thousands of US clinical laboratories, how many laboratories require the time of last digoxin dose and sample collection

time be submitted with the test request? (The answer is only a few.) This simple step would prevent many iatrogenic digoxin toxicities. **Pharmacokinetic realities dictate the practice of TDM**. The laboratory must not disregard its obligation to be informed and when informed to institute policy.

Action: A concentration is only valuable when associated with a time. We support laboratory enforcement of appropriate sampling time relative to time of drug administration. This is not easy and requires interdisciplinary collaboration. Remember, nursing cooperation is required. If your hospital has a phlebotomy team insure that they have the inservice education necessary to perform their function properly.

8. Commitment and Quality Assurance – Sometimes there appears to be more commitment to TDM in Europe and Japan than in the United States. Even with our immense economic resources we find ourselves followers rather than leaders. Contributions to the major clinical journals and international forums sometimes seem to be dominated by other nations, considerably less resourceful financially than our own, but who achieve their successes because they perceive the latent value of their studies. What is the message when European laboratories can belong to a monthly quality control program rather than a quarterly program (Quarterly?)? Ask yourself which is more responsive. Proficiency testing has been the microscope of TDM development, but we must ask ourselves if our current programs serve our needs. The CAP program is the standard in the US, but how has it improved with time? We believe that it has begun to hold us back. It offers less incentive than punishment, it is too infrequent to be responsive and new analytes seem to foster whole new programs with increased costs. European surveys will generally provide access to pooled laboratory results on internet websites. The Europeans publish their results: CAP circulates them only to their members. We believe that proficiency testing is such an importantly powerful tool that it is difficult to do it badly. But we must ask ourselves whether we can do it better.

Action: Take a moment and evaluate the websites for HeathControl (www.heathcontrol.com), UKNEQAS (www.ukneqas.org.uk), Analytical Services International (www.asi.uk) and the Ontario Medical Association Quality Management Program (www.lptp.on.ca). If a more immediate, more responsive survey is more valuable, why not start one in your area? It has been done before and, while it may not last forever, it may ultimately produce a better system.

9. New technologies – We must continually strive to develop and support technological advances. The cost of LC/MS has greatly decreased in recent years. Tandem mass spectroscopy is a major technological break-through with tremendous TDM potential. These advances are readily accessible to commercial laboratories and large hospitals despite the expense and the requirement for highly skilled technicians. The clinical application of TDM requires rapid turnaround times. We must constantly pursue the development of high specificity TDM technologies, which provide assays that can be performed anytime, anywhere in the world.

Action: Hospitals above 750 beds can justify the expense of LC/MS, but the challenge is what to do with it. Establish your priorities, do your homework, be realistic and work hard to follow through on your initiatives.

10. Continuing Education – Physicians and health care professionals must be the masters of the molecules they use to treat disease. Currently TDM continuing education programs for health care professionals are not readily available. (A review of the same basic material once a year doesn't count.) Emphasis on continuing education for doctors, pharmacists, nurses, laboratory personnel and allied health care professionals is essential to provide the best possible patient care. CE must not be throwaway publications for specific disciplines. The premise is that the health care professional must think about performing TDM when appropriate on outpatients or when they hit the ER door. CE requires an interdisciplinary effort.

Action: We strongly support regional programs and associations. Size can be a disadvantage if an organization loses its focus and its sense of purpose. Each professional organization should develop a continuing education program and base it on its website or provide it by mail for a fee. Links should be in place to other programs through cooperative arrangements. The answerman approach is a

good way to access impending issues with appropriate disclaimers. Recognition of continuing education should be by reflex documentation.

11. Medical Training – Medical students receive minimal exposure to TDM principles during the first 2 years. Theoretically they receive training in the clinical and residency portions of their education. In reality what they experience is catch-as-catch can. How much any physician learns depends on the value their mentors place on TDM. What is the message when a major pediatrics text (Beernan, Textbook of Pediatrics, 2001) begins the Neurology section with the statement "Therapeutic drug monitoring is not cost-effective."?

Action: Standardized educational materials need to be incorporated into both pharmacology and therapeutics courses. The medical specialties should develop self-learning programs emphasizing the key TDM principles applicable to the specialty.

12. Mentors Needed – Young People Needed – Encourage young people to enter the discipline. Young people need job security to survive, but they need something to hang their hats on which is intellectually challenging. Molecular Biology will be the driving force of medical advances for the next generation. TDM and pharmacogenetics is a good match. We must attract the younger generation to actively participate in TDM.

Action: We strongly recommend the development of Summer Internship programs in clinical laboratories for college students with majors in science. We encourage the interaction between hospital laboratories and local high schools.

13. Pharmacokinetics Simplified – Any health care professional can perform simple kinetics in their head. Predication of anticipated steady-state concentrations is simple using Concentration/Dose Ratios (CDR). Common sense dictates that you need to check blood concentrations because of patient non-compliance, failure to achieve the desired therapeutic (pharmacodynamic) response and individual phenotype differences. We need to teach these principles; busy clinicians do not have easy access to pharmacokinetics services.

Action: We will dedicate a series in PK Korner to the basics of pharmacokinetics. Instead of dealing with advanced topics we will emphasize the primary skills and foundational learning. We will provide materials that can be presented in your own laboratory as continuing education. We will provide this on the MATT website to all MATT members.

14. Drug Information Services – Knowledge is the key to expertise and the basis for quality. The number of new drugs approved increases every year bringing new challenges and questions. Funding for internal DIS is becoming more difficult. We must make a major effort to encourage drug information agencies to provide access to TDM educational materials not just numbers.

Action: The professional organizations should be encouraged to band together to develop and to support a common TDM website. Until that time we should make the MATT website an example for the world.

15. Publications – Communication is the key to progress and data is the key to value. As new drugs enter the TDM environment optimization studies must be implemented. Clinical Pharmacology is an important medical discipline and must be supported in principle and in practice. The focus must return to rational drug use complemented with scientific measurements.

Action: Keep publishing TDM analtyical and basic research in our journals, but publish clinical applications and practical issues in the specialty clinical journals. This is the only way we can keep practicing clinicians aware of new advances and the usefulness of TDM in their practice. Clinicians do not read our journals. We must go to them: they won't come to us

16. Off-Label Drug Usage – The FDA requires each new drug to have an application, but the reality is that the value of many drugs is still largely undiscovered by the time it comes into use. Physicians must continue to record and communicate their experiences in the off-label use of medications and TDM must be encouraged. The best time for monitoring is when the least is known. Don't make the patient a victim of experimentation. Patients are still non-compliant, genetically different, subject to adverse drug reactions and drug-induced toxicity. TDM brings an important level of control to this practice.

Action: Monitoring is necessary for all drug usage, not just approved applications. The knowledge gained can be significant in improving patient treatment strategies.

17. Pharmacogenomics – Genotypes put you in the game; phenotypes let you win. Pharmacogenomics of drug interactions allow us to anticipate how the rules will change, but cannot provide the precision necessary to guide therapy for the individual patient. It is valuable to know how a given patient's genotype for increased or decreased metabolism, or whether an individual is at risk of increased or diminished pharmacodynamic response. If not properly positioned pharmacogenomics, cancer genotyping, and phenotyping may provide a false sense of secutiy because they imply you don't have to monitor. TDM does and always has allowed individual phenotyping.

Action: Pharmacogenomics has still not been effectively employed to produce*a priori* dose predictions. The studies need to be done to improve the efficiency and accuracy of initial dosing regimens. But monitoring must be continued because an individual is still subject to disease and drug-drug interactions which can affect his response to therapy.

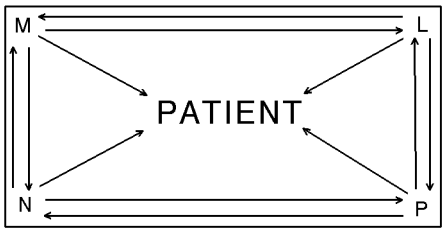
18. The New Analytes - Immunosuppressants – Transplants require frequent TDM for immunosuppressant drug therapy adjustments. Thus developing new transplant assays is perceived as a good investment for the diagnostics manufacturers. Conversely the volume of tests per year is small compared to other analytes. Psychotherapeutic drugs – The '70's saw tremendous changes in the practice of Psychiatry in the United States. The recognition that mental illness has physical causes makes the use of medication and TDM axiomatic. The door was opened by monitoring of Tricyclic Antidepressants, but similar work must be done with serotonin-reuptake inhibitors and drugs with mixed targets. Fluoxetine, Citalopram, Venlafaxine, Sertraline, Paroxetine, Quetiapine, Fluvoxamine, and Clozapine need dose ranging studies tied to outcome and concentration. A major evolution in Psychiatry has been the use of anti-epileptic medications for the control of mood in addition to antidepressant and antipsychotic medications. The use of Carbamazepine, Valproic Acid, Gabapentin, Lamotrigine, Topiramate and others need to be associated with therapeutic targets specific for their intended use rather than to use a therapeutic range developed for the treatment of epilepsy. Many of these medications are prescribed as add-ons increasing the potential for drug-drug and drug-disease interactions which only TDM can effectively identify and control. Chemotherapeutic Agents – Monitoring Methotrexate, 6-Mercaptopurine, Busulfan, Protease Inhibitors, and other antiretroviral agents are becoming more common in well managed programs but much is still to be done.

Action: Each institution has its own strategies for success and excellence. It is likely that clinicians in your facility will benefit from efforts to provide additional TDM capability in their specialty. We encourage you to seek them out, talk to them, listen, assess and act. Do what you can do well, then publish the results. Quality Improvement projects and outcomes research may provide significant opportunities to play an increased role and improve the scope of care.

19. Turf Wars – The creation of political boundaries is a major problem. We have quickly forgotten one of the fundamental principles of TDM. TDM requires an interdisciplinary team. This mandates collaboration across disciplines. The uniform sharing of resources is essential for successful patient care, but the truth is people are hesitant and don't really want to share resources they have worked hard to develop. They believe their control of these resources assures their survival. In reality, each discipline has something to offer, analytical skills, pharmacokinetic and pharmacodynamic knowledge, nursing care, expertise and precision, medical diagnostics and management and, yes, administrative support and review. When necessary components are missing or don't communicate, the system functions poorly or not at all. Survival is based on successful outcomes, and is a result not a strategy. Turf warriors may hold ground, but

not improve it; they will expend their energy in their own interests rather than the patient and, ultimately, they will not survive because the outcome of the patient will be the measure of success.

Action: The Patient is the Center – One must always remember that the patient is in the center of a box impacted by each of the following disciplines: Pharmacy (P), Laboratory (L), Medicine (M) and Nursing (N).



20. Humans are Systems – Numerous factors, genetics, diet, presence or absence of disease, age, sex and many others all influence drug concentration at the receptor and the observed clinical response. TDM is a powerful definitive tool telling you how the systems are interacting and if you are right or wrong in your treatment regimen.

Action: An environmental principle applied to Medicine – TDM conserves resources, is cost-effective and prevents toxicity. If you care about the environment, shouldn't you care about the people on the planet? Shouldn't you care about what we are doing or not doing with TDM to protect the health of your loved ones? If the TDM Renaissance does not start now, it never will.

In large part Renaissance as we view it is renewal. It is the reestablishment of basic principles, of essential axioms, of successful practices and common sense. We end this piece as we began, with an eye to the beginnings, revisiting our objectives and our principles. No longer is the fate of a journal at stake, but the state of the art. The years that have passed have set our sights higher, but made the risks greater. To paraphrase from reference 1, "Let all of us who work in therapeutic drug monitoring, in whatever discipline, cooperate in this venture to ensure that we achieve our ultimate goal of improved patient care. *We begin . . ." Anew.*

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The Poisoned Patient with Metabolic Acidosis: A Medical Toxicologist's Perspective

Suzanne White, MD, FACEP, FACMT

Overview:
Acidosis is one of the most common pathologic processes encountered by medical toxicologists who care for severely poisoned patients. There are few other clinical scenarios where successful diagnosis and management hinge so critically upon the information provided by the chemistry and toxicology laboratories. In addition to being a frequent adverse effect from poisoning, acidosis is worthy of discussion for several reasons: 1) the degree of acidemia is often reflective of the severity of the poisoning 2) untreated, severe acidemia impacts other physiologic processes such as myocardial function 3) untreated, acidemia may promote distribution of intoxicants to target tissues and 4) unrecognized, certain treatable intoxicants that cause acidosis may cause permanent injury.

General Principles:
A careful history is always the most important initial step in the evaluation of poisoned patients, but unfortunately it is not always obtainable or reliable. Often patients with acidosis have nonspecific physical signs such as hyperpnea, vomiting, weakness or mental status changes. Infrequently, one can begin to refine the differential diagnosis upon the discovery of physical findings such as the odor of ketones on the breath (seen with diabetic ketoacidosis, alcoholic ketoacidosis, or starvation ketosis), cyanosis (seen with methemoglobinemia), diaphoresis (seen with salicylates or sympathomimetics), seizures or twitching (seen with strychnine, isoniazid, or sympathomimetics). Nonetheless, if the history and physical are not immediately helpful, the clinician will rely heavily upon the laboratory for diagnostic assistance.

Laboratory:
The two most important initial laboratory results, from a medical toxicologist's perspective are the arterial blood gas and the electrolyte panel. With this information in hand, one can immediately diagnose the presence of acidemia, the etiology of the acidemia (respiratory, metabolic, or mixed), and whether physiologic compensation is appropriate. (As a bonus, information about the presence of an abnormal hemoglobin will be available from the co-oximeter). The next step is a quick calculation of the anion gap, which provides additional clues as to the underlying process involved. This calculation is as follows:

anion gap = Na - (Cl + HC03) should equal 8 to 16 meq/L

An increased anion gap in the setting of severe poisoning is common. Classical causes are listed in Table 1. (Some remember these using the mnemonic MUDPILES). The degree of anion gap elevation may have prognostic significance and may point toward specific etiologic agents. (Additional calculations at this point such as the delta gap, or change in anion gap relative to the change in pC02, provide further clarification. The delta gap allows the determination of the presence of a pure normal or high anion gap acidosis versus the simultaneous presence of metabolic alkalosis, often the case if severe vomiting is present). Once a high-anion-gap acidosis is discovered, additional key laboratory tests will likely be requested by the medical toxicologist. These include serum lactate, ketones, osmolality, salicylate level, acetaminophen level, and iron level, if vomiting is present. Additional tests that may be helpful are a urinalysis and a urinary ferric chloride. The rationale for the use of each of these tests is discussed below.

Serum Lactate:
While MUDPILES (Table 1) brings to mind a few toxicologic causes of high anion gap acidosis, it should be kept in mind that *most* intoxicants can cause lactic acidosis with severe exposure, making this a

common diagnosis. There are several mechanisms that lead to the development of lactic acidosis in poisoning. Increased oxygen demand may be caused by seizures or agitation secondary to withdrawal states or secondary to intoxication with agents such as cocaine, phencyclidine, strychnine, methylxanthines, amphetamines, camphor, or isoniazid. Another mechanism, decreased oxygen delivery, may result from drug-induced hypotension (from cyclic antidepressant, calcium channel blocker, or beta-blocker overdose) or from abnormal hemoglobin (from exposure to carbon monoxide, methemoglobin- or sulfhemoglobin-inducing agents). Drug-induced hypoxia may occur following exposure to pulmonary toxins (paraquat) or those that cause pulmonary edema (opiates or salicylates). Impaired oxygen utilization at the mitochondrial level results from poisoning from cyanide, iron, hydrogen sulfide, carbon monoxide, or with thiamine deficiency (seen in chronic alcoholics). Drug-related hepatic failure from acetaminophen or other hepatotoxins can cause failed lactate metabolism. Finally, biguanides such as metformin, impact lactate metabolism, and propylene glycol is metabolized to lactate. Clearly the "L" in MUDPILES encompasses many intoxicants.

Serum Osmolality:
Once a high anion gap acidosis has been diagnosed, a serum osmole measurement by freezing point depression allows one to calculate the osmolal gap (the difference between the measured and calculated serum osmolality). Osmotically active agents are those which freely cross cellular membranes, are of small molecular weight, and are present in large quantities. Examples include sodium, chloride, glucose, and BUN. An increased osmolal gap suggests the presence of additional small, uncharged species in significant quantities, possibly methanol, ethylene glycol, isopropanol, ethanol, acetone, propylene glycol, mannitol, glycerol, or ethyl ether. One formula for calculating osmolality is as follows:

> Calculated serum osmolality (mOsm/kg) $=2(Na^{+})$+BUN/2.8 +glucose/18 + ethanol*/4.6
> (*where the blood ethanol is in mg/dL)

A “normal” osmolal gap is often cited to be less than 10 mOsm/kg when the above equation is used. This is in fact an arbitrary number, and considerable variability in baseline osmolal gaps in patients, particularly children, has been observed.(1) If significantly greater than 10 mOsm/kg, the osmolal gap may be a useful aid in the diagnosis of toxic alcohol ingestion. Caution should be taken, however, in ruling out toxic alcohol ingestion with a "normal" osmolal gap for several reasons. First, calculated serum osmolality results may vary among laboratories and must be done by freezing point depression method. Also, delayed presentation following toxic alcohol ingestion may be associated with prior metabolism of the parent alcohol. There may be little or no osmolal gap elevation in this setting. Finally, a toxic level of either methanol or ethylene glycol may be present with a gap of only 10 mOsm/kg. If there is clinical suspicion of toxic alcohol ingestion, direct measurement of the serum toxic alcohol levels is necessary, and if not readily available, empiric treatment is warranted. (2,3) Incidentally, by unclear mechanisms, increased osmolal gaps can be seen with lactic acidosis, cirrhosis, alcoholic ketoacidosis, and other forms of critical illness. (4,5)

Serum/Urine Ketones:
Measurement of serum and or urine ketones will aid in the work-up of acidosis. Intoxicants associated with **ketosis** include vacor, salicylates, and isopropanol. An important distinction to make here is that isopropanol ingestion leads to *ketosis without acidosis*. The osmolal gap will be increased, but the anion gap should be normal. A significant acidosis in the setting of isopropanol ingestion mandates a search for co-ingestants. Ketosis occurs as isopropanol is metabolized to acetone, which can be detected in the blood as early as 15 minutes after ingestion and in the urine 3 hours after ingestion. (6,7) Acetone is uncharged, therefore it does not elevate the anion gap. In theory, 1 mg/dL rise in blood isopropyl alcohol concentration should result in a 0.17 mOsm/kg rise in serum osmolality. One early, very helpful laboratory clue to the diagnosis of isopropanol ingestion is "pseudo renal failure" or isolated false elevation of creatinine with a normal BUN. This results from interference of acetone with colorimetric

methods of creatinine determination. In this setting, creatinine is expected to rise by 1 mg/dL for every 100 mg/dL acetone.
Vacor, a rodenticide toxic to pancreatic cells causes diabetic **ketoacidosis**. Another common cause of **ketoacidosis** in malnourished alcoholics who stop drinking is alcoholic ketoacidosis. In this condition, betahydroxybutyrate is the main ketone body present, and this level may be requested by the medical toxicologist to clarify the diagnosis. Salicylates also cause ketonuria (see below).

Serum Salicylate Level /Urinary Ferric Chloride:
Since salicylate intoxication remains common, another important test in the work-up of high anion gap acidosis is a quantitative salicylate level. Salicylate-induced metabolic acidosis is multi-factorial and most commonly occurs as a mixed acid/base disorder- metabolic acidosis with a respiratory alkalosis. These acid-base disturbances result from the direct stimulation of the CNS respiratory center, uncoupling of oxidative phosphorylation, inhibition of the Kreb's Cycle, stimulation of gluconeogenesis, stimulation of lipid metabolism (ketosis), stimulation of glycolysis, and accumulation of salicylate, a weak acid. Early detection and correction of metabolic acidosis is critical in this setting. As blood pH drops, more unionized drug enters the CNS which is the target organ of toxicity. If available, a urinary ferric chloride test also provides rapid bedside evidence of the presence of salicylates.

Serum Iron Level:
Iron intoxication remains a serious cause of pediatric morbidity from poisoning and is invariably associated with an increased anion gap metabolic acidosis. (8) The mechanism for this acidosis is multi-factorial. Direct myocardial depression, the vasodilatory effect of ferritin or free iron, and the loss of fluid into the gut lumen all contribute to decreased perfusion and therefore decreased oxygen delivery (increased lactate). Other suggested mechanisms for acidosis include the production of hydrogen ions by the oxidation of iron from the ferrous to the ferric state and the interference with oxidative phosphorylation by direct mitochondrial membrane injury. (9) Protracted vomiting is the best clinical marker of significant iron ingestion, and without it, iron poisoning is unlikely. Therefore, the medical toxicologist will generally request the rapid determination of a serum iron level in acidotic patients who are vomiting.

Serum Acetaminophen Level:
This drug has become the most common cause of fatality related to pharmaceutical overdose. (8) Early signs of ingestion are often absent. Therefore, it is prudent to obtain a quantitative serum acetaminophen level in all patients with a history of intentional ingestion or with an unexplained metabolic acidosis.

Urinalysis:
Urinary ketones are discussed above. The presence of crystalluria can also be a useful diagnostic tool in the work-up of the acidotic patient. Although crystalluria is considered the hallmark of ethylene glycol ingestion, its absence does not rule out the diagnosis, since less than one half the patients will have this finding. (10,11) Crystalluria may take the form of envelope-shaped calcium oxalate dihydrate crystals or needle-shaped calcium oxalate monohydrate crystals, occasionally mistaken for hippurate crystals. (12,13) Other crystal shapes and composites have been noted. This has led some to propose that in the setting of combined anion and osmolal gap elevation, the presence of *any* type of crystalluria warrants a search for ethylene glycol. The monohydrate crystals are thought to be more specific for ethylene glycol poisoning. (10, 14) A qualitative but useful test in the ED involves examining freshly voided urine for fluorescence with a Wood's lamp. (15) Sodium fluorescein is added to antifreeze to aid in the detection of radiator leaks. Urinary fluorescence may be seen up to six hours post-ingestion of fluorescein-containing antifreeze. Gastric contents and patient's skin or clothing may also fluoresce under Wood's lamp examination. The lack of fluorescence of any of these samples, however, does not rule out the diagnosis of ethylene glycol ingestion, since the test has a negative predictive value of only 0.50. Specimens should

be collected in borosilicate glass test tubes, since many plastic specimen containers are fluorescent. The urine pH should also be checked and adjusted to 4.5 or greater prior to Wood's lamp examination.

Other Labs:
In addition to the laboratory tests discussed above, others may be useful on a case-by-case basis, and should ideally be available "stat." These include: carboxyhemoglobin, methemoglobin, ethanol, digoxin, lithium, theophylline, carbamazepine, and phenytoin levels. These results will all potentially allow for the timely administration of specific antidotes or interventions that could ultimately improve outcome.

Normal Anion Gap Acidosis:
A normal-anion-gap acidosis in the setting of poisoning is unusual, and signifies either abnormal renal or gastrointestinal losses of bicarbonate or the ingestion of a strong acid (see Table 2). A common cause of this acid-base disorder in poisoned patients is iatrogenic- i.e., the over-administration of cathartics resulting in excessive diarrhea. Another common cause is solvent abuse. Sniffers, huffers, or baggers who chronically inhale toluene are at risk to develop renal tubular acidosis. Interestingly, a few intoxicants such as lithium, bromide or iodide may actually cause a "lowered" anion gap. Their presence may mask that of toxic unmeasured anions and make the work-up and diagnosis even more challenging.

Conclusion: Acid-base disturbances are common in severely poisoned patients and require rapid identification, classification, and investigation. Often the history and physical examination are unrevealing. Services provided by the toxicology laboratory are frequently the most important resources available to the treating medical toxicologist and are invaluable to successful diagnosis and management.

Table 1. Causes of High Anion Gap Acidosis

Methanol
Uremia (Renal failure)
Diabetic Ketoacidosis
Paraldehyde
Iron/Isoniazid
Lactate
Ethylene Glycol/ethanol (alcoholic ketoacidosis)
Salicylate/starvation ketosis

Table 2. Causes of Normal Anion Gap Acidosis:

Diarrhea
Ureterosigmoidostomy
Small bowel/pancreatic fistula
Anion exchange resins
Primary hyperparathyroidism
Hyperalimentation
Post-hypocapnic state
Ingestions (addition of acids)
- Sulfur
- Chlorine
- Hydrochloric acid
- Ammonium chloride
- Calcium chloride
- Magnesium chloride

- Lysine hydrochloride
- Arginine hydrochloride

Renal Tubular Acidosis
** Causes of drug-related renal tubular acidosis

Type I
- Amphotericin
- Lithium
- Toluene
- Vitamin D
- Analgesics
- Cyclamates

Type II
- Outdated tetracycline
- Carbonic anhydrase inhibitors
  mafenide acetate, acetazolamide
- Cadmium
- Mercury
- Lead
- Uranium
- Toluene
- 6 mercaptopurine
- Methyl-5-chrome
- Streptozotocin

Type IV
- Amiloride
- Spironolactone
- Lithium
- Triamterene
- NSAIDS
- Ace inhibitors
- Cyclosporine
- Beta blockers

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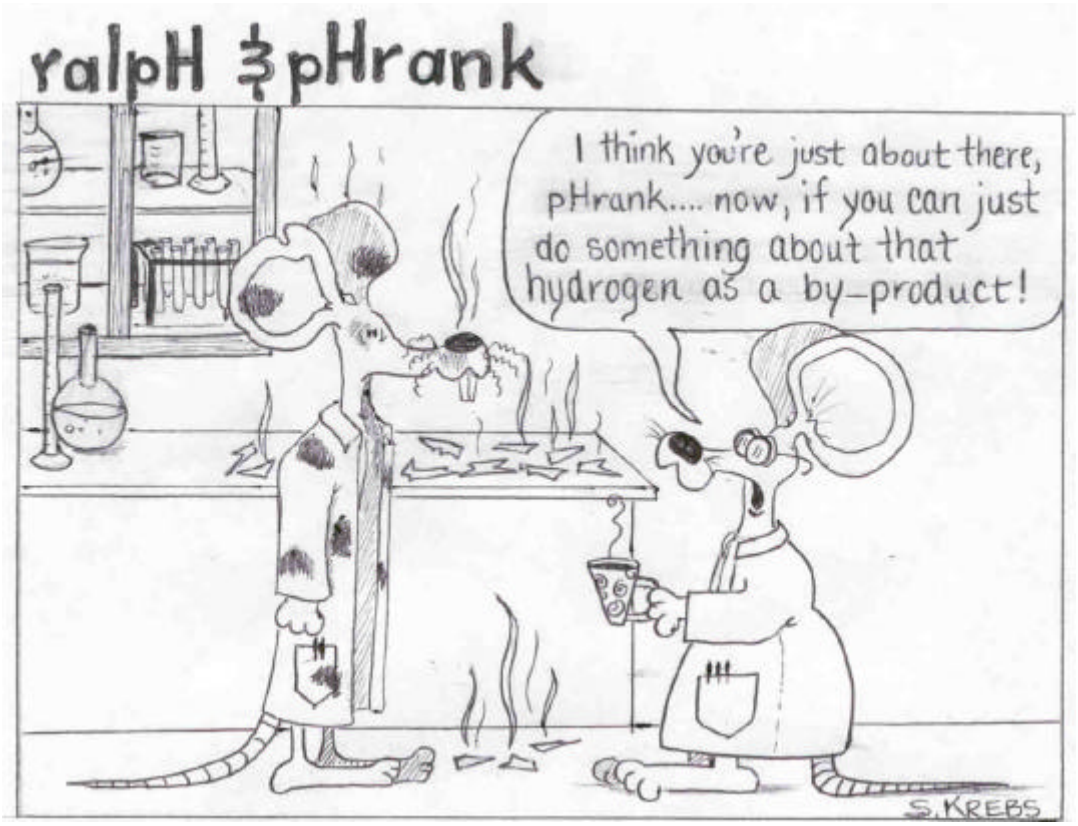


sMATTerings Meeting Calendar

2002 American Chemical Society Meeting, April 7-11, Orlando, FL. Contact: American Chemical Society Meeting Department, 1155 16th Street NW, Washington, D.C. 20036-4899. Tel.: (202) 872 6059, Fax (202) 872 6128, email: natlmtgs@acs.org

2002 Annual Meeting of the Association of Clinical Scientists, Salt Lake City, UT, May 8 to 12. Contact: Association of Clinical Scientists, PO Box 1287 Middlebury, VT 05753, USA Tel: (802) 462-2507 Fax: (802) 462-2673 eMail clinsci@sover.net

Pharmacogenomics: Improving Pharmacotherapy and Avoiding ADRs. May 9-10, 2002, Philadelphia, PA.. Contact: AACC, 2101 L Street, N.W., Suite 202, Washington, D.C. 20037-1526. (202) 857 0717 or (800) 892 1400, Fax (202) 887 5093, email custserv@aacc.org

50th ASMS Conference on Mass Spectrometry and Allied Topics, June 2-6, Orlando, FL. Contact: American Society for Mass Spectrometry., 1201 Don Diego Ave., Santa Me, New Mexico, 87505. (505) 989 4517, Fax (505) 989 1073. email: asms@asms.org

2002 Annual Meeting of the American Association for Clinical Chemistry, July 28- August 1, Orlando, FL. Contact: AACC, 2101 L Street, N.W., Suite 202, Washington, D.C. 20037-1526. (202) 857 0717 or (800) 892 1400, Fax (202) 887 5093, email custserv@aacc.org

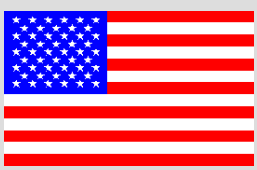
40th Triennial Meeting of the International Association of Forensic Toxicologists(TIAFT), August 27-30, Paris, France. Contact: TIAFT 2000 marc Deveaux, Institut de Legale Medicine Place Theo Varlet, 59000 Lille, France, http://www.sfta.org/tiaft/paris 2000.htm

16th Meeting of the International Association of Forensic Sciences, September 2-7, Montpellier, France. Contact: Societe International de Congres et Services, 337, ure de la Combe Caude, 34090 Montpellier, France, +33(0) 4 67 63 53 40, Fax + 33(0) 4 67 41 94 27, email : algcsi@mnet.fr.

31st American College of Clinical Pharmacology Annual Meeting, September 21-23, Chicago, IL . Contact: Susan Ulrich, ACCP Executive Director, 3 Ellinwood Ct., New Hartford, NY 13413-1105, (315) 768 6117, Fax (315) 768 6119, email ACCP1ssu@aol.com

2002 National Association of Medical Examiners Annual Meeting, September 25- October 3, Shreveport, LA. Contact: Mary Fran Ernst, Meeting Planner of NAME, 1402 South Grand Blvd., R512 St. Louis, MO 63104. (314) 577 8299, Fax (314) 268 5124, email: ernstmf@slu.edu

2002 Annual Meeting of the Society of Forensic Toxicologists(SOFT), October 13-17, Dearborn, MI. Contact: Dr. Daniel Isenschmid, (313)833 2557, Fax (313) 833 2534 email: disench@co.wayne.mi.us



Presents
MATT 2002
Madison, Wisconsin
April 25-26, 2002

Registration Information

The meeting site is The Pyle Center, 702 Langdon Street, located in the heart of the UW campus on the shores of Lake Mendota. The facility has state of the art media capabilities and comfortable lounges, dining areas and reception space. The basic meeting registration includes scientific sessions, posters and exhibits, program book, continental breakfast and luncheon Thursday and Friday, and all coffee breaks. Registration is encouraged prior to April 1st, 2002. Accompanying persons may purchase tickets for breaks and meals. Prices are noted on the registration form. On-site registration will require a late fee.

Hotel Registration and Transportation

Reservations for rooms should be made directly with the hotel. Rooms have been blocked at the Lowell Center, 610 Langdon Street. Current room prices are $62 for a single and $72 for a double. Suites are also available at additional cost. ***Reserve early, space is limited!*** The Lowell Center is a seven-story hotel with excellent amenities, fitness equipment, complimentary continental breakfast and meeting facilities. In addition, you are just steps away from the conference site, State Street and downtown Madison. Limited on-site parking is available at the Lowell Center. Information is provided with your room confirmation. ***Call (608) 256-2621 to reserve your room***. For alternate lodging options, please contact Chris Goodall.

Abstract Submission

MATT 2002 is pleased to offer the opportunity for poster presentations. We encourage subjects related to toxicology, either clinical or forensic. We will also consider general laboratory subjects such as quality control practices. This is an ideal opportunity to present for the first time. Do you have a great method that could benefit other members of the toxicology community? Please share it with us!

Preliminary Program

Many excellent speakers have committed to presentations at MATT 2002. Topics will span forensic and clinical toxicology. Examples include: new therapeutic approaches in TDM, use of gabapentin in pain control, monitoring of anti-viral drugs, alcohol and drugs in the workplace, new tests for monitoring alcoholism, forensic blood alcohol issues, update on drugs and driving and a forum on new analytical techniques. The complete program will be published in the spring 2002 issue of sMatterings. The meeting will run from 8:30 AM to 5:00 PM each day. Plans are in progress for a wine and cheese reception on Thursday evening.

Entertainment

Madison offers a host of activities. Home to the University of Wisconsin, member of the Big Ten, you may enjoy exploring the campus. State Street offers shopping and a variety of entertainment. Restaurants abound in the city. Just a few blocks from the meeting you can tour the Wisconsin State Capital. It is a beautiful, historical landmark that just reopened after an eleven-year $141 million renovation project. The campus is located on an isthmus between two lakes, Mendota and Monona, surrounded by bicycle or roller blade paths. You may want to extend your stay for a golf outing. There are many nice local courses. If you want assistance with golf arrangements, contact Don Wiebe. For all other questions, e-mail Chris Goodall.

PRELIMINARY MEETING SCHEDULE

Wednesday, April 24, 2002

Board Meeting 6-8 PM

Thursday, April 25, 2002

7:30-8:10	Registration and Continental Breakfast
8:10-8:15	Welcome
8:15-9:15	Tom Moyer, PhD, "Immunosuppressants"
9:15-10:15	Paul Hutson, PharmD, "Toxicology of Herbs and Teas"
10:15-10:45	Break
10:45-11:45	Pamela Bean, PhD, MBA, "Choosing the right approach to detect and monitor heavy drinking in the new millennium"
11:45-12:30	Paul Janetto, PhD, "Pharmacogenetics as an Adjunct to Pain Management Therapy"
12:30-13:30	Lunch served in Vendor area Abstracts displayed same area
13:30-14:15	Jonathan Lewis, RN BSN, "Organ Donation: The Gift of Life"
14:15-15:00	Greg Grinstead, PhD, "What's New in Federal Workplace Drug Testing?"
15:00-16:00	Tentative: Antiepileptics and/or Antidepressants
16:00-16:15	Break
16:15-17:00	Member's Meeting
17:00-19:00	Tentative: Wine/Cheese Reception with Vendors

Friday, April 26, 2002

7:45-8:15	Registration and Continental Breakfast
8:15-9:00	Kathryn Coyle, DVM, Milwaukee Zoo pathologist "Where the Wild Things Are (With Sincere Apologies to Maurice Sendak)"
9:00-10:00	Andrew Urban, MD, "The Role of Antiretroviral Drug Level Monitoring in the Management of HIV"

10:00-10:30 Break

10:30-13:00 "Forum on new analytical techniques (LC/MS, NCI-GC-MS, SFE)" Adam Negrusz, PhD, Chair

10:30-11:00	Gary Lensmeyer – Effective Use of Solid Phase Sorbents for Drug Extractions
11:00-11:45	Paul Zavitsanos – The design, implementation and searching of LC/API-MS spectral libraries
11:45-12:30	Adam Negrusz - Practical aspects of NCI-GC-MS
12:30-13:00	Discussion and closing remarks

13:00-14:00 Luncheon in Vendor area

14:00-16:00 "Forensic Symposium: Alcohol Drugs and Driving" Wisconsin State Laboratory of Hygiene Toxicology Staff

- Clinical vs. Forensic Blood (and Breath) Alcohol Testing: Differences and Challenges - Patrick Harding
- Alcohol Results in the Courtroom; Fun with Numbers: Extrapolation and Impairment - Thomas Neuser
- Driving Under the Influence of Drugs: The Wisconsin Experience - Laura J. Liddicoat

For information or presentation of posters contact:

Chris Goodall Phone: 608-263-7031
E-mail: cr.goodall@hosp.wisc.edu

Don Wiebe Phone: 608-263-1495
E-mail: da.wiebe@hosp.wisc.edu

MATT 2002 Registration Form
Madison, Wisconsin ↔ April 25-26, 2002

Name_____
Last First

Name to appear on name badge_____

Title_____ Agency_____

Address_____

_____

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Guest(s)_____

	MATT MEMBER	Non-MEMBER	TOTAL ENCLOSED
Basic Meeting Registration Includes all scientific sessions, posters and exhibits, program book, continental breakfast and luncheon Thursday and Friday, and all coffee breaks	$90	$110	$_____
Daily Registration Inclusions as above, for day of attendance only	$50/day (Indicate day)	$60/day	$_____
Extra Meal Tickets: $27 per day includes: breakfast, lunch and coffee breaks	_____# of tickets		$_____
Membership renewal for 2002	**$20**		**$**_____
Late Fee: $20 for registration received after April 21, 2002 or on site			$_____

Method of payment:
Check drawn on USA bank or Money Order. All funds must be paid in US dollars. Make payable to **MATT**.

MAIL TO: **Christine Goodall**
UW Hospital & Clinics
600 Highland Avenue
Toxicology D4/248
Madison, WI 53792-2472

MATT 2002 Madison

UW Madison April 25-26, 2001

Instructions for Abstract Preparation

General Instructions:
The program committee solicits abstracts on all clinical and forensic toxicology topics. Abstracts are to be presented as posters. Tack boards and thumbtacks will be provided. An original and one copies of the abstract must be submitted on the official abstract form. Please also submit the abstract on a computer disk. Electronic submissions must be in IBM word processing format (MS Word for Windows preferred) or ASCII format. Please label the disk with the first author's name and the word processing program utilized. **The deadline for submission of abstracts is April 1, 2002**. The presenting authors of all papers will be required to register for the meeting. Only abstracts written in English will be considered.

Content of Abstract
1. Author(s) names and addresses
2. Short specific title
3. Statement of paper's objectives
4. Statement of methods, if pertinent
5. Statement of results
6. Statement of conclusion
7. Key words (3 each)

Format of Abstract
Abstracts must be typed and submitted in a neat legible format following the instructions and style provided in the sample below. Type the entire abstract within the boxed area, single-spaced with 11 or 12-point font. Type the title in upper and lower case, followed by the author(s) names and addresses. Use an Asterisk (*) to identify the presenting author. Separate the author(s) names from the body of the abstract by a single blank line. Indent each paragraph three spaces. Identify three key words at the bottom of the abstract.

Notification of Acceptance
All submitting authors will be notified of receipt of the abstract. Notification of acceptance of the abstract will be mailed or sent by fax or e-mail no later than April 10, 2002.

Specific Instructions
Complete the attached form and follow the sample provided below. Proofread all information provided. Send the original, one additional copy and an IBM disk with the abstract to the mailing address.

Mailing Address:

Don Wiebe, PhD
UW Hospital & Clinics
Toxicology D4/252
600 Highland Avenue
Madison, WI 53792-2472

Phone: 608-263-1495
Fax: 608-263-1568

Sample Abstract:

Title: Type Upper and Lower Case. Use Significant Words Descriptive of Subject Content

Author(s) Names and Addresses: Type Upper and Lower Case; Spell Out First and Last Names, Use Middle Initial, *e.g.* John B. Smith

Indent each paragraph three spaces. Type the entire abstract within the boxed area, single-spaced. Do not type in all capital letters. Capitalize and punctuate exactly as you wish the abstract to appear in the program.

Key Words: Type three key words or phrases in upper and lower case.

MATT 2002 Madison

UW Madison April 25-26, 2002

Abstract – Deadline for Submission April 1, 2002

All abstracts related to toxicology will be considered for presentation.

The meeting host(s) reserves the right of final placement of the poster. The presenting author(s) of all papers is required to register for the meeting.

Signature of presenting author

Name of presenting Author:

Name of Responsible Author for correspondence (please type):

Address:

City: Province/State: Postal/Zipcode: Country:

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