sMATTerings

Midwest Association for Toxicology and Therapeutic Drug Monitoring

Volume 8 Issue 2 October 2002

From the Editor's Desk

Greetings MATT Members;

Here we are, one year later…and everyone knows the implication of that phrase. Chris Goodall shares some timely thoughts with us on what's important. Paul Jannetto introduces us to that new discipline that promises to change, in a fundamental way, how medicine will be dispensed in the future. Start learning now to wrap your tongue around "Pharmacogenomics." John Wilson never ceases to wrap my mind in tight little circles as I digest his offerings in the pK Korner.

Finally, a few quick words about the Spring Meeting in East Lansing. The program has not been finalized at this point, so if you have some thoughts about what should be presented, please let me know. As information becomes available, updates will appear on the web site. It can be found at www.midwesttox.org. You can find me at HouseF@michigan.gov.

There when it sMATTers most!

Fred

IN THIS ISSUE

President's Korner

When I composed my first message to you as President of MATT, it was just weeks after 9-11. It was difficult for all of us to attend to business at that time. Here we are, one year and one week later. The media provided poignant reminders of the tragedy and our national spirit. In the large part, we have all picked up and moved on with life. I continue the daily struggle of balancing the love for my two children with the fact that they are two teenage girls (that require a modicum of discipline). Maybe you have heard the phrase: All you ever do is yell at us!

MATT has made progress as a professional organization but we still have business to do. The minutes from the members meeting are posted on the web site. This message will focus on the past year of MATT and the future needs as addressed at the meeting. I encourage your support and participation. As you will see, we need your input to make some changes and to continue with future growth. Feel free to contact me or any other officer if you have questions or ideas.

The annual meeting was held in Madison and it was a great success. The evaluations were excellent regarding the location and facilities, the food and overall meeting value. We had 15 speakers over the two-day program that covered a variety of clinical and forensic topics and all speakers received great evaluations. In addition, we had 12 vendors present and many participated in the scientific sessions. Okay, so I hosted the meeting and I am bragging. The point I make is that MATT has a tradition of providing an excellent, local scientific meeting that is affordable to all. Please come see us in East Lansing in the spring of 2003. The meeting information will be posted on the MATT web site as soon as it is available. The site for 2004 will be in the

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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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Chicago area. Beyond that, we need volunteers to host a meeting. The guidelines for hosting a meeting are posted on the web site. In addition, all of the officers are skilled at meeting organization and would be able to assist you should you desire to host a meeting.

The treasury for our organization has a modest but healthy balance. At the executive board meeting, it was decided that MATT should host some type of award at the annual meeting. It will probably be along the lines of a young investigator award. This has not been finalized and we would appreciate suggestions from the membership.

The by-laws are being considered for update. We would like to make changes in the committee structure and the election of officers. Other suggestions are welcome as well. The suggested changes will be presented at the members meeting in 2003 for approval. The bylaws have been posted on the web site for your review. They can be found as a link in the About Matt section. If you have not yet seen the web site, it is located at www.midwesttox.org

Last but not least, I ask that you ***please submit your membership renewal***. According to the by-laws, renewals are due on or before December 1st each year. The membership renewal form is included in the newsletter. Please help promote MATT as well. Encourage your friends and colleagues to join. If you are attending meetings this fall and winter, such as SOFT or AAFS, use the opportunity to seek out your colleagues from the Midwest and tell them about MATT.

I close my message with a question. What has changed in your life in the past year? After the tragic events of a year ago, I realized that it is too easy to procrastinate on doing or changing the things that one believes to be important in life. For many years I spoke of graduate school, but always found an excuse to put it off. As of two weeks ago, I started class as a graduate student at Edgewood College in Madison. I hope that the lessons of the past year have brought you all the incentive to do something special for yourself or the ones that you love.

Introduction to Pharmacogenomic and Applications for Toxicology

Paul J. Jannetto, Ph.D.
Postdoctoral Fellow in Clinical Toxicology, Therapeutic Drug Monitoring, Pharmacogenomics, and Proteomics
Department of Pathology
Medical College of Wisconsin
And
Milwaukee County Medical Examiners Office

With the completion of the Human Genome Project, pharmacogenetics is a rapidly advancing field poised to make an impact in the diagnostic, clinical, and forensic laboratory[1]. Pharmacogenomics is the study of the linkage between an individual's genotype and that individual's ability to metabolize a foreign compound[2]. The cytochrome P450 family of enzymes is primarily involved in drug metabolism that results in the detoxification and elimination of the drug or the activation of the prodrug to its biologically active form. However, cytochromes P450 show a wide interindividual variation in their protein expression and/or catalytic activity, resulting in unique drug metabolism. This variation can be due to transient causes such as enzyme inhibition or induction, or to permanent causes such as genetic mutations or deletions.

Pharmacogenomics is an emerging field that has the potential to make a significant clinical impact on patients. Genetic variations (polymorphisms) have been shown to alter drug concentrations and response. These genetic differences are partly responsible for the various drug concentrations seen in patients who receive the same dose of a particular medication. Pharmacogenetics is the genetic link that can help explain why some patients respond well to drugs and others do not, or why one drug is toxic to one individual but not another. Using pharmacogenomics, it might be possible to predict these various outcomes and prevent the toxicity.

Therefore, pharmacogenomics represents the concept of individualized and rational drug selection based on the genotype of a particular patient [3] Pharmacogenomics provides the genetic basis for pharmacokinetics (drug absorption, distribution, metabolism, and excretion) and pharmacodynamics (drug receptors). Pharmaceutical agents are one of the most commonly identified causes of adverse events, resulting in significant patient morbidity, mortality, and excess medical care costs [4, 5]. In fact, adverse drug reactions ranked between the fourth and sixth leading cause of death in the United States in 1994 [6]. A recent US study estimated that 106,000 patients die and 2.2 million are injured each year by adverse drug reactions to prescribed drugs [6]. Clinically important drug metabolizing enzymes and drug receptors have been shown to be polymorphic (posses stable genetic variations in ≥1% of the population).

The cytochrome P450 enzyme, debrisoquine hydroxylase (*CYP2D6*), metabolizes a wide variety of pharmaceuticals, and the variation in activity of this enzyme between individuals can be greater than a 100-fold [7]. Recently, it has been estimated that *CYP2D6* may be responsible for the metabolism of 25% of all prescribed medications including drug groups such as β-blockers, antiarrythmics, tricyclic antidepressants, antipsychotics, analgesics, and many others [8]. Although *CYP2D6* has a wide range of genetic polymorphisms, they can be categorized into four groups; ultrarapid metabolizers (UM) containing multiple copies of the *CYP2D6* gene, extensive metabolizers (EM) with a single wild-type copy of the *CYP2D6* gene, intermediate metabolizers (heterozygotes) exhibiting decreased enzymatic activity and poor metabolizers (homozygotes) with no detectable activity [8]. As a result, steady-state drug concentrations can significantly vary in individuals with genetic polymorphisms. Therefore, individuals receiving a standard dosing protocol may be more or less

likely to experience adverse drug reactions due to their increased or decreased metabolism and elimination of various drugs, resulting in a change in their capacity to metabolize drugs.

Currently, phenotyping and genotyping are the two main strategies that are used to screen for various polymorphisms in individuals. Phenotyping determines the presence and activity of a particular metabolic enzyme by measuring the metabolites after a person takes a drug. However, phenotyping is not clinically efficacious and potentially dangerous since the drug has to be administered and the patient may experience adverse drug reactions. On the other hand, genotyping poses less of a risk since DNA can be extracted from whole blood or a buccal swab to determine the genetic code of a particular individual. Genotyping can identify various polymorphisms in patients that have been correlated to particular phenotypes.

Since pharmacogenomics has such great potential, it is also being applied by the pharmaceutical industry to develop better drugs and minimize costly adverse effects. Other areas that are beginning to use pharmacogenomics include: cardiology, neurology, oncology, asthma, pain management, psychiatry and autoimmune disorders (HIV). Currently, pharmacogenomics is even being used to assist in the certification of the cause and manner of death in forensic toxicology[9]. In the near future, health care professionals may utilize genetic tests to predict how a disease may respond to a particular therapy, or monitor the progression of a disease, or aid in the selection/modification of a therapy, and be used in the development of new medications. As a result, drugs may one day be prescribed based on "personal pharmacogenetic profiles" for every individual[10].

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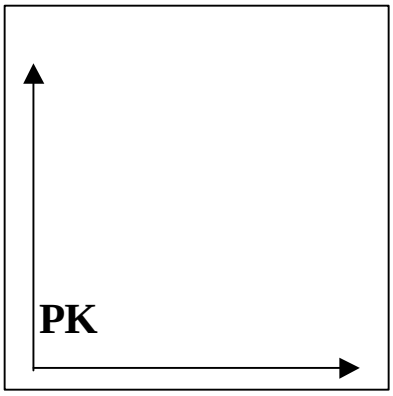

Pharmacokinetics Korner

By John M. Wilson

A Pharmacokinetic Basis for Creatinine Normalization in Urine Drugs of AbuseTesting

Since the eighties we have learned to live with Urine Drugs of Abuse Testing. We have learned to expect it before being hired for a job, before entering and leaving the military service, and in the investigation of accidents of varied kinds. We have also seen its use by parents who monitor their children, social workers and parole officers who monitor their clients, and physicians who monitor their rehab patients. We have learned to deal with issues such as specificity, cutoffs, confirmation methods, and adulteration. We have been concerned about chain of custody, specimen integrity and individual rights. We have calculated costs and profit margins, true and false positive rates, and weighed the incidence and variability of drug use in the population. Under the weight of all this information have we lost sight of our primary activity? Do we know enough about what we are measuring? What is the basis for the drug concentration that we measure, and what does that concentration mean?

As a starting point I'd like to refer your attention to a paper published in the journal, Clinical Chemistry, in 1991 by Lafolie et al.[1]. Here the authors argue that there is considerable added value in reporting the urine drug concentration divided by the urine creatinine concentration. Instead of ng or μg of drug per milliliter of urine we would report ng or μg per mg of creatinine. They support their suggestion by serial urine collections from a heavy cannabis user in a monitored environment for an extended period and conclude, "we recommend measurements of creatinine or osmolality in urine for detection of presumably false-negative samples when testing for drugs of abuse . . . Quantitative measurements of creatinine and cannabinoids make it possible to calculate a ratio that eliminates falsely increased cannabinoids in urine due to metabolism rather than resumption of marijuana smoking."[1] Are these legitimate conclusions? Is there a pharmacokinetic or physiological basis for using creatinine measurements in this way? And what can we learn from the application of these two measurements?

There is an interest in addressing two problems: the first involves urine dilution. An individual attempts to defeat the testing process by water loading prior to submitting a urine sample. This can be an effective strategy when combined with abstinence for cannabinoid testing. It is possible to dilute a urine multiple-fold and reduce a very positive test to a value below 50 ng/mL. By correcting a sample for creatinine concentration, the low creatinine concentration will increase the cannabinoid concentration to restore it to a value above the cutoff. The second

situation is in monitoring an individual who is abstaining in the context of rehabilitation. Submission of a concentrated urine could produce a result above the cutoff even though previous cannabinoid tests had been negative and without additional cannabinoid exposure.[2] Dividing the cannabinoid concentration by a high urine creatinine concentration will lower the result so that it can be interpreted within the context of previous and future results.[3] Reference 1 presents the figures below to justify their recommendations:

Fig. 1

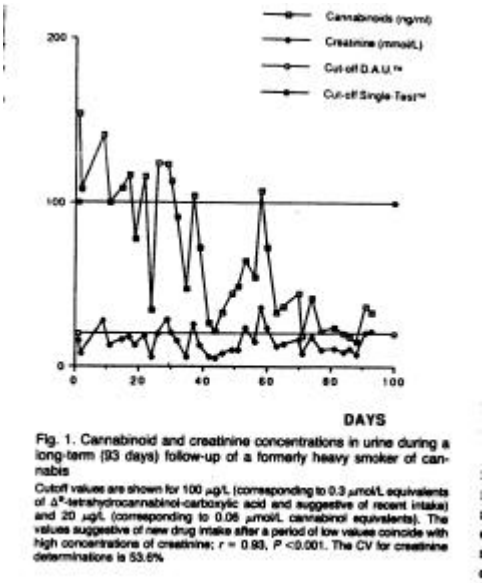

Fig. 1. Cannabinoid and creatinine concentrations in urine during a long-term (93 days) follow-up of a formerly heavy smoker of cannabis

Cutoff values are shown for 100 μg/L (corresponding to 0.3 μmol/L equivalents of Δ^9-tetrahydrocannabinol-carboxylic acid and suggestive of recent intake) and 20 μg/L (corresponding to 0.06 μmol/L cannabinol equivalents). The values suggestive of new drug intake after a period of low values coincide with high concentrations of creatinine; $r = 0.93$, $P < 0.001$. The CV for creatinine determinations is 53.6%

Fig. 2

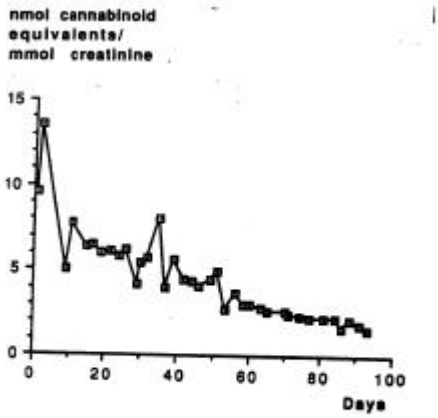

Fig. 2. The ratio of cannabinoids and creatinine (nanomoles of Δ^9-tetrahydrocannabinol-carboxylic acid per millimole of creatinine) revealed a steady decline, with a half-life of 32 days; the equation for the line obtained by linear regression is $y = 8.3150 - 0.0605x$

the samples being <0.7 mmol/L during this time (Table 1).

Reprinted with permission from Clinical Chemistry.

In fig. 1 there is wide variability in the urine cannabinoid concentration and concentrations even on consecutive collections are both above and below the 100 ng/mL threshold. It is not easy to accurately predict a subsequent drug concentration from any combination of previous urine collections and drug measurements. Creatinine concentrations vary as well, but there does appear to be a tendency for low cannabinoid concentrations to be associated with low creatinine concentrations. In fig. 2 the ratio is plotted and, while a great deal of the variability has been removed, there are still points that appear to be lower or higher than might be predicted from previous and subsequent data. Clearly there is value in the recommendations and some variability that still cannot be explained.

The presentation of drug in urine is not too difficult to characterize pharmacokinetically. To appear in the urine a drug in the blood must be filtered in the glomerulus, pass through the kidney tubules and arrive in the bladder. A variety of significant things can happen to the drug during this period, such as metabolism, reabsorption, secretion and degradation, not to mention recycling by absorption from the bladder. If we consider a simplified example where none of these occur we can predict the excretion rate of a drug with the expression

$$\text{Excretion Rate} = dXu/dt = k_e X_0 e^{-Kt} \qquad (1)$$

where *Xu* is the amount of drug in the urine up to time t, k_e is the renal elimination rate constant, X_0 is the amount of drug in the urine at time zero, and K is the elimination rate constant for the

drug that includes all forms of elimination, such as metabolic and renal routes. A series of urine collections after a dose of drug would produce a plot of excretion rate(Concentration times Volume/Collection Interval) versus time that would resemble the plot of serum concentration versus time, though on a different scale. The slope of the later points on such a curve would represent the terminal elimination rate of the drug, K, and could be used to calculate the drug half-life (0.693/K). One of the problems that we have in the interpretation of Urine Drugs of Abuse data is that we use concentrations as parameters instead of excretion rates. The urine excretion rate is predictable and will decline according to the concentration of drug in the blood, but the urine concentration will depend on the volume of urine that contains the drug. Many laboratories have difficulty calculating excretion rates because they do not collect timed urines and because they accept aliquots rather than complete specimens. Without a urine volume and the span of collection, calculation of an excretion rate is impossible.

Drug concentration may be measured as milligrams or micrograms or nanograms per volume, either milliliters or liters. Creatinine concentration is reported in the same fashion. Flow has units of volume per time. Excretion rate has units of milligrams per time. Excretion rate of drug or an endogenous chemical like creatinine can be written as the multiple of the concentration and the rate of flow of urine

$$\frac{mg}{mL} * \frac{mL}{min} = \frac{mg}{min} \qquad (2)$$

If you were to divide the excretion rate of a drug by the excretion rate of creatinine, the volume of water that contains the creatinine and the drug is the same as is the time of collection. These measures will divide out leaving the following

Excretion Rate of Drug/Excretion Rate of Creatinine = mg Drug/mg of Creatinine (3)

This is the relationship that is explored in reference 1. There may be a factor here to reconcile units but you are left with the finding that dividing concentrations in the same fluid is the same as dividing excretion rates. If the excretion rate of creatinine is constant, or at least reasonably constant, then serial collections will be corrected by a constant. When log concentration is plotted against time the scale of values will be shifted but the value of the slope will be the same. Therefore, the slope of a plot of serial urine cannabinoid concentrations corrected for creatinine concentration will be an accurate reflection of the elimination rate constant of the drug and can be used to calculate the half-life of the drug.

The water volume in urine is dependent on many things, but importantly, on water intake. The body, to maintain homeostasis, attempts to eliminate as much water as it takes in. If insufficient water or fluids are ingested then an individual can become dehydrated and the consequent urine will be concentrated to conserve the body's store. To be useful as a correction factor, creatinine in urine must have some important characteristics. First, the excretion rate of creatinine must be constant. Several factors are essential for this to be true. Since the excretion rate is dependent on blood concentration the serum creatinine must be at steady state, that is, the formation rate of creatinine by the body must be the same as the elimination rate of creatinine. Creatinine is formed from creatine, which is in turn formed from amino acids, arginine and glycine. Changes in the intake of amino acids in the diet, such as the frequency one eats meat or the use of dietary supplements or weight loss strategies could theoretically influence the creatinine concentration.

Creatine is formed in organs such as the kidneys, liver and pancreas and transported to muscle for storage as phosphocreatine where it assists in muscle contraction. Creatinine is formed in the muscle and its concentration correlates to muscle mass. The extent that serum creatinine is dependent on a storage form of creatinine is a stabilizing factor for concentration and should minimize the effect of diet. If creatinine were extensively formed in other organs then creatinine might change throughout the day with meals, exercize, or diet. Of some interest is the use of large quantities of creatine by athletes and body builders. I am not aware of studies that demonstrate a marked change in serum creatinine through this practice, but if someone does know of any please let me know. While it is reasonable to expect controlled dietary intake to achieve a new steady-state creatinine concentration and make intraindividual use of creatinine measurements of continued use, a greater problem may be analytical. Many assays for creatinine lack specificity, others involve conversion to creatine and enzymatic measurement with creatine kinase. It would be expected that dietary creatine would be incompletely stored and that very large amounts of creatine would be excreted in the urine. Clearly it is important that urine creatinine measurement must be accurate to be useful in correcting urine drugs of abuse concentrations.

While serum creatinine does not change greatly as a person ages, the storage of creatine and the amount of muscle mass decreases and the glomerular filtration rate decreases with age. These combine to keep serum creatinine concentrations relatively unchanged.

For creatinine correction to be useful over time in an individual renal function must be stable. The serum concentration of creatinine is a dependent parameter and represents a balance between formation rate in muscle and clearance by the kidneys. Likewise, the excretion rate is derived from the serum concentration and the renal clearance. When there is a change in renal function then the serum concentration will be affected.

$$Cr_s = \text{Formation Rate}/Cl_{Cr} = \text{Excretion Rate}/Cl_{Cr} \qquad (4)$$

where Cr_s is the serum creatinine, and Cl_{Cr} is the creatinine clearance.

For example, a decline in glomerular filtration rate will cause a decline in creatinine clearance and, without a decline in formation rate, will produce an increase in the serum creatinine concentration. We would not expect to see a decrease in excretion rate unless we saw a total decrease in flow.

Obviously, variability is a factor we must consider and we can expect more natural variability in creatinine excretion than in the analytical variation in our drug measurement. We shouldn't expect corrected plots of drug excretion rates to have the same predictability as plots of serum drug concentrations. It is also critical to remember that in most instances the immunoassays that provide the concentration estimate are relatively non-specific. They will typically respond to metabolites as well as the target substance. A non-specific assay has significant consequences in pharmacokinetics. Metabolites can be formed from the parent drug or other metabolites and are eliminated separately. They may have individual half-lives that are longer or shorter than their precursor. At any moment in time the urine may possess a different metabolite mix as substances with different rates of excretion are eliminated. A nonspecific assay will then produce a composite result that will change based on specific cross-reactivities and metabolite concentrations. Internal consistency could be hard to establish and making judgments on a small

number of urine measurements could be quite risky. Even though many collections are plotted in reference 1 there are a number of points that appear to be divergent from the rest. It is interesting to note that better consistency seems to be present at later time points which could be due to the presence of only those metabolites with the longest half-lives.

The take home message is that concentrations of drugs in urine is only part of the answer to the question of possible drug ingestion. If the question is simply whether a drug has been taken then any concentration of drug above the limits of quantitation is sufficient evidence. If the question has to do with repeated use then more information is needed and the use of creatinine measurement does decrease the imprecision, increase the predictability and provide a better picture. To use this tool effectively we must be conscious of the factors that affect creatinine excretion, measurement as well as measurement of the drug. Since the database of excretion rates of drugs is not well documented I would not advocate use at this time unless there is an effort to evaluate the drug:creatinine ration in the context of serial measurements. It is always preferable to calculate drug excretion rates directly by keeping track of urine collection intervals and volumes.

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MATT Meeting Calendar

Critical Care and Point of Care Testing: Connecting Technology to Patient Care 19th International Symposium , September 11 - 14, 2002, Monterey, CA. Contact: AACC, 800-892-1400, or web site: http://www.aacc.org

AACC and the Association of Clinical Biochemists present**Pharmacogenomics UK: Improving Pharmacotherapy and Avoiding ADRs**, September 26-27 2002, Robinson College, Cambridge, UK, . Contact: AACC, 800-892-1400, or web site: http://www.aacc.org

Society of Forensic Toxicologists Annual Meeting, October 13-17, Dearborn, MI. Contact: Brad Hepler, 313-833-2552, website: http://www.soft-tox.org

18th International Congress of Clinical Chemistry and Laboratory Medicine
October 20-25, 2002 , Kyoto, Japan, . Contact: AACC, 800-892-1400, or web site: http://www.aacc.org

14th Annual Forensic Science Seminar, sponsored by the Milwaukee County Medical Examiners' Office, October 30-31, 2002, Milwaukee, WI. Contact: Ms. Eileen Weller, 414-223-1207.

LabMed2002 October 24-26, 2002 New York, NY Sponsored by The Alliance of Northeast Sections and the Division of Animal Clinical Chemistry. . Contact: AACC, 800-892-1400, or web site: http://www.aacc.org

Using Evidence-Based Medicine to Provide Cost-Effective Quality Care
October 30, 2002 - Chicago, Illinois, . Contact: AACC, 800-892-1400, or web site: http://www.aacc.org

The 28th Annual Meeting of the Northeastern Association of Forensic Scientists, November 4-7, 2002, Atlantic City, NJ. Contact: Christopher Huber, 609-671-0022, email**:** NO11HUBERC@gw.njsp.org

Laboratory Automation 2002: Smart Strategies for Success November 7-8, 2002
Chicago, IL, . Contact: AACC, 800-892-1400, or web site: http://www.aacc.org

Cool Tools II: New Technologies for Molecular Diagnostics November 14-16, 2002
San Diego, CA, . Contact: AACC, 800-892-1400, or web site: http://www.aacc.org

Therapeutic Drug Management Renaissance Forum 2003, January 31 – February 1, 2003, Baltimore, MD, contact: AACC, 800-892-1400, or web site: http://www.aacc.org

LabAutomation 2003, February 1-5, 2003, Palm Springs, CA. Contact: webmaster@labautomation.org

35th Annual Oak Ridge Conference - Brainstorming for Clinical Laboratories:
New Approaches to Understanding and Diagnosing Neurological Diseases
April 10-11, 2003, Pentagon City, VA, . Contact: AACC, 800-892-1400, or web site: http://www.aacc.org

Professional Practice in Clinical Chemistry: A Review & Update
April 27 - May 1, 2003, Arlington, VA, . Contact: AACC, 800-892-1400, or web site: http://www.aacc.org

American Association for Clinical Chemistry 2003 Annual Meeting, July 20-24, Philadelphia, PA. Contact: AACC, 800-892-1400, or web site: http://www.aacc.org

Presents MATT 2003

East Lansing, Michigan May 8-9, 2003

Registration Information

The meeting site is The Student union at Michigan State University. 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 15, 2003. Prices will be noted on the registration form. On-site registration will require a late fee.

Hotel Registration and Transportation

Rooms have been blocked at the Kellogg Hotel and Conference Center at Michigan State University. Reservations for rooms should be made directly with the Kellogg Center. Room Rates are $90.00 for a standard double and $99.00 for a deluxe queen. Parking is available at the Kellogg Center Parking Garage. Call 1-800-875-5090 to reserve your room. For alternate lodging options, contact Fred House.

Abstract Submission

MATT 2003 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!

Entertainment

There are a host of activities available on Campus and in the area. Miles of pathways wind around a beautiful campus and museums, fine arts entertainment, botanical gardens and golf are just a few of the amenities to be experienced.

For additional meeting information contact:

Fred House
Phone: (517) 322-5536
e-mail: HouseF@michigan.gov
fax: (517) 322-5508

Laureen Marinetti
e-mail: LMarinetti@aol.com

MATT 2003 East Lansing

MSU May 8-9, 2003

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, 2003**. 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 14, 2003.

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.

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