1st Congress of the European Confederation of Laboratory Medicine (ECLM)

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Düsseldorf, November 20 - 22, 1997

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Autorenverzeichnis

Future Management of Good Laboratory Services

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In the last years economical problems had priority in many laboratories very often leading to a reduction of resources spent for quality assessment programs. It appeared, therefore, necessary to counteract this development by reinforcing quality aspects, however, by developing new strategies. These strategies will become a major concern of laboratory management.

A working group of ECLM has developed a vision of good medical laboratory services (GMLS) including the 3 quality levels of Donabedian: structure, processes and outcome. Quality of management has been added as a further, separate level. Multidimensionality of the term quality is characteristic for the comprehensive quality processes in medical laboratories.

It is not sufficient to develop good services, if the laboratory is unable to survive. Therefore future laboratory management has to take care of survival aspects much more than it was necessary in the past.

Total quality management (TQM) is a new, recently becoming very popular management concept which is focussed on the satisfaction of the customer by motivating the employees to concentrate their efforts on this goal. TQM means a customer oriented business culture by a continuous improvement process with employees highly motivated by alteration of thinking, organization, information and rewarding. „Human resource management" leads to a new culture of communication.

Many elements of this comprehensive concept are mentioned in international norms for certification and accreditation of laboratories. Interpretation documents developed for medical laboratories by professional societies include specific customer needs, especially in the pre- and postanalytical phase, however, have to be further extended to cover all aspects of the GMLS vision.

Keywords: Total Quality Management; Laboratories.

Symposium I
Modern Aspects of Drug Testing

Drug Testing with Special Attention to the Workplace in America

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Drugs of abuse workplace testing has undergone a significant increase in the past ten years. The primary reasons for this is an effort to provide a safe drug-free environment for individuals and decrease the large costs associated with the use of drugs. It is estimated that the abuse of drugs and alcohol by employees costs American businesses over 100 billion dollars every year.

In 1969 the Federal Government mandated[1] that all individuals directly involved in public transportation be tested in accordance with strict standards and procedures. This testing presently covers 20-25 million people and requires testing in five categories: preemployment, suspicion of use, random, after accidents and return to duty after testing positive. The drugs tested include alcohol, cocaine, marijuana, amphetamines, opiates and phencyclidine. The urine specimens are collected under controlled conditions and handled using chain of custody procedures. The specimen is split into two containers at the collection site, sealed and sent to the laboratory[2]. One specimen is analyzed and the other available to be tested by another accredited laboratory if the result is challenged. The testing carried out by the laboratory requires the initial use of immunoassay and if positive confirmation by gas chromatograph-mass spectrometry. The concentration of the drug in the urine must exceed a predetermined cutoff for both methods in order to be reported as positive. Testing is also carried out to ensure that the specimen has not been intentionally adulterated. The results are sent from the laboratory to a physician for interpretation and then to the company for appropriate action. Although Federally mandated testing comprises less than 40% of the workplace testing these procedures and methods are generally followed by all companies.

This discussion will deal with the methods and procedures utilized for collection, testing, result reporting and the accreditation of the laboratories. Statistics will be presented that asses the impact of the testing.

References

1. DOT Final Regulations, Federal Register, Friday, December 1, 1989, 49 CFR part 40, pg. 49854-49876.
2. Procedures for transportation workplace drug and alcohol testing programs, Federal Register, Part Viii, 49 CFR 40, Friday, August 19, 1994, pg. 42996-43019.

Keywords: Substance Abuse Detection; Accreditation.

Drug Testing with Special Attention to the Workplace, Recommendations in Europe

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The increase in the abuse of illicit drugs in recent years is a matter of growing concern within society. Demand-reduction strategies are based on prevention, treatment and education programmes, including more and more *drug abuse testing (DAT)*. Therefore, DAT, which mainly consists of urine analysis, has been progressively extended from its original clinical setting to other sectors like social medicine, *workplace safety* and forensics. Several anonymous surveys (e.g. in Sweden and Switzerland) have shown that the majority of the questioned employees is for example in favor of eliminating drug use from the workplace, thinks that DAT is a good method to achieve a drug-free work-place, and is not offended giving an urine sample. But for DAT at the workplace (e.g. public transportation, industry, construction, military, school) - where a positive result can have a serious impact on the individual's freedom and livelihood - ethical, political and economic issues have to be considered. As the European countries have different approaches to the drugs of abuse problem, different drug policies and legal systems, each country has also a different approach to DAT. Consequently, the European Union (EU) decided to convoke 1996 in Barcelona an European toxicology expert group, representing 25 countries and/or professional organizations as well as the United Nations Drug Control Programme (UNDCP), to harmonize DAT in Europe. The resulting *EU recommendations* were especially focussed on DAT at the workplace, covering

(1) Sample handling and chain of custody: to ensure the donor's privacy, the sample's integrity and to maintain confidentiality envolving administrative tracking of all processing steps; sample splitting (aliquot A and B) is preferred.
(2) Cut-off values: for screening and confirmation, e.g. 300 µg/L opiates and 200 µg/L total morphine.
(3) Analytical methodology: preliminary screening (validated group-specific immuno-assays) and confirmation techniques (chromatography, quantitative GC/MS preferred).
(4) Educational requirements and aspects: permanent education of all personnel.
(5) External quality assessment programmes and laboratory accreditation: proficiency testing programmes, accreditation according to EN45001/ISO Guide 25.

Keywords: Substance Abuse Detection; Accreditation.

Clinical Applications of Testing the Methadone Metabolite

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Screening urine samples from patients being treated with methadone is used as a clinical tool for evaluation compliance. Over the past two years, cases have been identified where patients known to be continually methadone produced negative urine screens using conventional immunoassays. We have evaluated the clinical use of immunoassays specific for the principal methadone metabolite, 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP), and compared it to an immunoassay for methadone in 1495 patient urine samples. The incidence of EDDP positive samples were similar to the incidence of methadone positive samples. However, 19 samples tested negative for methadone but positive for EDDP while 6 samples were similar to the incidence of methadone positive samples. However, 19 samples tested negative for methadone but positive for EDDP while 6 samples contained only methadone. All the specimens, which screened negative for methadone but positive for metabolite, were confirmed by GC/MS to contain EDDP. We believe these are from patients who exhibit either genetically determined or drug induced rapid metabolism of methadone and for whom a methadone screen. used alone, would return false negative results and a possibly incorrect conclusion. The clinical utility of screening for methadone , as well as methadone metabolite, in the context of methadone treatment will be discussed.

Keywords: Methadone/urine; Compliance.

Immunoaffinity Purification of LSD Prior to Confirmation by GC/MS

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In order of simplify GC/MS confirmation of LSD, we developed a sample preparation method based on immunoaffinity chromatography. A highly-specific monoclonal antibody to LSD was attached to cyanogen bromide-activated Sepharose 4B. Urine samples contained LSD were incubated with affinity resin, the resin was washed and bound drug eluted in a small volume of methanol. Greater than 95% recovery of LSD added to drug-free urine was obtained; recovery could be monitored by addition of lysergic acid methyl-propylamide (LAMPA) or deuterated LSD as in-

ternal standards. Recovery of the weekly cross-reactive LSD metabolite, 2-oxo, 3-hydroxyl LSD was 65%. Affinity resin extracts were derivatized for GC/MS analysis with N, O-bis (trimethylsilyl)trifluoro-acetamide (BSTFA) and subjected to gas chromatography on a Model DB5-MS column (15x0.2mm x 0.33µ, J&W, Folsom, CA). Immunoaffinity extracts gave dramatically reduced background signal as compared to conventional solid-phase extraction. An LOD of 50 pg/ml and an LOQ of 61 pg/ml were obtained using a Hewlett Packard model 5971 mass spectrometer with electron ionization. The immunoaffinity resin also appears to extract metabolites of LSD. Urine samples testing positive for LSD by immunoassays and GC/MS were extracted by the immunoaffinity method and further by reserve-phase HPLC. Testing of the resulting fractions by immunoassay (CEDIA®method, Boehringer Mannheim Corp.) showed an immunoreactive peak eluting earlier than LSD, and separate from the peak resulting from injection of 2-oxo, 3-hydroxy LSD. Studies to characterize the metabolite further by mass spectrometry are ongoing.

Keywords: Lysergic Acid/urine; Chromatography, Affinity; Mass Fragmentography.

Cedia® Sample Check Assay for Urine Drug Testing

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The CEDIA homogenous enzyme technology has been utilized to develop an optimized assay system for the detection of urine samples which depress the signal of CEDIA DAU assay. In the CEDIA method, the enzyme β-galactosidase is split into two inactive fragments: a large fragment (EA) and a smaller polypeptide (ED), which can spontaneously recombine to form active enzyme. This assay will detect if the sample contains a material which either inhibits the formation of active enzyme or inhibits the turnover of substrate by the enzyme. The assay is particularly suited for detecting many common adulterants that have been used to generate false negative results in the immunoassays used for rapid screening of large numbers of urine samples. For example, the assay will detect detergents, bleach, drano, ammonia, hydrogen peroxide and glutaraldehyde.

On BM/Hitachi analyzers, the assay is calibrated with a normal urine sample that is assigned a value of 100. A sample that completely inhibits signal generation is assigned a value of 0. These two values are used to generate a linear dose response curve that is used quantify unknown samples as a percent of normal.

In a normal range study of the 1086 samples fell within the range of 82 to 103% of normal. Two samples had rates below this range. Any sample having a result outside the normal range should be analyzed further for possible adulteration and at the very least another sample should be obtained prior to reporting a result. A control, at a value of approximately 75%, containing a detergent as an adulterant is available. Intra and inter-assay precision CVs of less than 2% were obtained on the control using an NCCLS protocol. Minimal to no interference was observed for acetone, ascorbic acid, ethanol riboflavin, creatinine hemoglobin, human serum albumin, gamma globulin, galactose, glucose, oxalic acid, NaCl, urea, or pH from 3-10.

Keywords: Substance Abuse Detection; False Negative Reactions.

Symposium II
Diabetes, Point-of-Care Testing

Point-of-Care Testing in Diabetes Mellitus: Blood Glucose Determination

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An immediate and reliable blood glucose (BG) determination is often required in the treatment of diabetic in- and outpatients but not sufficiently provided at the point of care by the standard clinical chemistry lab for various reasons. This has resulted in the widespread use of BG-test systems originally developed for self-monitoring of BG by the diabetic patient. But these BG-test systems are not as reliable as established lab methods within the clinical relevant BG-range (30-350 mg/dl), particularly in the hypoglycemic range, and do not provide a quality control (QC) comparable to the one required for clinical chemistry lab BG-methods. To avoid serious clinical consequences due to insufficient BG-results at the point of care several approaches have been tried:

the handling of the clinical chemistry lab method at the point-of-care site by specially trained and supervised members of the diabetes treatment team,

the combination of immediately available BG-self monitoring test systems with delayed confirmation by standard lab methods and

the use of a BG-test system that combined the ease of handling and the BG-availability with the reliability of a clinical chemistry lab method including its standards of QC management, i.e. the HemoCue-B glucose test system.

While the approaches 1 and 2 have obvious limitations #3 offers promising perspectives for more widespread applications.

Therefore, the practicability of the HemoCue B glucose system under point-of-care conditions has been examined for 4 months at 2 metabolic wards by 34 nurses at day and night. The overall positive experience of the participating nurses after 11.500 BG-determinations will be presented in detail. Special supervised repeated training including the daily QC management was necessary and required on average 35 min./nurse. It was essential to instal a supervisor experienced in the detailed handling and programming of the test system and QC control.

Compared to the costs of a BG-measurement in the clinical chemistry lab the higher price of the HemoCue B glucose micro cuvette is already more than balanced by the price of the lab test system. In addition, there have been considerable savings due to lesser emergency time use of the lab technician on duty.

The cost/benefit ratio of the described BG-determination at point-of-care conditions in a hospital clearly supports the use of a BG-test system like HemoCue B glucose provided nurse skill training and QC-management are taken care appropriately.

Keywords: Blood Glucose; Point-of-Care Testing; Blood Glucose Self-Monitoring.

Blood Glucose Determination: Point of Care Testing and Self-Monitoring in the Future

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Monitoring of glycemic control is one of the major preconditions of intensified insulin therapy and thus of diabetes care. In the past researchers concentrated on s.c. electrodes for measurement of the glucose concentrations in the interstitial fluid of the s.c. tissue. However, up to now none of the implantable sensors has worked on the long run in humans with sufficient reliability. In order to circumvent the problem of biocompatibility a number of non-invasive or minimally invasive methods for glucose sensing are under development. Perfusion of a thin microdialysis fibre, which is inserted in the s.c. tissue, with an isotonic glucose-free solution resulted in diffusion of glucose through the dialysis membrane. This approach allows glucose sensing outside the body and can be assumed to be available in the near future. Another approach is to remove fluid transdermally, assuming blood glucose being in equilibrium with the extracellular fluid. Whether this measurement will be as accurate as current glucose meter techniques is uncertain. Optical glucose sensors have two great advantages: the possibility of continuous glucose monitoring and the non-invasiveness of the measurement. Measurement of absorption spectra is hampered by the fact that only light in the near-infrared region between 900 and 1300 nm can penetrate into the skin. However, glucose has no specific absorption properties in this frequency range. This and a number of other inherent problems has not allowed a reliable blood glucose quantification by this approach so far. Variation in blood glucose also changes the light scattering properties of the skin. Incoming light is scattered at the boundaries between substances with high and low refractive indices. If the ratio of the refractive indices is lowered by increasing the glucose concentration of the solution with scattering particles, the scattering properties are also lowered. With a so far complex and bulky experimental set-up we were able to quantify the effect of blood glucose changes on the light scattering properties of the skin tissue of patients with type I diabetes mellitus during glucose clamp experiments. As it was predicted by theoretical and in-vitro investigations, the rapid increase in blood glucose caused a substantial decline in the light scattering coefficient of approximately 0.7% per 5.5 mmol/l change in blood glucose. Thus, monitoring of changes in light scattering in tissue is feasible for a continuous blood glucose sensor. A good intra- and interindividual reproducibility of such changes in the scattering coefficient was observed. However, other physiological processes influence light scattering as well. Detailed research is necessary to compensate for such other interfering processes. In summary, a number of new technologies for glycemic control are in development. Before a reliable continuous glucose monitoring under daily life conditions will be possible, a number of problems has to be solved.

Keywords: Blood Glucose; Refractometry; Point-of-Care Testing; Blood Glucose Self-Monitoring

Point of Care - Analytes in Urine

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Until glucose testing in whole blood became widely available, urine testing for glucosuria was an essential parameter for monitoring of diabetic patients. Since the first test strips had some problems with interfering substances in urine especially ascorbic acid, some improvements have been made concerning specificity. Dipstick testing of urine for ketone bodies added more information for patients and physicians about metabolic situation. The American Diabetes Association states in its position paper about tests of glycemia in diabetes that urine glucose testing is a good measure of glycemia during the urine collection period or as an

second choice glycemia testing in patients who cannot or will not perform self monitoring of blood glucose. Urine ketone testing is stated to be an elementary part of monitoring, particularly in IDDM patients. POC testing for proteinuria soon became an important parameter in diabetes care. The conventional dipsticks for urine testing use the so-called pH-indicator-error of proteins method for detecting total protein in urine. This method does not detect total urinary protein but preferentially albumin and underestimates some proteins e.g. globulins and Bence-Jones proteins. Additionally analytical sensitivity is sufficiently low to detect an overt proteinuria but so called „microalbuminuria" cannot be discovered. Several studies have proofed that early detection of „microalbuminuria" and therapeutic intervention can prevent renal failure, one of the most serious late complications of diabetes. Several special dipstick tests which specifically detect small amounts of albumin in urine have been developed and proofed their usability to screen diabetic patients for „microalbuminuria". Since diabetic patients often suffer from infections of urinary tract, that should be carefully be treated, dipstick tests for leukocytes, nitrite and pH are useful parameters of POC urinary testing. Some years ago testing of specific gravity of urine was added to dipsticks, using a cation exchanger and a pH indicator to measure the free cations in urine. But in diabetic patients not only cations but especially glucose accounts for urine specific gravity therefor this parameter should be interpreted carefully in presence of glucosuria.

POC-testing of several parameters in urine is - or should be - an important part of diabetes care.

Keywords: Reagent Strips; Point-of-Care Testing; Proteinuria.

Quality Assurance of Glucose Analysis Using Blood Glucose Meters

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The focus of attention in laboratory diagnostic in primary health care world wide is regarded to be orientated to capillary whole blood glucose testing. Standardization bodies take care about these systems, for example the German Institute for Standardization DIN/NAMed C10: „Performance evaluation procedures for IVD medical devices including IVDs for self-testing"; Netherlands TNO Centre for Medical Technology: „Quality Guideline Non-implantable portable Blood Glucose Monitors for Self-monitoring"; Canadian Standards Association CSA Z316.4-94: „Performance Specifications for Portable Whole Blood Glucose Monitoring Systems for Use in Diabetic Management"; CEN TC 140/WG 8: „General Requirements for IVDMDs for self-testing" and „Blood glucose meters for self testing"; ISO/TC 212/WG3: „Determination of desirable performance criteria for blood glucose monitoring systems for use in diabetes management". The latest draft of WG 3, rev. 2.0 has been submitted to the International Organization for Standardization, ISO/TC 212 by Dr. Müller, Roche Boehringer, and an analogous proposal submitted for standard to the European Standardization Organization CEN/TC 140/WG 8 by Dr. Stinshoff, Dade AG., the author being member of both working groups.

The revised draft proposal for a Directive of the European Parliament and Council for revision of the proposal for a directive on in vitro diagnostic medical devices dated 18-03-1997 covers the original demands to manufacturers of IVDs for self testing practically unchanged. Measures of Quality Assurance have to be provided by manufacturers for the use in hands of lay people and (at part) of physicians likewise.

INSTAND reg.ass. and the author have organized external quality assurance studies since 1990 and EQA surveys since 1995, in 1996 with the National Reference Laboratory of IRAN, Teheran and in 1997 with SEKK, the official organizer of NEQAs in the Czech Republic, Pardubice. INSTAND reg.ass has collected unique knowledge on Quality Assurance with these devices meanwhile. Examples of results of evaluation, Internal Quality Control and External Quality Assurance will be presented in this lecture.

Keywords: Blood Glucose Self-Monitoring; Quality Control.

Point of Care Testing, Self-testing and the IVD-Directive

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The IVD Directive will be designed to guarantee the safety and efficacy of reagents and instruments for laboratory medicine (IVD devices). This follows from Considerants 3,5 and 7 in the introduction of the Directive, and especially from the Essential Requirements listed in Annex 1. The Essential Requirements encompass an exhaustive list of safety and performance aspects that IVD devices will have to comply with. This includes, among others, stability, accuracy, repeatability and traceability of calibrator and control material values (Annex 1, section 3). Compliance with the Essential Requirements has to be validated and documented (Annex 3, section 3).

Point of care devices are not specifically mentioned in the Directive. However, frequent reference is made to the 'intended purpose and anticipated use of the device' (Annex 1, sections 4-8, 11, 13). Devices for point of care testing thus will have to be designed and validated for safety and efficiency in the point of care environment.

Self-testing devices, in contrast, are specifically quoted. Emphasis is put on their safe and easy use, the understandability of their instructions for use, the validation and correct interpretation of results and the requirement of medical expertise in case of unexpected results (Annex 1, sections 12 and 13). In addition, the design of devices for self-testing has to be examined and certified by an independent, qualified test house, a Notified Body (Annex 3, section 6).

Keywords: Point-of-Care Testing; Self-Monitoring

Symposium III
Preanalytical Factors

Unexpected Results from the Laboratory: Case Reports on Non-analytical Variables in Laboratory Medicine

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Strategies are needed to detect non-analytical variables that can impact upon the accuracy of clinical laboratory results. One such strategy is the use of delta checks which involves verifying the results obtained with at least two different analytes that are together expected to be affected in parallel when a disease is present. A negative anion gap or an unusually low or even zero calculated low density lipoprotein (LDL) level is a definite indicator of a non-analytical variable contributing to the spurious result. When confronted with a clearly abnormal result the question that needs to be asked is whether that test result is possible or impossible in terms of compatibility of life. An accurate case history including information on patients diet and life style is useful in isolating a non-analytical variable that is contributing to the laboratory result. Awareness that elevation of certain chemical analytes such as glucose and sodium can affect hematological measurements such as the mean corpuscular volume should be kept in perspective. Attention should also be given to specimen collection variables and analyte instability.

Case reports will highlight presence of non-analytical variables using strategies outlined above.

References

1. Guder WG, Narayanan S, Wisser H, Zawta B. Samples from the patient to the laboratory. The impact of preanalytical variables on the quality of laboratory results. GIT VERLAG, Darmstadt. 1996.
2. Narayanan, S. Interpretation of laboratory data: problem solving using case histories . Proc 7th Asian-Pacific Congress Clin Biochem, Bangkok, Thailand 1995: 85-90.

Keywords: False Positive Reactions; False Negative Reactions; Diagnostic Errors.

Quality Criteria: From Information to Organization

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In the first age of our profession - lasting into the seventies - we were preoccupied mainly with analytical difficulties. With the appearance of sophisticated analyzers those analytical problems seem to be mostly solved. The term „difficult determination" has receded into some special areas as absorption or some PCR techniques.

The second age has been characterized by the recognition of the impact of preanalytical factors on result quality. It has produced numerous table works on pertinent factors, one of the latest of them compiled under the auspices of our chairman. And it has culminated in countless educational events trying to convince every person involved of the importance of preanalysis. First our own colleagues (the easiest task), then our technical assistants, finally nurses and doctors (mostly without success).

In the nineties, at a time when every profession in the health business concentration on its core tasks due to cost constraints, the readiness of acquiring extra-functional skills is declining. So is sample quality. In addition, nursing tends more and more to concentrate on social aspects, neglecting scientific ones. This situation forces us to diversify our efforts in the preanalytical field: Direct our educational efforts to nursing staff on those analytes which are tested on the pont of care by non-specialized personnel using dedicated equipment (e.g. i-stat). For all other purposes it seems mandatory to develop - together with industry - means and processes able to cope with preanalytical intricacies even without the performing person knowing about them and how to avoid the pitfalls. Examples in this field include syringes, anticoagulants, sample containers, urine or other body fluid sampling devices, and sample handling by robotics.

Keywords: Specimen Handling; Education; Automation.

Quality of Samples: Defining Size of Laboratory Blood Samples

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Modern analyzers generally require only small amounts of analytical sample. As blood losses from phlebotomy may cause iatrogenic anemia, it is an ethical obligation to ensure that excessive amounts of blood are not obtained by the laboratory [1]. A working

group on preanalytical quality of the DGKC and of the DGLM has proposed an algorithm to calculate the optimal size of the laboratory blood samples [2]. It considers (i) volume of analytical portion, (ii) dead volumes, (iii) hematocrit value, and (iv), volume of analytical sample eventually needed for replicate analyses:

$$Volume_{laboratory\ blood\ sample} = 2 \times ([\{V_{analytical\ portion} + D_{pipettor}\} \times R] + D_{PRIMARY\ TUBE} + D_{secondary\ cup})$$

V, volume; D, dead volume; R, replicates; the factor of 2 considers a packed cell volume of 0.5.

The following measures may help to minimize the volume of the laboratory samples:

- Processing of primary sample tubes,
- Use of heparin plasma instead of serum,
- Preference of sample tubes with low diameter,
- Use of separating gels or other mechanical barriers.

The following standard volumes for primary blood samples are recommended:

- Clinical chemistry: 4-5 ml (if plasma is used: 3-4 ml). This volume will be sufficient for at least 95% of the tests usually requested.
- Hematology: 2-3 ml EDTA blood;
- Coagulation testing: 2-3 ml citrate blood;
- Immunoassays: 1 ml for each 3-4 immunoassays;
- Blood gas analysis: 1 ml;
- Blood sedimentation rate: 2-3 ml.

The documentation of analytical procedures should always list the volume of analytical sample needed. It is hoped that the recommendations given will encourage the laboratories to review their minimum sample volumes for phlebotomy.

References

1. Second draft ISO/WD 15189: Quality management in the clinical laboratory. 1997.
2. Guder WG, da Fonseca-Wollheim F, Heil W, Müller-Plathe O, Töpfer G, Wisser H, Zawta B. Wahl des optimalen Probenvolumens. Deutsche Gesellschaft Klinische Chemie Mitteilungen 1996;27:106-7.

Keywords: Blood Specimen Collection.

Drug Interference - The Unsolved Problem

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Drug interferences are a well known problem in interpretating laboratory results if they do not agree with the clinical situation. Frequently the clinician does not believe the results of the laboratory and will send a fresh sample to the laboratory. If the previous results are not confirmed by the second analysis the false result will be perceived as "lab mistake". In this situation the laboratory must consider a drug interference as a possible reason for the variation in results. The conversation between the laboratory and the clinician starts.

With selected case studies we will learn and better understand why interpretation of an erroneous result caused by interfering substance is important. Furthermore knowledge of the causative mechanism is essential to clarify the contradictory laboratory results compared to the clinical picture.

Keywords: Drugs; False Positive Reactions; False Negative Reactions; Diagnostic Errors.

Endogenous Errors Caused by Serum Constituents, Antibodies, and Anticoagulants

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Serum obtained from whole blood by centrifugation after completion of the platelet and clotting factor coagulation process is still the standard analytical sample in clinical chemistry, immunochemistry, and other parts of laboratory medicine. In contrast to plasma, which represents the physiological extra-cellular fluid of blood, serum creates several artefacts which have to be considered.

Thus, lysis of platelet leads to platelet count-dependent increases in potassium, phosphate, and some enzymes. Acid phosphatase and neuron-specific enolase can therefore not be correctly determined in serum.

On the other hand, plasma cannot be obtained without addition of anticoagulants during blood sampling. Even international standardization of anticoagulants as defined in ISO 6710 cannot prevent interference due to added anticoagulants and/or preservatives. Thus several assays exhibit interference by fibrinogen and/or heparin, By comparing results of all diagnostically relevant tests from heparin plasma compared to serum in normal and diseased patients, plasma can be recommended for most analytes because of the following advantages compared to serum:

- Waiting for blood to clot is eliminated: centrifugation period can be reduced considerably by increasing rotation speed.
- Approximately 15-20% more plasma than serum can be obtained from whole blood.
- Post-centrifugal coagulation occurring in serum of heparinized patients is prevented in plasma.
- Lower risk of hemolysis and platelet-independent results for potassium, phosphate, LDH, and other platelet constituents.

On the other hand, introducing plasma needs careful analysis of the test methodology used to exclude cation and anticoagulant or fibrinogen interferences. Plasma can be recommended as the preferential analytical sample in clinical chemistry. Information concerning the analytical procedure should contain information on the applicability of plasma samples using the various anticoagulants.

Keywords: Anticoagulants; Antibodies; Plasma; Serum.

Symposium IV
Consolidated and Integrated Automation Systems

Introduction

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The third generation of laboratory systems includes not only reagent kits and analytical systems. It also covers the whole range of pre- and postanalytical procedures such as sample sorting, decapping, centrifugation, aliquotting, analyzer loading and unloading as well as sample storage and retrieval.
The two key words of this new type of automation are:

- Consolidation of analytical instruments (so-called clusters or workcells)
- Integration of analytical instruments into an automated pre- and postanalytical workflow.

Examples will be demonstrated in a short video documentation called "The third generation of laboratory systems".

Keywords: Automation; Laboratories.

State-of-the-Art in the Development of Consolidated and Integrated Laboratory Systems

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External factors like cost pressure, changed reimbursement structures etc. strongly enforce the restructuring of laboratories to enhance their process efficiency and quality. This restructuring will provide the transition from organization by technology into organization by process.

Consolidation and integration are the key words for system development activities, which support the needs of those organizational changes.
Consolidation means to combine analytical technologies into work areas covering a broad spectrum of analytes from different disciplines such as clinical chemistry and immunochemistry.

Integration means the combination of such work areas with the mechanization of pre- and post-analytical work steps like centrifugation, aliquotting, sorting etc. to support the sample delivery process within the laboratory.

The combination of consolidation and integration will lead to solutions for *total laboratory automation.*

State-of-the-art in development of consolidated and integrated laboratory systems is the modular approach, which allows the stepwise entry into laboratory automation and provides flexibility to follow changing requirements.

A typical example for this new development strategy is shown by the new Boehringer Mannheim/Hitachi system MODULAR. This system will initially provide a modular platform to consolidate clinical chemistry and immuno-chemistry and to integrate the pre-analytical work steps centrifugation, de-capping, aliquotting and tube labeling.

Keywords: Automation; Laboratories, Specimen Handling.

Systemization in the Medical Laboratory

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All laboratories are faced with increasing workloads and diminishing financial resources. These stimulate the need to rethink laboratory operation and organisation. In hematology during the past 30 years while workbench automation has increased, the potential for an automation cycle (starting with patient specimen collection and transportation and ending with the trans-mission of meaningful reports to the clinician) has received scant attention.

The technology now exists to change this through the process of systems integration, the harnessing of robotics and information technology not simply within the laboratory but on a hospital-wide basis. In order to achieve this the laboratory must establish an analytical platform capable of interfacing seam-lessly with mechanical specimen transportation and afferent and efferent computer links. This objective may be achieved by one of two routes, either by *Total Laboratory Automation* (TLA) or alternatively by a *Modular Automation* (MA) approach.

Toa Medical Electronics offers potential platforms for either approach with the Sysmex HST as the basis for TLA or the Sysmex SE-Avante for the modular approach. A powerful new data processing package (PC-DPS) can interface with either.

Keywords: Automation; Laboratories, Specimen Handling; Automatic Data Processing.

Laboratory Automation: Planning, Implementation, and the Future

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For twenty years or more, we have seen advances in the integration and automation of manual laboratory procedures. Instruments such as the Technicon Auto-Analyzer and Coulter® S are representative of those early efforts. About ten years ago, Japanese scientists such as Dr. Masahide Sasaki and entrepreneurs such as Teruaki Itoh extended the concept of automation beyond the single instrument. Today, automated transport and communication systems link entire laboratories into one coherent mechanism.

It is now possible to purchase everything from a simple pipetting station to a completely integrated, multi-disciplinary, transport system. Understanding the laboratory's current situation, refining existing processes, and setting definite goals are all critical to a successful implementation. Computer modeling may help both in the design of a system and in the prediction of the improvements to be gained from automation.

Future developments in laboratory automation will include more integrated methods to communicate patient information and to control operations. Internet links and enterprise-wide intranets will allow distant facilities to be controlled and monitored from a central location.

Keywords: Automation; Laboratories, Specimen Handling; Computer Simulation.

Laboratory Automation: a Stepwise Approach

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A viable strategy for Laboratory Automation was recently introduced. The focus of this strategy is to explore and implement Lab Automation in a step by step process.

Concepts like Total Lab Automation (TLA) are not the only solutions available. Laboratories must examine the areas of the laboratory that have the greatest impact in terms of efficiencies. Generally, data indicates that Front-End automation has the greatest impact on efficiencies.

The next area that deserves focus is the actual processing of samples: instrumentation and their configuration within the laboratory. Consolidation of workstations within the lab is a major priority. Examples include Abbott's ARCHITECT system, Abbott's Cell Dyn 4000/ slide maker strainer, the Sysmex HST Alpha system and the Coulter Gen-S S*SM. Such work cells should be modular building blocks that allow expansion of instrument capabilities while maintaining a single user interface with the analyzer.

As laboratories consolidate, so do vendors. The providers of laboratory instrumentation must provide solutions for customers that include both Front-End systems and Workcell analyzers. Total lab Automation (TLA) is here and has its place, but for the vast majority of labs, a more flexible solution is the key to long term viability.

Keywords: Automation; Laboratories, Specimen Handling; Automatic Data Processing.

Preparing Your Laboratory for Automation

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Many laboratories worldwide are challenged to maintain quality and services and improve productivity. An example of how productivity was improved in preparing for robotic automation of the laboratory will be discussed.

The first phase was to modernize the analyzers so that they can do primary tube sampling. The analyzers need to be full menu random access systems that can be electronically programmed from the laboratory information system. This improves the efficiency of the workstations and reduces the labor required to run the tests.

The second phase was to improve the information flow from the point of order to the point of report generation. Examples of solutions used to improve information flow and reduce labor will be presented.

The third phase was to physically re-arrange the laboratory so that central processing and the high volume analyzers are arranged in a core lab configuration. An example arrangement of a core laboratory and the flow of samples will be discussed.

Productivity metrics will be discussed that are used to evaluate laboratory efficiency. This laboratory has doubled its volume while reducing the number of employees.

With these improvements this laboratory is now well set up to automate central processing as the volume justifies the investment.

Keywords: Robotics; Automation; Laboratories, Specimen Handling; Automatic Data Processing.

A New Approach in Laboratory Automation

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Successful laboratory automation requires a new approach, a new way of thinking about the laboratory as an integrated system whose product is information. This is equally true for both automated work cells and total automation systems.

Successful laboratory automation is not simply the incorporation of robotic hardware to reduce labor costs, but rather the application of process simplification, intelligent automation products and vendor partnerships to improve overall productivity.

Product requirements to address the new integrated laboratory are fundamentally different than traditional system requirements. Automation products must enhance the overall ease of use and productivity of the system, while still complementing the inherent user friendly features of the instrumentation. This includes true automation-ready analyzers, intelligent process management software and flexible automation track systems.

The elements required for successful laboratory automation implementation, examples of successful installations and future product direction will be discussed.

Keywords: Automation; Laboratories; Automatic Data Processing.

A Modular Platform for Pre-analytical Automation

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The ongoing concentration process in laboratory medicine has created an urgent need for cost-effective automation of labor-intensive tasks in the pre-analytical process. Flexibility and adaptability to future analyzer generations are becoming major issues of pre-analytical automation, in addition to the traditional challenges of laboratory automation such as sample throughput, turn-around times, and return on investment. The major dilemma for many laboratories is that pre-analytical automation must be installed right now, while the next generation of consolidated analyzer clusters is not available yet.

Based on their broad range of liquid handling instruments and micro plate devices, the TECAN group of companies has always marketed customer-specific solutions. The flexibility and experience needed for traditional tasks such as sample splitting and ELISA assays can now also be found in TECAN's new concept for automation of the pre-analytical process, which will be based on modular work cells.

Different work cells are scheduled. As a first step an aliquotter and secondary tube labeler will be launched, followed by other modules such as a sorter, decapper and fully automated centrifuge. All work cells will able to handle different types of sample racks and have open interfaces to transport systems which can also be provided by TECAN. The work cells are designed in such a way that they can be combined to offer a solution to each and every type of laboratory organization. The solutions provided by TECAN will be based on thorough sample flow and simulation studies.

Keywords: Automation; Laboratories, Specimen Handling.

Laboratory Automation: State of the Art and Trends

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Laboratory automation tailored to almost any laboratory budget is beginning to appear on the market. Successful total laboratory automation (TLA) systems have been installed in over 18 hospitals and reference laboratories across North America and several installations are under construction in Europe. Most laborato-

ries are predicting 2 to 3 year pay back for their automation investment.

While total laboratory automation (TLA) systems initially caught the attention of most clinical laboratories, it is now clear that the TLA will not solve the automation needs of medium to small hospitals. Modular automation will allow laboratories to adopt a stepwise approach to pre-, peri-, and post-analytical processing. Novel technologies such as automated centrifuges, automated microscopes, sample aliquotters, mobile robots, and analytical work cells will provide "focused automation" aimed at labor intensive tasks.

Laboratories must implement process control, process management, and process analysis software before they can realize the full value of their automation hardware. Laboratory information systems (LIS) do not have the necessary machine intelligence and input/output capabilities to control automation systems. Software must become sophisticated enough to link, coordinate, and optimize the various activities taking place in the automated laboratory including point-of-care testing.

The next challenge that will face clinical laboratories is providing near-patient laboratories with wide menus and rapid response. Only rapid response laboratories can provide the necessary turnaround time and low costs to maximize the efficiency of patient care. Near patient automation will create the virtual laboratory, which provides its services where and when it is needed at a cost of less than half of a centralized laboratory.

Laboratory automation, process control, and robotics will provide new standards of quality and throughput for clinical laboratories. In the future, laboratories will be configured around a specialized core with real-time connections to rapid response laboratories that will perform much of the routine work.

Keywords: Automation; Laboratories, Robotics, Pont-of-Care Testing; Automatic Data Processing.

Symposium V
Quality Specifications in Laboratory Medicine

The Need for Numerical Quality Specifications in Laboratory Medicine

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The several types of stakeholder in laboratory medicine have very different views of which characteristics constitute good quality results. The customer (patient and health care professional) could stress, e.g., reliability and timeliness while the administrator looks at costs. In any case, the properties expressed on an ordinal scale such as 'poor' and 'good' should be related to quantities with numerical values to allow monitoring.

The reliability of laboratory data is influenced by many variables during the preexaminational, examinational, and postexaminational phases of production. The combined effects determine the accuracy of measurement that has two aspects, namely trueness related to systematic error and expressed as bias, and precision related to random error and expressed as, e.g., standard deviation.

Trueness requires metrological traceability to the highest possible reference and precision requires an uncertainty budget according to the International Bureau of Weights and Measures. An examination procedure should have been purged of known biasses, but its quality control system may have separate control rules for systematic and random effects. With the measurements in statistical control, the symmetric uncertainty measure applies.

The setting of an allowable uncertainty limit depends on intra- and interindividual variabilities, clinical setting, technical possibilities, and resources. Implementation of a chosen examination procedure is linked to a reference examination system which provides documentable quality.

Keywords: Quality of Health Care; Quality Control.

Quality Specifications in Laboratory Medicine: Solutions for Qantitative Analyses

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Many strategies have been suggested for the setting of quality specifications for the performance characteristics of quantitative tests: all have advantages and disadvantages.[1] The best approach must clearly be to consider the ramifications of test performance on clinical utility.

Irrespective of the supposed problem for setting quality specifications that test results are used in many clinical situations, the aspirations must be to ensure that the dispersion of the single result is not made unduly large through analytical precision, that a change in serial results does reflect patient improvement or deterioration and not simply analytical random error or changes in bias, and that common population-based reference values can be used throughout a geographical area. To achieve these laudable aims, it is widely agreed that *desirable* performance is

- precision must be < 0.50 within-subject biological variation and bias must be < 0.25 group [within- plus between-subject] biological variation.

The main problem with these general goals are that they may appear too stringent or too loose. Where they are too stringent and cannot be achieved with current technology and methodology, the multipliers for interim *minimum* specifications for precision and bias are 0.75 and 0.375 respectively. Where they seem too loose and are easily achieved with current technology and methodology, the multipliers for *optimum* specifications for precision and bias are 0.25 and 0.125 respectively.

Expansion of these concepts mean that quality specifications solely based on biology can be easily generated for use both for reference methods and as fixed limits in external quality assessment.

Reference

1. Fraser CG. Clin Biochem Revs 1996;17:109-114.

Keywords: Quality of Health Care; Quality Control.

Approach to Goal-Setting for Tests Measured on Ordinal Scale

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Whereas analytical quality goals (quality specifications) for medical tests measured on ratio scales are numerous, no analytical quality specifications have been published for the ordinal scale. Measurements performed as real ordinal measurements, e.g. 0 and 1 (negative or positive) and where the underlying scale is a ratio scale, are dealt with here.

As the underlying scale is a ratio scale, any sample to test must have a defined (known or unknown) concentration for which the measurement on the ordinal scale is either 0 or 1. By repeating the measurement of a sample the results may be both 0 and 1 and the fraction of positive results can easily be calculated. If, further, a series of samples with increasing concentrations are tested several times each on the ordinal scale, then the fraction of positive results can be plotted as function of concentration displaying a sigmoid curve. This may be approximated by a cumulated Gaussian distribution with the parameters mean and s and plotted on a probit scale as a straight line, whereby, fewer points are needed.

The basis for evaluation of the analytical quality specifications is the clinical goal, defining the probabilities for detecting and not detecting well defined concentrations. These lines are drawn in the probit plot and the lines characterizing the tests (fraction positive as function of concentration) are drawn. The fractions must exceed the clinically defined probabilities within the two concentration limits if the test should fulfil the criteria. By this method the number of experimental data can be reduced considerably compared to a direct test of the clinical goals. The principles for evaluation of analytical quality specifications based on the clinical goals are applied to a test for early detection of pregnancy.

Keywords: Diagnosis, Laboratory; Statistics; Pregnancy Tests, Immunologic.

Quality Specifications for Analyses Performed Outside the Main Laboratory

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When analyses are performed outside the main laboratory e.g. in general practice, it is often the user of the analyses who have the responsibility for the equipment. They will have to handle tasks which is usually confined to the laboratory e.g. quality control of the instruments. To assure good co-operation and communication with these clinicians, it is important to assure that they consider the quality specifications rationally. Quality specifications for analyses performed outside the hospital should generally be similar to the specifications for analyses performed on the laboratory. This will ease the interpretation of results since the interpretation will be independent of where the analyses have been performed. When other quality specifications are given (usually broader) it must be underlined to the clinicians in which clinical situations these tests should be used.

Information about analytical and biological variation is useful when clinicians are making their decisions. T set clinical actions limits in a sensible way, one should, in each clinical setting, evaluate how many „!false positive" ore false negative" actions which can be tolerated. An adaptation of quality specifications based on biological vat´rations to the clinical situation may therefore be necessary. This can be obtained by registering how clinicians handle laboratory results either by observing their actions „ in vivo" or, more commonly, by simulating a clinical situation by case stories.

In some of our EQA schemes for primary health care we distribute both analytical material and case stories to examine the relation between analytical quality and clinical decisions. The analytical quality specifications are based on this information as well as "target intervals" and biological variation.

Quality Specifications for Pre- and Post-analytical Characteristics

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According to the strategies exposed by the Boehringer Mannheim - Hitachi companies this area, pre- and post-analytical testing, is the prime target for further quality improvement in laboratory medicine. Here the majority of errors occur, here the manual labor is the most intense, and here the money can be saved. Sample splitters, track/trace devices, selfreporting modules etc. are supposed to be the future solutions.

One should wonder if and when it makes sense to differentiate, from a quality thinking perspective, between pre-analytical, analytical, and post-analytical laboratory phases. This because the integral quality is the only thing that counts. However the types of errors made in each of the three phases differ much. So does the type of approach to avoid them as well. In the pre- and post-analytical phase the errors occurring are very often from the Yes/No type. It concerns for instance sample interchanges, sample got lost and ID mix-ups. How often is it allowed to let a baby fall, or to mix up a sample or patient ID? The answer is that this is not allowed to do so at all. One only accepts *zero errors*! Right now we only check; we do not double check! This results in a definite need to improve the current quality especially in the pre-analytical phase.[1] In the post-analytical phase the quality delivered is insufficient considering the turn-around time and the fact that data, instead of information, are reported. [2]

Minimal requirements should be defined including a structured and formalized complaint registration as well as a hazard analysis and identification of critical control points (CCP). Customer driven laboratory procedures will enhance the quality of patient care.

References

Goldschmidt HMJ, Lent RW. Gross errors and work flow analysis in the clinical laboratory. Klin. Biochem. Metab. 3:24 (1995), 131-140.

Goldschmidt HMJ, Lent RW. From data to information: how to define the context? Chemometrics and intelligent laboratory systems 28 (1995), 181-192.

Keywords: Quality of Health Care; Total Quality Management; Accreditation.

Symposium VI
Guidelines for Clinical Urinalysis

Guidelines for Clinical Urinalysis: Urine Microscopy*

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Urine microscopy (UM) is a valuable tool for the clinician in the handling of the disorders of the urinary system. Three points are important when dealing with UM:

The methodological approach
This should include proper patient guidance, standardized collection, transport, and handling of specimens, as well as proper microscopic techniques.

The knowledge of the clinical significance of the different urinary elements

Erythrocytes, the morphology of which can differentiate glomerular from non glomerular bleeding and allows an early orientation of the work-up of patients with isolated microscopic hematuria.

Leukocytes, which are a frequent finding not only in urinary infections and urological diseases, but also in glomerulonephritis and interstitial nephritis.

Renal tubular cells, which are found in proliferative glomerulonephritis as well as in nephrotic syndrome and acute tubular necrosis.

Transitional cells, which indicate a lesion of the uroepithelium, especially when deriving from the germinative layers.

Lipids, which are a typical finding in patients with heavy proteinuria.

Casts, which have different clinical meanings depending on their nature: erythrocyte/hemoglobin casts indicate renal bleeding; fatty casts, nephrotic syndrome; waxy casts, renal failure; bacterial/fungal casts, renal infection, etc.

Crystals, which are usually devoid of clinical importance, but may indicate in some instances acute renal failure caused by intratubular precipitation of oxalate, uric acid, or drugs (e.g., sulphadiazine, acyclovir).

Microorganisms (bacteria, yeasts, protozoa, or parasites), which may be due to either infection or contamination from genitalia.

The interpretation of the urinary findings
Different elements can be combined into profiles, suggesting for instance urinary infection, nephritic syndrome, nephrotic syndrome, etc. These findings, however, must be integrated with other diagnostic tests and with the clinical features of the patients.

References

Fogazzi GB, Passerini P, Ponticelli C, Ritz E. The urinary sediment. An integrated view, London, Chapman & Hall, 1994.

Keywords: Microscopy; Urinalysis/standards.

Protein Analysis a Part of a Qualified Examination of Urine

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Traditionally, measurements of total protein in urine either by test strip or by quantitative methods have been used to screen for renal diseases.

However, we have learned during the last years that these measurements are not sensitive enough to detect early changes related with those diseases. In particular, early diabetic and hypertensive nephropathies are associated with slightly elevated albumin excretion rates ("microalbuminuria") which are of prognostic significance.

Determination of additional proteins has been shown to improve clinical diagnostics. Such proteins are α_1-microglobulin (marker for the detection of tubulo-interstitial dysfunction), α_2-macroglobulin (marker to differentiate renal from postrenal hematuria), and immunoglobulin G (IgG) (marker for the selectivity of leakage through the glomerular basement membrane).

Although an international consensus has been achieved for diagnostic of diabetic nephropathies, we still need to define what are the medical situations where we should use the specific and sensitive measurements of proteins, an when a traditional screening for proteinuria is acceptable (as applied e.g. to general adult and pediatric patient populations, pregnant women, or screening for toxic side effects of drugs, etc.). In addition, we should define optimal utilization of measurements of proteins and particular elements excreted into urine, as well as those measured from sera (such as creatinine or cystatin C) in diagnosing renal disease. Interpretation of results from the traditional as well as the modern specific protein measurements need an agreement when applied to different clinical needs (screening, monitoring or prognosis).

Currently, guidelines are still insufficient in advising how to prepare the patients, what type of specimen to collect, how to preserve it, and how to calibrate the measurement (the reference material, such as CRM standard is missing).

We attempt to collect different European experiences to work out a consensus recommendation for strategic procedures with respect to kidney diseases.

The presentation will summarize the state of the process.

Keywords: Urinalysis/standards; Proteinuria.

Guidelines for Clinical Urinalysis: Urinary Tract Infections on Behalf of the European Urinalysis Group

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Infection of the urinary tract is the most common pathological event affecting that organ system. Because it is so common, requests to the clinical microbiology laboratory for investigation of possible urinary tract infection (UTI) represent in volume terms the largest contribution to the laboratory's workload. This group's preliminary studies of how such samples are requested, produced, processed, transported, and analyzed have demonstrated very large variation both within- and between- European countries. there is furthermore much variation in the laboratory location, procedures, and workflow relating of additional investigations relevant to UTI such as the detection and enumeration of both white and red cells. Finally, diagnostic thresholds for detection of any and all abnormal elements in urine as they to UTI also vary, often from laboratory to laboratory within one large city. Such variations prevent performance indicators being set for both laboratories and evidence-based medicine across Europe; and the absence of widely adopted guidelines makes it very difficult for industrial concerns to design and build *in vitro* diagnostic devices to a minimum specification. The purpose of this preliminary presentation is to show examples of such variation in clinical, laboratory, and diagnostic practice across Europe, and to discuss the group's strategy for developing guidelines for the laboratory investigation of UTI which be both easily followed and immediately practical, in addition to being sensitive to the equally wide variation in the resources available for health care individual European member countries.

Keywords: Urinary Tract Infections/diagnosis; Urinalysis/standards.

Development of European Urinalysis Guidelines

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A framework of urinalysis which is responsive to clinical need and which describes how, and when, such elements should be analyzed is important for maximizing diagnostic accuracy whilst minimizing unnecessary clinical and laboratory costs.

To this end an European group under ECLM was established in February 1997 to assess the various European styles of requesting, analyzing, and reporting urinalysis. We intend to produce guidelines which will include the following recommendations:

- Methods for microbiological (bacterial culture), morphological and chemical assessment shell be included as they may all relate to the same specimen an clinical situation. Medically justified components will be defined as appropriate.
- We consider the variation in approach to urinalysis within the 45 European countries with a total of 790 million inhabitants: nation organizations, member organizations of ECLM, and personal contacts will be consulted.
- The guidelines will be sensitive to the variation in resources available for health care. Strategies for cost containment will the be discussed. For simplicity, only the most common indications for urinalysis will be considered.
- We shall seek to improve the quality of urinalysis results through suggesting standard procedures and methods. Two levels of analysis will be outlined:
  (a) minimum requirements for a routine urinalysis; and
  (b) optimum standards of investigation for purposes of standardization, audit, and instrument development.
- We anticipate benefiting from the active and fair participation of both clinical and industrial representatives (customers and manufacturers) in order that our guidelines should be practicable, sensitive to need, and easily adopted.

The presentation will summarize the work of the European group to date, and discuss future strategies for completion, and dissemination.

Keywords: Urinalysis/standards; International Cooperation; Europe.