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Future Perspectives of Automatization in Clinical Chemistry

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Summary: In planning the internal organization of central laboratories, the future needs for clinical chemistry in hospitals must be considered. For the next decade the medical laboratory will primarily be concerned with the interpretation of laboratory data and with organizational problems, such as sample identification, specimen splitting and especially the timing of its service. The consequences for instrumentation, newer technology for routine clinical chemistry, and recommendations for the future development of analytical systems are discussed.

Zukünftige Perspektiven der Automatisierung in der Klinischen Chemie

Zusammenfassung: Bei der Planung der internen Organisation von Zentrallaboratorien sind die zukünftigen Bedürfnisse der Kliniker für klinisch-chemische Untersuchungen zu berücksichtigen. Das medizinische Laboratorium wird sich in der nächsten Dekade vorwiegend mit der Interpretation von Labordaten und Organisationsproblemen, wie Probenidentifikation, Probenverteilung und insbesondere mit dem Timing seiner Dienstleistungen beschäftigen müssen. Die Konsequenzen für die instrumentelle Ausrüstung, neuere Technologien für die klinisch-chemische Basisroutine sowie Empfehlungen für zukünftige Entwicklungen von Analysensystemen werden diskutiert.

Introduction

Before discussing the automatization required by a medical laboratory in the next one or two decades, it is necessary to define the term automatization, then to reflect on the future needs of hospitals for chemical tests and on their influence on organisational structures of the laboratory.

The Commission on Automation of the International Union of Pure and Applied Chemistry (IUPAC) (1) differentiates between the terms mechanization, automatization and automation: table 1. At the present time most analyzers are automatic.

Tab. 1. Definitions according to an IUPAC recommendation (1).

Mechanization (mechanized)	The use of mechanical devices (machines or mechanisms) to replace, refine, extend or supplement human effort (e.g. use of dilutors)
Automatization (automatic)	Mechanical devices which perform in accordance with a manually preset set of conditions (e.g. use of analyzer, synonym to the term full-mechanization)
Automation (automated)	Mechanical devices which are regulated by feed-back of information, so that the apparatus is self-adjusting

Future needs for the management of patients

Future needs of the clinicians which can be foreseen from the present situation are summarized in table 2. Whereas many methods are now performed with sufficient reliability, there are still some procedures which require improvements of precision and accuracy as e.g. the determination of iron and creatinine.

For most tests the diagnostic reliability is only poorly investigated, especially for use in preventive medicine

Tab. 2. Future needs for clinical chemical services in hospitals.

1.	Test program
1.1	Tests of the present program
1.1.1	Improvement of analytical criteria of reliability (precision, accuracy, specificity)
1.1.2	Improvement of diagnostic criteria of reliability (diagnostic specificity and sensitivity)
1.2	New tests for diseases which cannot yet be detected (e.g. carcinoma)
1.3	New tests for drug monitoring
2.	Test availability
2.1	High emergency (during 10 min)
2.2	Basic routine (as soon as possible: e.g. 2 hours)
2.3	Special analyses (if required 1–2x per week)
3.	Computer assisted interpretation of test results

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(2). A further research goal for the early detection of many diseases is to find new tests with better analytical and diagnostic reliability criteria.

Many drug monitoring tests are now introducted into medical laboratory services. It appears that this area will become increasingly important for the management of patients in the near future. Here, the clinical chemist must assist the clinician to interpret the results. This offers an opportunity for clinical chemists to improve their relationship with the clinicians.

Concerning the test availability (tab. 2) many laboratories still have problems in satisfying the demands of the clinicians.

At the present time it is common practice to discriminate between emergency cases, for which the analysis must be performed during a time period of less than 2 hours, and normal routine cases which have to be processed during 6 hours. This procedure causes a significant duplication of work and should be abandoned in the future. Furthermore, the basic routine results, which in clinical chemistry consists of about 20 tests, are more and more required during the morning hours.

In larger hospitals with a high percentage of intensity care beds 3 priority stages should be distinguished in future planning of central laboratories:

A small group of tests, for example potassium, glucose and blood gas analyses are needed very urgently; for some specific cases (e.g. reanimation, cardiac surgery), this means in less than 15 minutes. This aspect has significantly increased during recent years, and such analyses should be performed either at the bedside or at least close to the patients in small satellite laboratories; alternatively, there may be an efficient pneumatic tube system for direct transport of the specimens. All other tests of the basic routine should be performed during approximately 2 hours. A third group may consist of a few special tests with less priority.

The most important point of future needs is probably the computer assisted interpretation of test results (tab. 2).

The information content of many laboratory data is probably greater than their present utility. It is accepted worldwide that physicians are overloaded with laboratory data. Possibilities for computer assisted interpretation of test results are:

- Individual reference values, especially with respect to sex and age.
- For special diseases individual decision criteria are required instead of reference values presently used. Several techniques, e.g. the receiver operating characteristic curve, have been adapted to this purpose from the information theory (3).
- The value of cumulative reports has already been recognized by many laboratories.
- Lists of possible explanations for abnormal tests results have been published for SMA 12 profiles. Such lists, however, can be relatively long and then do not lead to data reduction (3).
- Therefore, a decision strategy may be more useful which suggests the next action to be taken. The laboratory should not try to find the diagnosis as soon as required. The corresponding term is decision support instead of computer diagnosis (4).

An important research goal for the next decade must be to develop decision strategies, especially for the interpretation of biochemical profiles.

If more tests are considered in a profile, statistical procedures like multivariate and discriminant analyses must be included in the diagnostic strategy (2, 3). The applications of these procedures, although well known, still needs further evaluation and stimulus. Besides this, sufficient computer capabilities must be available.

Another area where more computer capacity is desirable is monitoring of quality and plausibility. Procedures which include directly results from patient specimens, e.g. the average-of-normals method, require computer assistance.

Development of internal organization and instrumentation

The flow chart in figure 1 shows how the organization of present laboratories could be modified to meet the future requirements just outlined.

The request, somehow attached to the specimen container receives an identification-number, either on the ward or when entering the laboratory. Parts of the specimen will be analyzed directly as whole blood, (e.g. electrolytes, glucose). The rest is centrifuged and the plasma mechanically distributed into several secondary specimen containers.

Mechanization of specimen or sample splitting with automatic transfer of identification from the specimen container to the secondary specimen or sample cups is an urgent need which has been recognized for many years. Several solutions are now offered which either transfer the sample automatically but not the identification (positional identification), e.g. Labtronic Service KG (D-6000 Frankfurt) (5), GFC GmbH (D-1000 Berlin 27) and Medizinische Feinwerktechnik E. Harig OHG (D-2000 Hamburg 74) or transfer the sample and the identification partly mechanically, e.g. Eppendorf Gerätebau GmbH (D-2000 Hamburg).

The basic routine analyses will be performed by a selective multichannel analyzer with about 20 channels and a high through-put rate. Multi-channel analyzers are particular important as long as the problems of identi-

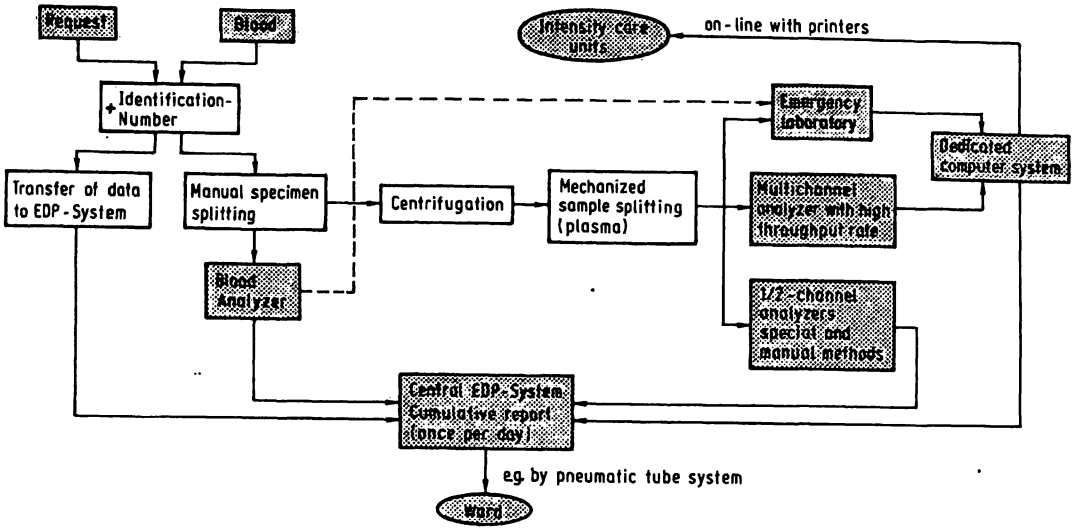

Fig. 1. Flow chart of the possible future organization in a central laboratory for clinical chemistry.

fication and sample splitting are not solved satisfactorily. A high through-put rate is required to avoid queueing of samples.

The results of the multi-channel system can be checked and released within 60 or 120 minutes to all those wards that require the data (i.e. all intensive care units). This provisional report could be printed out directly on these wards and could be replaced by a complete and more informative cumulative report which is only distributed once per day, probably in the late afternoon.

During the last 1–2 decades the basic routine of clinical chemistry was mostly requested as indiscriminated profiles. At the present time there is a world-wide trend to the abandonment of this strategy and a return to selective requesting. It cannot be foreseen whether indiscriminated profiling will have a renaissance towards the end of this century, in the event that we learn to get more useful information from the data produced.

Besides the multi-channel machines, single channel analyzers will also be needed, either flexible with regard to methodology or dedicated to specific problems, e.g. analyzers for immunological techniques.

Recommendations for future developments

In table 3 some recommendations for future developments of chemical analyzers are summarized which have been claimed by the IUPAC Commission on Automation and other individual experts (1, 6, 7):

- The through-put rate is usually more important than the processing time.
  The through-put rate for single channel analyzers should be above 200 tests per hour, a recent development offers 1000 kinetic measurements per hour in a single channel system (8). The processing time should be less than 10 minutes if emergency cases are included.
- Sample reagent volumes required will probably be further miniaturized. The present status for the minimum of assay volume is about 200–300 µl.
- The fast progress in microprocessor techniques should integrate system control into all analyzers to achieve true automation. Automatic recognition of faults should be available even for smaller instruments, such as photometers.
- The reliability of the measuring unit could be improved in most cases. This may concern accuracy and precision of the photometric measurement, as well as drift and noise phenomena.
- With regard to the sample, more attention should be drawn to the detection of interfering endogenous chromogens, to a means of warning if the volume in the sample cup is not sufficient for the test required

Tab. 3. Recommendations for future developments of clinical chemical analyzers.

1. Higher speed
2. Miniaturization of sample and reagent volumes
3. System control, recognition and identification of trouble causes, easy servicing by interchangeable units
4. Improvement of the reliability of the measuring units
5. Suitability for emergency tests
6. Avoidance of carry-over and contamination effects
7. Reduction of space requirement
8. Avoidance of special services such as air conditioning, drainage, gases, etc.
9. Detection of endogenous chromogens which may cause interference
10. Detection if sample volume is unsufficient
11. Preservation of specimen during storage
12. Integrated direct sample identification
13. Improvement of temperature control
14. Automatic counting of test number
15. New technologies for special tests (heterogeneous enzyme immunoassay and other immuno techniques)

and to the preservation of the sample during storage in the analytical system. Evaporation can lead to considerable overestimation especially if small cups with a relative large surface are used.

- In most systems now available temperature control is unsufficient for kinetic reactions. Independent of the control it must be possible to measure the temperature in the reaction mixture.
- In the future the need for statistical analyses of the laboratory workload will probably increase. These data will be required as an essential basis for management decision. Therefore analyzers should count their number of tests automatically.

There can be no doubt that more computer facilities are required if the clinical chemists want to satisfy their clinical collegues as outlined above:

- A faster and automatic transfer of sample specification into the computer system is required.
- For emergency cases, the data transfer to the ward should be automatic.
- The trend to improve the intelligence of the periphery will continue. The function of the central computer is reduced to data collection and shifted towards more sophisticated control tasks.
- Cheaper and more flexible interface units are required which are interchangeable between various instruments.
- Mechanization of sample identification is requested by clinical chemists for many years. *Keller* has recently reviewed identification techniques and pointed out that their development is at present stagnating. "The Barcode or the OCR system appear to have the best chances for the future. With both systems, however, there are still certain technical difficulties and as yet there is no sign that these will be overcome" (9).

Newer technologies for automatization

Some technologies, which at the present time are already available and promising for clinical chemistry, but not fully adapted to routine purposes are summarized in table 4:

Tab. 4. Newer technologies for basic routine in clinical chemistry.

1.	Unbloody sampling techniques
1.1	Transcutaneous
1.1.1	Transcutaneous electrodes
1.1.2	Infrared laser spectroscopy (lips)
1.2	Saliva
2.	Ion selective electrodes
3.	Calorimetry
4.	Derivative spectroscopy
5.	Dry reagent carrier systems
6.	Luminescence spectrometry (ATP, NADH, H_2O_2)

- pO_2 determination in capillary blood from newborns is problematic. Therefore the development of the transcutaneous measurement overcame some of these problems. The transcutaneous electrodes have already proven its validity. Furthermore this new technique allows continuous monitoring. Arterial changes can be registered with approximately a 10 second delay. This technique is currently further developed for transcutaneous CO_2 measurements (10–12).
- Ion selective electrodes will probably replace flame photometry, because they are better suited for automatization, and they do not require a flame with its attendant disadvantages.
- Calorimetric or thermal analysis depends on the direct proportionality between the heat changes that occur during chemical reactions and the amount of reacting substances. This technique does not require optically clear specimens in complex matrix systems. At the present time its application in clinical chemistry is limited primarily by its slowness.
  Heat is measured by recording the voltage output from the calorimeter as a function of time and then integrating the area under the curve, which is called a thermogram (fig. 2). The shape of the thermogram depends on the response time of the calorimeter and the kinetics of the measured reaction.

The sensitivity of present calorimeters is in the range of microcalories. The instruments can be used to measure heat changes that take place in solutions of micromolar concentrations. Thus the term "microcalorimeter" refers to the sensitivity of the instrument.

The good agreement between the theoretical and experimental values of heat change is important, because it implies that calorimetric analyses can be performed despite the unavailability of primary standards and, therefore, may also be suited for reference methods (13).

The ability of calorimetry to measure an overall process can be utilized for differentiation of two simultaneous or sequential reactions that proceed at different rates.

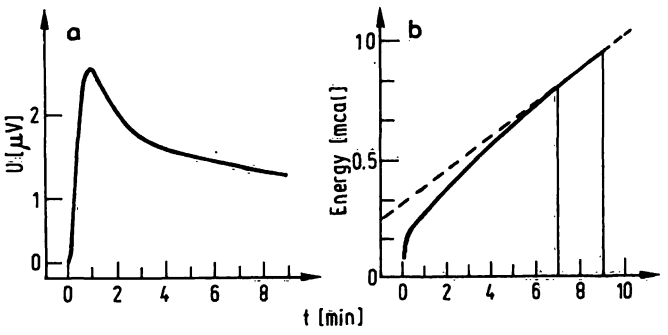

Fig. 2. Thermogram (a) and thermogenesis curve (b) obtained by calorimetric measurement of two simultaneous reactions: the enzymatic oxidation of free cholesterol (fast reaction) and the enzymic hydrolysis of cholesterol ester (slow reaction). From l. c. (13).

The coupling of two enzyme reactions, one of which proceeds rapidly and the other slowly and is rate limiting, allows simultaneous measurement of two analytes, e.g. of free cholesterol and cholesterol ester (fig. 3): the concentration of cholesterol ester can be determined from the rate of the slow enzymic hydrolysis reaction, while the amount of free cholesterol was measured from the total heat that was evolved through the fast enzymic oxidation ratio.

The rate of hydrolysis is determined from the slope of the broken line which corresponds to the linear part of the thermogenesis curve between 7 and 9 minutes. The amount of free cholesterol is determined by subtracting from, this measured heat, the heat produced by hydrolysis.

- The utility of derivative spectroscopy has already been shown for the measurement of porphyrins in urine (14). Now instruments are able to derive up to the 9th order. With this technique it has been claimed that drugs can be detected in complex matrix systems, e.g. serum samples (15).
- Nobody can foresee how fast wet chemistry will be substituted by the so called dry chemistry. "Dry chemistry" is not a good term, since the chemistry still takes place in a fluid medium. With these techniques the reagents are stored in dry form on a reagent carrier material.

A very promising technique could be the Ektachem system from Kodak (16–18). The major advantage of this multilayer film technique is that the same principle is applicable for the combination of several steps into "quasi one step", e.g. the combination of a main reaction with a separation step and an indicator reaction. Several other companies are developing alternate systems applying different reagent carriers. These systems will also influence the automatization process in our laboratories.

Although fast progress may be possible in this field, the present "wet" chemistry will probably for a long time continue to be used for reference and special methods.

In addition to all these new trends and aspects we should not forget the present situation, and we should encourage industry to improve our present instrumentation. In subsequent years the clinical laboratory will be primarily concerned with the investigation and interpretation of laboratory data and with organisation problems, e.g. specimen and sample identification, sample splitting, and especially the timing of its service.

References

1. Hjelm, M., Bierens de Haan, J., Büttner, J. & Young, D. S. (1978), IUPAC Inf. Bull. *3*, 233–240.
2. Haeckel, R. (1979), Dt. Ärzteblatt *76*, 713–720.
3. Büttner, J. (1977), this j. *15*, 1–12.
4. Reece, R. L. (1978), Unified interpretative reports: An important consequence of multichannel instruments and new computer technology. In: AutoAnalyzer Innovationen, Technicon GmbH, 6368 Bad Vilbel, Band 1, 304–311.
5. Sauermann, F. (1979), GIT Labor-Medizin *1*, 46–47.
6. Okuda, K., Collombel, Ch., Geary, T. D., Haeckel, R., Mitchell, F. & Nadeau, R. in preparation.
7. Haeckel, R. (1979), Rationalisierung des medizinischen Laboratoriums. GIT-Verlag E. Giebeler, 2nd ed., D-6100 Darmstadt.
8. v. Froreich, A. (1979), GIT Labor-Medizin *1*, 42–44.
9. Keller, H. (1979), this j. *17*, 57–64.
10. Evans, N. T. S. & Nayler, P. F. D. (1967), Resp. Physiol. *3*, 21–37.
11. Huch, R., Lübbers, D. W. & Huch, A. (1974), Arch. Dis. Childhood *49*, 213–218.
12. Huch, R., Huch, A., Albani, M., Gabriel, M., Schulte, F. J., Wolf, H., Rupprath, G., Emmrich, P., Stechele, U., Duc, G. & Bucher, H. (1976), Pediatrics *57*, 681–690.
13. Rehak, N. N. & Young, D. S. (1978), Clin. Chem. *24*, 1414–1419.
14. Schmidt, A. (1977), this j. *15*, 303–306.
15. Talsky, G. & Glasbrenner, M. (1979), this j. *17*, 192.
16. Curme, H. G., Columbus, R. L., Dappen, G. M., Eder, Th. W., Fellows, W. D., Figueras, J. Glover, C. P., Goffe, C. A., Hill, D. E., Lawton, W. H., Muka, E. J., Pinney, J. E., Rand, R. N., Sandford, K. J. & Wu, T. W. (1978), Clin. Chem. *24*, 1335–1342.
17. Sprayd, R. W., Bruschi, B., Burdick, B. A., Dappen, G. M., Eikenberg, J. N., Esders, Th. W., Figueras, J., Goodhue, Ch. T., La Rossa, D. D., Nelson, R. W., Rand, R. N. & Wu, T. W. (1978), Clin. Chem. *24*, 1343–1350.
18. Haeckel, R. (1979), GIT Labor-Medizin *2*, 201–205 and 317–327.

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