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AUTOMATION IN CLINICAL CHEMISTRY: CURRENT SUCCESSES AND TRENDS FOR THE FUTURE

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Abstract - In this paper, the main technological and organizative aspects of the automation in clinical chemistry procedures are presented and discussed. After a short presentation of the main features of the continuous flow and discrete automation, the most relevant advances in analytical methodology and instrument design are illustrated. The present state and the probable future trends of clinical chemistry automation are evaluated.

INTRODUCTION

All the papers and all the conferences on clinical chemistry automation, generally start with some consideration or detailed statistics on the increasing number of clinical chemistry tests. So I will not waste words on this subject; I only want to emphasize that the history of automation in clinical chemistry is the history of how and when the techno logical progress in the field of analytical methodology as well as in the field of instrumentation, has helped clinical chemists to mechanize their procedures and to control them after mechanization. In my lecture I will mention in brief the main steps of historical development of mechanization in clinical chemistry. I will take into consideration the most relevant technical advances in the field and finally I will try to give an idea of what we can expect from automation in the future years and how this can be obtained.

In Fig. 1 I have summarized, from a general point of view, the main steps of a clinical chemistry procedure.

- GENERAL STEPS OF A CLINICAL CHEMISTRY PROCEDURE -

1 - PRELIMINARY TREATMENT (DEPROTEINIZATION)

2 - SAMPLE + REAGENT(S)

3 - INCUBATION

4 - READING

5 - CALCULATION

Fig. 1 General steps of a clinical chemistry procedure

Especially in the classic clinical chemistry methods, a preliminary treatment of the sample (in most cases a deproteinization) was an essential step. This was a major constraint on the first tentative steps in automation and we will see how this problem was faced and which new problems arose from avoiding deproteinization. Mixing samples and reagents is the next step; then there is a more or less long incubation at different temperatures and finally reading, which means detection of modifications of some physical property of the mixture; in most cases the development of a colour can reveal the reaction but, as well known, many other possibilities exist; finally the result is calculated.

CONTINUOUS FLOW AND DISCRETE AUTOMATION

Some 25 years ago, Skeggs (1) presented his paper on continuous flow automation that was the basis of very successful instruments still used all over the world. As we can see in the upper part of Fig. 2 the continuous flow automation reactions take place in an hydraulic route common to all samples.

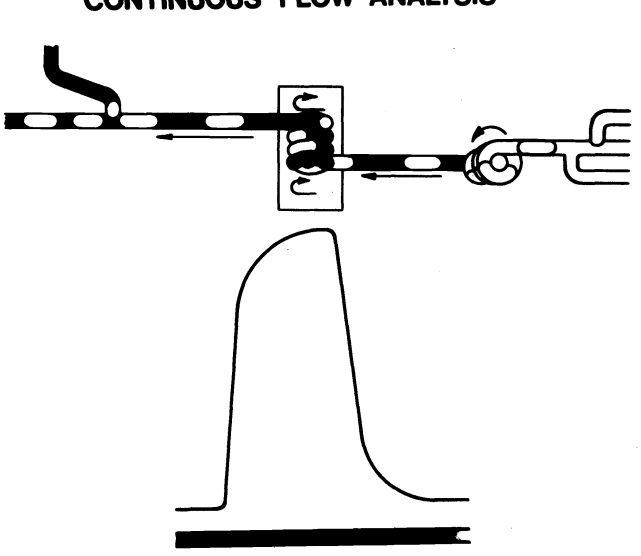

Fig. 2 Continuous flow analysis

Standards and samples enter the analytical stream segmented by air bubbles and, as they circulate, specific chemical reactions and physical manipulations continuously take place in the stream. Finally, after the air bubbles are vented, the colour intensity, proportional to the solute molecules, is monitored in a detector flow cell as we can see on the right side of the upper figure. In the lower part of the same figure we can see the registration of the colour intensity from the beginning to the end of the segment.
In Fig.3 we can see the basic characteristics, advantages and problems connected with continuous flow automation (ref. 2 - 3 - 4).

- CONTINUOUS FLOW AUTOMATION -

BASIC CHARACTERISTICS	ADVANTAGES AND PROBLEMS
- Reaction in an Hydraulic Route	- Homogeneous Treatment of All Samples
- Peristaltic Pump	- No Protein Interference
- DIALYSIS	- Carryover
- Dwell Time - Steady State	- Reaction Rate Measurements
	- Relative Slowness

Fig. 3 Continuous flow automation.

I already mentioned the common hydraulic route where reactions take place.
The peristaltic pump forces the fluid down the tube at a linear rate set by the roller speed, the function of air bubbles, in appropriate samples and reagents mixing and in avoiding sample contamination is well known. The interference of proteins is avoided through the dialysis, which played an essential role in the success of the continuous flow automation. Depending on the dwell time, that is the time a sample-reagent mixtu-

re spends in each segment of the hydraulic route, the reaction will be complete or incomplete; in any case the degree of completeness is identical for all samples as well as for all portions of each. This introduces the concept of steady state condition. Homogeneous treatment of all samples through the common hydraulic route is a major feature of continuous flow automation. I already mentioned the importance of dialysis to avoid protein interference. In this system there is a risk of carryover, with contamination between high and low content samples. Repetition of some samples in these cases is essential to avoid errors due to carryover. Means of controlling and correcting drifts are essential in continuous flow systems. In fact, drifts can derive from many factors: temperature change, tubing characteristic change, change in dwell time and so on. Continuous flow systems are not particulary suitable for reaction rate measurements. Relative slowness of single channels has been complained about by some authors. Continuous flow automation was and still is applied to many instruments, single and multichannel. Multichannel can be considered as the sum of a number of single channels. Each channel is devoted to a single analysis. In recent years, all the operations in continuous flow systems have been computer controlled. In the sixties and seventies, when continuous flow automation was very successful, a great effort was made to develop alternative technologies to continuous flow automation in clinical chemistry. While in continuous flow analysers all specimens occupy one single greatly elongated container, several specimens being present in different portions of it, in the so called discrete analysers, each specimen, with its reagents, occupies a separate container in all phases of the reaction, with the exception of reading (in fact, in many discrete analysers, reading takes place in a flow cell, like in continuous flow analysers). Besides sophisticated and completely automated instruments, the so called semi-automation, that is automation of some operations only, achieved a great success. Automation in clinical chemistry can be classified in the following pairs of contrasting properties (Fig. 4) (ref. 1): complete and partial automation, continuous flow against discrete flow; what we described before as continuous flow, should better be defined segmented flow automation to distinguish it from the so called flow injection automation (ref. 5 - 6).

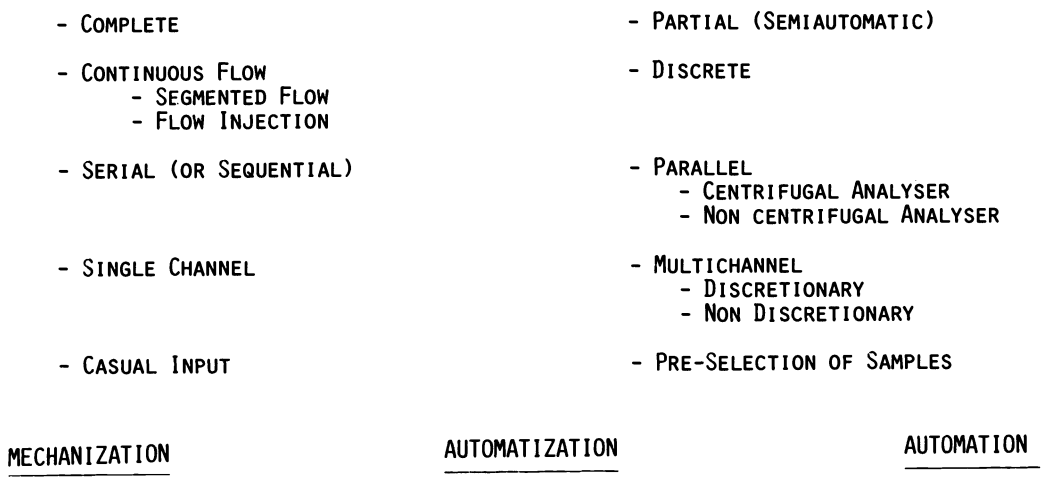

Fig. 4 Automation in clinical chemistry. Alternative approaches.

I will mention briefly the flow injection automation later, describing new tecnologies. In the serial or sequential analysers, the instrument works on each sample in sequence and no two specimens occupy the same stage of the procedure. On the contrary, in parallel analysers, centrifugal or non-centrifugal, many samples go through the same analytical step contemporarily.

I already mentioned single channel and multichannel analysers, both can be based on continuous flow or discrete automation. The classic multichannel analysers can perform a large number of tests on the same specimen. First models were non-discretionary, as they carried out a fixed list of analysis on all samples, sometimes suppressing the results of unrequested tests. The large multichannel analysers had great success; because of their large capacity, they reduced the organization required for specimen and work distribution in the laboratory.
As in these analysers the time required to process one sample is fixed and independent from the number of tests performed, the larger the number of tests performed for sample, the larger the production of results per unit of time.
Probably the great success of the so-called biochemical prophiles is at least partially based on this observation. This consumistic approach to the clinical chemistry automation was widely criticized in recent years. Large biochemical prophiles on non-selected people are now abandoned all over the world. Today, multichannel programmable analysers find their proper application for not too large but well programmed biochemical prophiles in selected people.
In most analysers, samples must be presented to the instrument in a well-defined order; for example at the beginning, all samples for glucose determination and then all samples for urea and so on.
In recent years, thanks to particular technological advances we will examine later, the possibility of a casual input of samples in the instruments has been obtained with obvious organization advantages. We will examine later this point in detail.
This figure deals with problems of classification and nomenclature. The last point, in this respect, is the use of the word Automation as synonymous of Mechanization and Automatization. According to a IUPAC recommendation (7), Mechanization means the use of mechanical devices to replace, refine, extend or supplement human effort (e.g. use of dilutors), Automatization means the use of mechanical devices which work in accordance with a manually preset set of conditions (e.g. use of analysers, synonym of the term full mechanization), Automation means use of mechanical devices regulated by feed-back mechanisms.

PROGRESS IN ANALYTICAL METHODOLOGY

It is evident that the most important aim of automation is to correctly process as many samples in as short a time as possible. This result can be obtained thanks to many technological advances either from analytical point of view or from the instrument technology. In Fig.5 progress in analytical methodology, relevant from this point of view, are summarized.

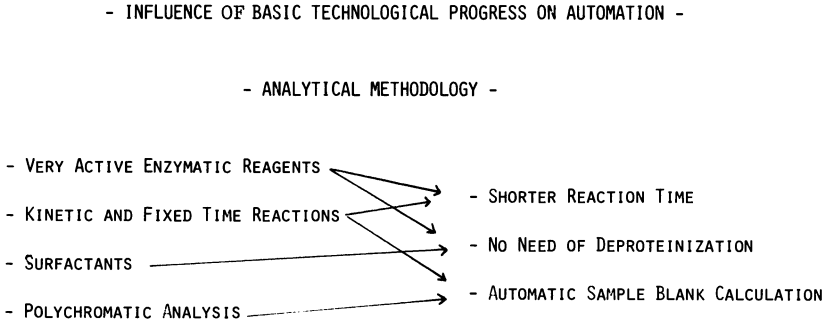

Fig. 5 Advances in analytical methodology.

The introduction of very active enzymatic reagents for determination of substrates resulted in shorter reaction times and possibly, in many cases, of avoiding deproteinization. Reaction times are also reduced by using kinetic and fixed time reactions instead of end points. In this case, the measurement of sample blank does not need a separate tube with separate reaction mixture. Deproteinization can be avoided also by using some surfactants in the reagent mixture. An automatic calculation of sample blanks is also possible by using polychromatic analysis.
As we can see from this figure, reduction of reaction times and elimination of tedious operations like deproteinization, are the main results of this analytical progress.

The sample blank interference, if not calculated, can often produce great errors; this problem is often underestimated (ref.8).

In Fig. 6 we can see how this problem can be faced from the chemical and instrumental point of view.

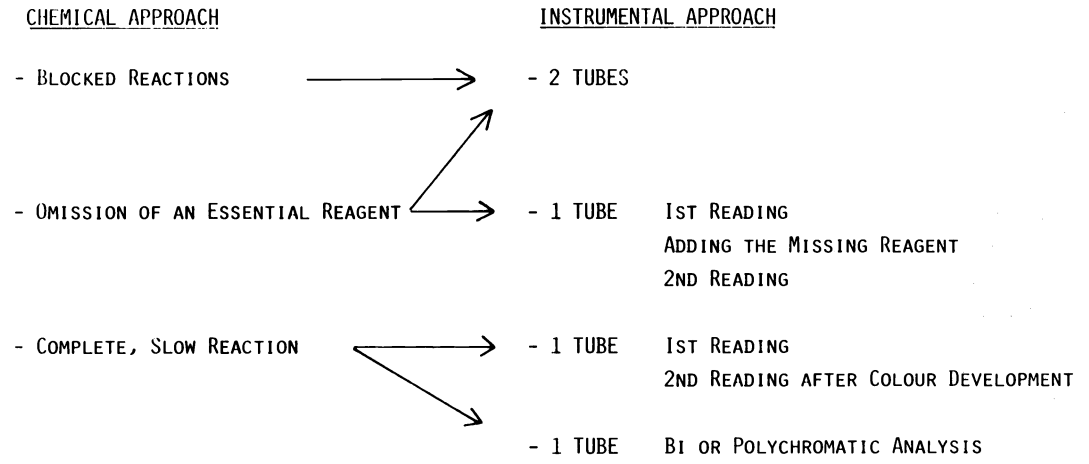

Fig. 6 The problem of sample blanks FROM C. FRANZINI, 1982

We can calculate the sample blank by using an additional tube for each sample, in which reaction is completely blocked; alternatively we can omit in the reaction mixture an essential reagent. In this case the two tubes procedure can be adopted or, alternatively, we can use only one tube, with a first reading corresponding to the sample blank, then we add the missing reagent and we make a second reading of a developed colour. In the case of slow reactions or reactions developing not too quickly, we can read the sample blank on the same tube and in the same conditions where the complete reaction develops, that is we adopt the one tube procedure with two operative alternatives. The first one includes a first reading just after mixing sample and reagent at approximately zero time and a second reading after colour development. This procedure is adopted in the case of kinetic measurements, it is also adopted to evaluate sample blank in centrifugal analysers.

The use of bi-chromatic or polychromatic analysis can offer an interesting alternative, largely used in many automatic procedures (ref. 9 - 10).

It is evident that the possibility of avoiding the two tubes procedure is very important in raising the sample throughput.

In Fig. 7 we can see how the sample blank interference can be eliminated by bi-chromatic analysis. The situation described in the upper part of the figure is a very particular and very lucky one, because the blank absorptivity, in this case, is the same at the main wavelength as at the secondary, and the chromophore absorptivity at the second wavelength is zero. So in this case, if we subtract from the observed absorbance at the first wavelength the absorbance at the second wavelength, we have a complete elimination of the sample blank.

A less fortunate case, but a more common one, is shown in the lower figure. In this case, at the secondary wavelength the blank absorption is different from that at the first wavelength and chromophore absorbance at the secondary wavelength is not zero.

When a number of interferents are present simultaneously, instead of bi-chromatic, we must use a tri-chromatic or polychromatic analysis (ref.10).

In the classic bi-chromatic instruments, two light beams at two different wavelengths, alternatively interrupted by a chopper, cross the reaction tubes.

In Fig. 8 we can see a spectrophotometer working either as a double wavelength instrument (lower part) or as a double beam instrument (upper part).

The light generated by the lamp, by appropriate coupling of mirrors (indicated with M1 M2 - M3) and beam shutters (S1 and S2) is directed to the mirror grating G1 in the upper figure; then the emerging selected wavelength, through the rotating chopper mirror M4 is sent alternatively to the sample and reference cuvette. Alternatively, as we can see in the lower figure, both mirror gratings G1 and G2 are activated and two light beams at different wavelengths are sent to the sample cuvette in an alternative sequence regu-

POLYCHROMATIC ANALYSIS

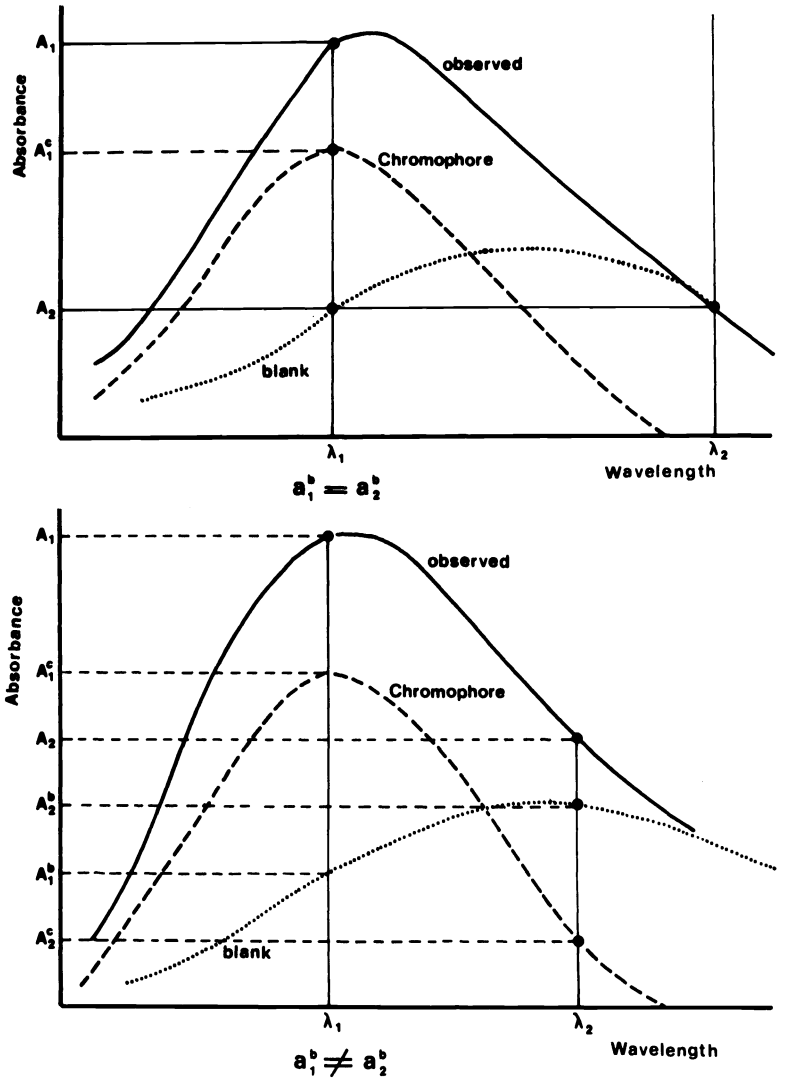

Fig. 7 Polychromatic analysis **From: B. Hahr et al. Clin. Chem. 25/6, 951-959 (1979)**

DOUBLE BEAM AND DOUBLE WAVELENGTH SPECTROPHOTOMETER

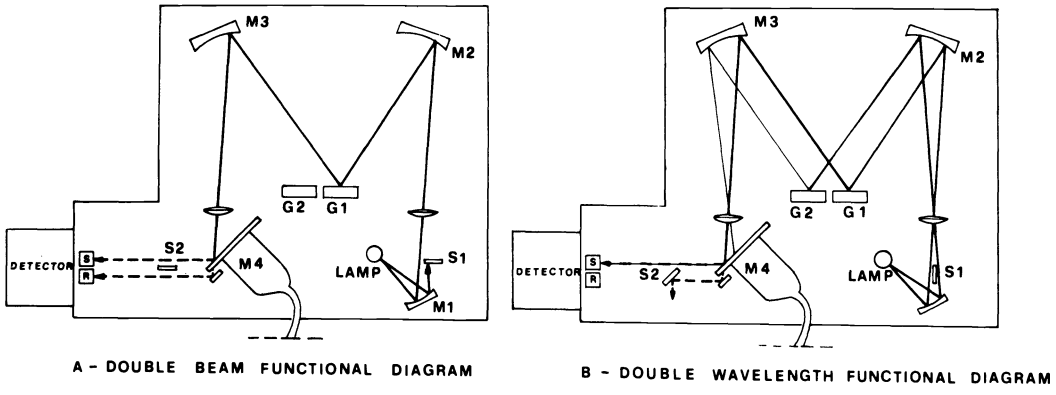

Fig.8 Functional diagram of a double-beam, double-wavelength spectrophotometer.

lated by the rotating chopper mirror M4.
As we will see later, in some recent automatic analysers, different technical solutions can be adopted which allow reading at multiple wavelengths. The possibility of reading the same tube at multiple wavelengths can bring other advantages, besides the sample blank subtraction (Fig. 9).

- MULTIPLE WAVELENGTH READINGS -

- COMPENSATION IN ELECTRO-OPTICAL INSTABILITY
- SAMPLE BLANK SUBTRACTION
- FLAGGING OF SAMPLES WITH HIGH INTERFERENTS
- SUBSTRATE DEPLETION
- DIFFERENT COLOURS IN SEQUENTIAL TUBES
- DIFFERENT COLOUR IN THE SAME TUBE, IN SEQUENTIAL TIMES
- EVALUATION OF MORE ANALYTES ON THE SAME TUBE: SAME CHROMOGEN, DIFFERENT ABSORPTIVITIES

Fig. 9 Multiple wavelength readings

It allows compensation of electro-optical instability, the possibility of flagging samples with high levels of interferents, the indication of a substrate depletion, masqued, for example, by sample turbidity.
Furthermore, we can read sequential tubes with different colours for different reactions or we can follow different colours in the same tube in sequential times for different reactions to be carried out in the same reaction mixture. We can also try to evaluate different analytes reacting with the same chromogen with different absorptivities in the same tube. Many instruments have adopted various technical solutions consistent with multiple wavelength readings as we will see later, and there is considerable evidence that further efforts will be made to improve this technique for future applications.

PROGRESS IN INSTRUMENTS DESIGN

Many relevant improvements in mechanics and optics over the last twenty years and the tremendous advance in electronics have largely contributed to the instrumental improvement of clinical chemistry automation (Fig. 10).

- INSTRUMENTAL ASPECTS -

MECHANICS	ELECTRONICS	OPTICS
STEP BY STEP MOTOR	MICROPROCESSORS TECHNOLOGY	MONOCHROMATORS
FLUIDIC SYSTEM		OPTICAL FIBRES
		PHOTODETECTORS TECHNOLOGY

Fig.10 Advances in instrument designs

In the next figures we will see some details concerning the step by step motor, computer application to automatic analysers, optical fibres and the technological advance in the field of monochromators and photodetectors.
As mentioned at the beginning, the measurement of fluid volumes (samples and reagents) is an important step in any clinical chemistry procedure: this step is generally mechanized through motor-controlled syringes.

In Fig. 11 we can see, in the lower part, the diagram of a syringe operated by a traditional motor: the rotation of the cam in the direction indicated by the arrow, moves the arm, which acts on a microswitch by interrupting the power supply to the motor.

With time, in this kind of motor, the mechanical play between cam and microswitch affects accuracy and precision of measurements.
Further, motor stop is due to a passive mechanism (suppression of power supply) with a consequent uncontrolled inertia. The stepping motor, illustrated in the upper part of this figure, is constructed using a central rotor, indicated by the arrow, and a concentric stator, made up of a number of windings (indicated with letters A - B - C - D), all energized when in the stop position. By suppressing the power supply to the single windings in sequence, the rotor moves step by step (from D to A, from A to B etc.). In such a motor, we can obtain a very reduced rotation angle of a rotor, and, consequently, very small and accurate movements of a syringe. Unlike the traditional motor, stopping is obtained here by an active coupling of tension rotor winding, with greatly reduced inertia.

As to the volume measures, I want also to mention the fluidic system, in which nor pumps neither syringes are used. A pressure system with a microprocessor controlled valve allows the fluids to pass through the hydraulic route in a well defined and controlled way.

The principle of the optical fibre technology is illustrated in the upper part of Fig. 12. By means of optical fibres, light can be transmitted along non rectilinear paths.

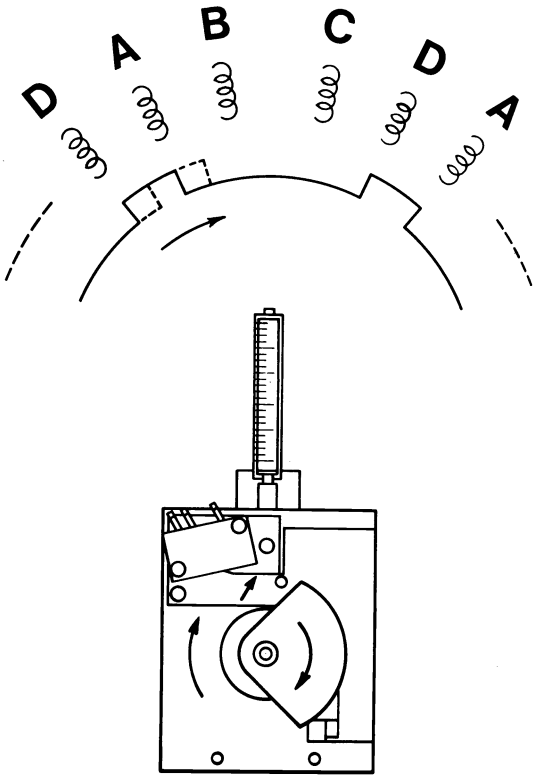

Fig.11 The traditional and the stepping motor

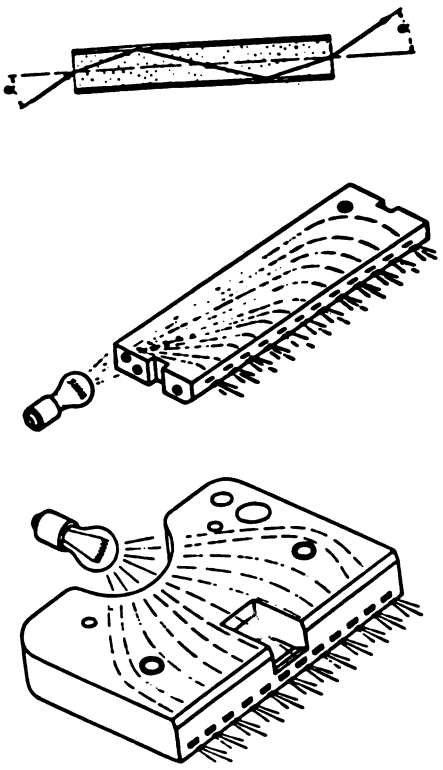

Fig. 12 Optical fibres: principles and technical applications

The basic element is a glass fibre, with a high reflection index nucleous wrapped in a low reflection layer. In the centre and in the lower part of the figure two technical applications of optical fibres are shown. This technology has been successfully applied to some automatic analysers especially the parallel non-centrifugal.
The technology of centrifugal analyzers (Fig. 13), largely exploits technological progress in mechanics and electronics.

The stimulus for the development of this technology was the difficulty of carrying out reactions in the absence of gravity in space; nevertheless, centrifugal force proved useful as a means of transferring and mixing samples and reagents independently of extra-terrestrial problems. (ref.11)
Samples and reagents are pipetted in appropriate wells placed on a centrifuge arm. Under the influence of the centrifugal field, the sample and reagents mix as they move outwards into the reaction reading cell. As the disc rotates, a light source provides the selected wavelength, which passes through the rotating cells and is then monitored by a photodetector. The output signal is finally stored and processed by a computer. Centrifugal analyzers are used for the determination of the substrates in end point or kinetic methodology and of the enzymes; they represent an excellent technology for kinetic reactions.
A recent interesting innovation in the field of centrifugal analyzers consists in the possibility of adding another reagent to an already mixed sample-reagent solution. This innovation allows a preincubation to be made and sample blanks to be read before adding the starter reagent.

The possibility to measure absorbances in cuvettes positioned longitudinally to the light path, realized in a recent model of centrifugal analyzers, is claimed to be advantageous to read absorbances in non homogeneous solutions, to avoid any influence of reagent volume errors on the absorbance and to have more suitable calculation factors.

The interest of fluorimetric assays is growing more and more, especially in connection with drugs immunofluorimetric assays. This technology (Fig.14) has been recently applied also to centrifugal analyzers technology. A Xenon lamp generates a high energy light, reflected by a mirror - holographic - grating operated by a stepping motor.
The selected wavelength of the exciting light passes through a split and reaches the rotating cuvettes. Fluorescence is then filtered, read by means of a photomultiplier and compared to the continuously monitored fluorescence of an appropriate reference compound. In this way, eventual instability due either to the electro-optical devices or to changes in physicochemical properties of solution is corrected.

As already mentioned, it is the tremendous progress in electronics, especially in the technology of large scale integrators and microprocessors and the reduction in costs of electronic components that can be considered responsible for the progress in automatic clinical chemistry instruments.

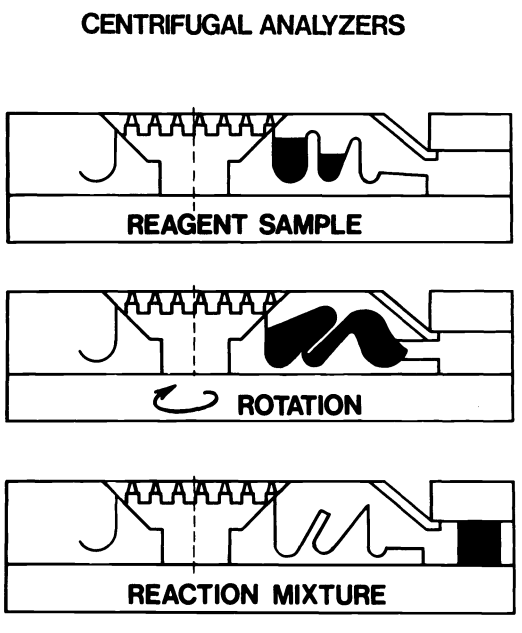

Fig.13 Centrifugal analysers

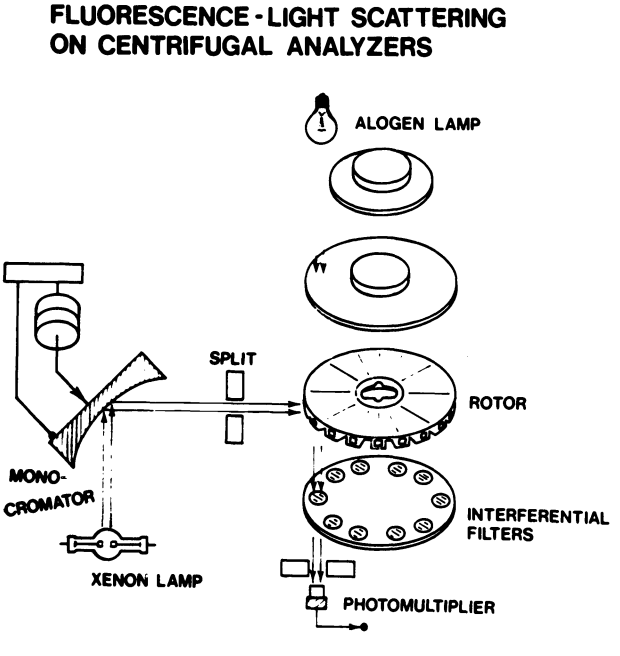

Fig.14 Application of fluorescence to centrifugal analyzers.

Let us consider how many functions, in a modern automatic analyzer, can be computer controlled (Fig.15); starting from the upper part we see the identification of the sample, represented by a camera, then on the right, the control of fluid volumes, represented by a syringe, time and temperature control, selection of appropriate wavelength, represented by a filter carousel and by a combination of a mirror-grating and a multiple photodetector system (we will discuss later this interesting device), calculations, control of kinetic reactions and, last but not least, automatic trouble detection and correction, to some extent.

In my opinion, three essential features of the last generation of automatic analyzers, are put in evidence in this figure as the results of the application of computers:

1 - the sample identification
2 - the operative flexibility, that is the possibility to pass from one analysis to another in the same or in different samples without manual intervention and waste of time
3 - the availability of a sort of self-assistance service that reduces times and cost of assistance.

Now I want to spend some words on the use of multiple wavelength systems which represent, in my opinion, a key point for the present and probably for the future. As we can see in Fig.16 the general model of discrete non-centrifugal and non-parallel automatic analysers, is represented by a light source, by a filter carousel, or another monochromatic device, and by a series of cuvettes with reaction mixtures of the same colour (and obviously different intensity), a detector and an analogical-digital converter. This system works at a wavelength fixed for each analytical batch. In the case represented in this figure, a kinetic reaction is followed in 8 tubes by means of five readings at 15 second intervals. This model represents a traditional solution, very appropriate, for example, for automatic kinetic measurements in automation, in not too large batches, or, in a slightly different solution, for automatic measurements of large end-point reaction batches. In such an instrument, specimen must be preselected according to the required test, that is, for example, all the samples for glucose at the beginning, then all the samples for urea and so on. This traditional model requires a non-insignificant organization of work to be carried out manually with all the inherent possibility of errors. In some instruments this work is done automatically after a certain number of samples is put in the sampler. This is no doubt a progress in the philosophy of casual input of samples.

A new technical approach to this organizational philosophy is illustrated in Fig.17.
A polychromatic light passes through the reaction tube, then it is reflected and dispersed by a mirror-grating; various photodetectors are then simultaneously activated by the reflected light beams at different wavelengths. This solution is possible thanks to the progress in the field of monochromators, with the introduction of mirror-gratings; the signal recorded by the different photodetectors are then processed by a computer. In this way, different colours, in sequential tubes can be read without problems and various different reactions can be performed and read in sequence on the same reaction mixture, by dispensing additional reagents.
In this way the problem of casual input of samples is solved; so it is the problem of sample blanks subtraction and the flagging of high interference samples, through the polychromatic technique.
The only disadvantage of the instruments adopting this technology, as I know, is relative slowness: in this kind of instruments the throughput, that is the number of samples completely processed per hour, is inversely proportional to the time of observation of each reaction mixture.
The longer the time of observation of each reaction tube, the smaller the number of tests performed per unit of time.

Is it possible in a multichromatic analyzer to elevate the instrument productivity without reducing below a reasonable level the time of observation? This problem has been faced with a new approach to the centrifugal analyzers philosophy (ref.6): instead of rotating samples, the light beam was rotated. The result is a multiple wavelength analyzer that can receive specimens continuously, which is supposed to have an elevated throughput and reaction time monitoring up to 30 minutes.

The possibility of scanning the whole optical spectrum by means of a television camera tube (vidicon) or other types of array detectors is illustrated in the Fig.18 (ref.12). These devices can offer an interesting alternative approach to analytical spectroscopy; there are some limitations connected with the sensitivity, lower than in other photodetectors and the need to adopt a compromise between spectral resolutions and spectral range. Further, illumination of the samples with the full intensity of undispersed energy could cause some problems in samples with photochemical activity or those that fluoresce.

CRUCIAL ASPECTS AND PROSPECTS

As we have just seen, important advances have been made in recent years in clinical chemistry automation. Although, certain aspects still remain really crucial (Fig.19). An ideal instrument should be characterized by:

- no need of manual operations
- possibility of casual input of samples, included stat samples
- reaction monitoring times sufficiently long
- possibility of starting with work as soon as the first samples arrive in the laboratory
- an elevated specimen throughput
- large selection of number and volumes of reagents to be used and times of adding them
- devices for multiple wavelength readings
- facilities for computer interfacies, identification of samples and/or automatic data processing (I will not discuss this last point because it will be dealt with in another session of this Congress).

In Fig.20, I have summarized some recommendations, made by different international organisms, for the future development of automatic analyzers (ref. 7 - 13). Some of them have been already mentioned (automatic identification and repair of troubles, detection of interferents), some others are important from the organizative point of view (suitability for emergency tests, presence of sensors for specimen volume, automatic counting of test number). The extreme importance of the reliability of the measuring unit is so important that it does not need any comment.

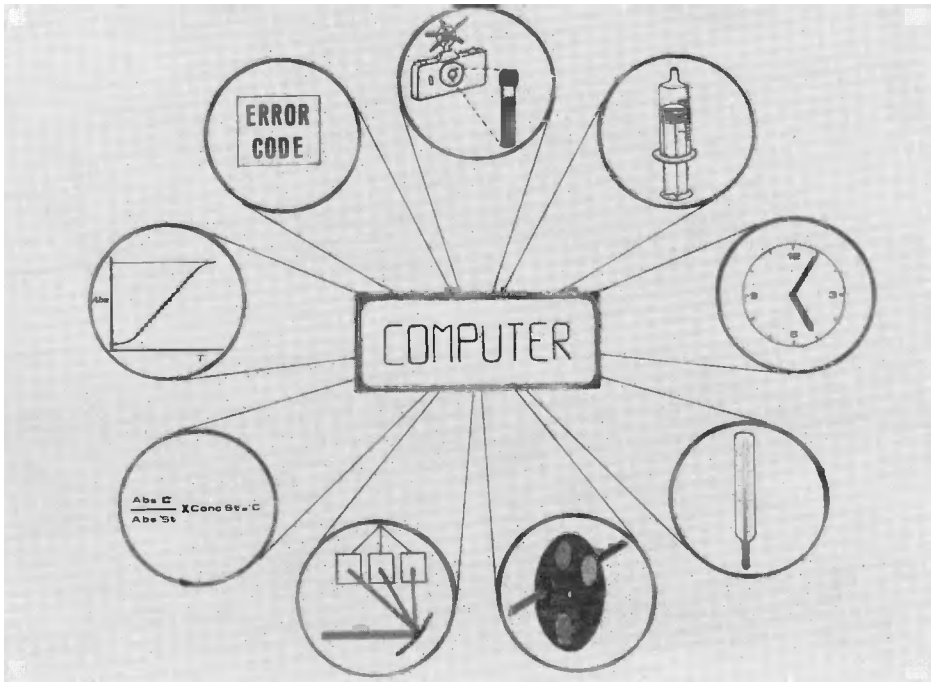

Fig.15 Computer controlled functions in a modern automatic analyzer.

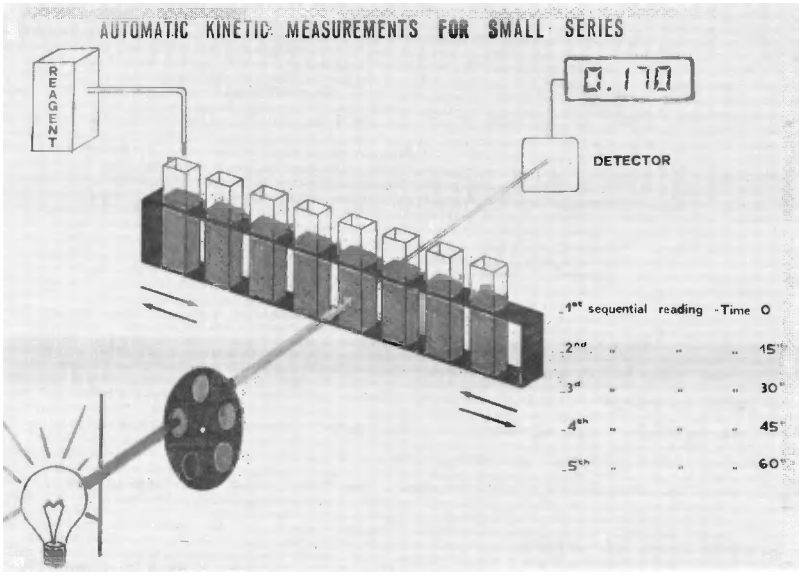

Fig.16 General model of discrete, non centrifugal and non parallel analyzer.

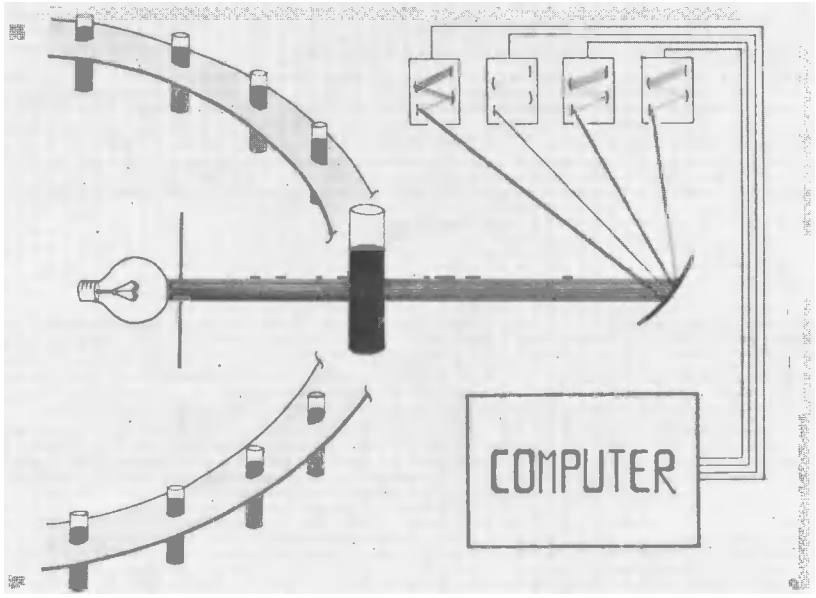

Fig.17 Polychromatic readings technology.

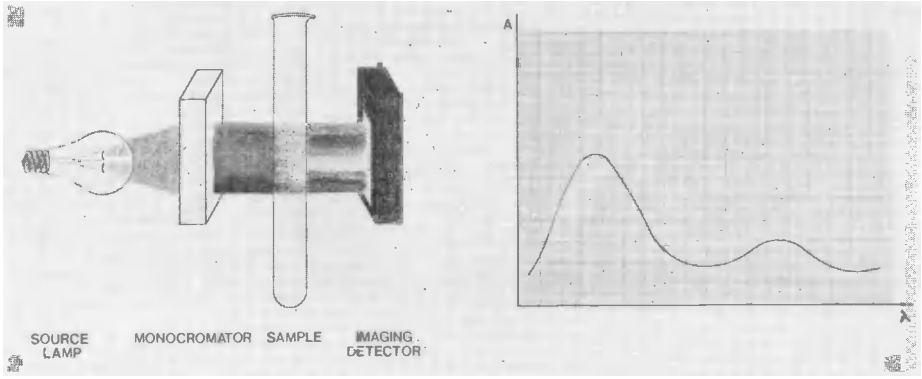

Fig.18 Multiple wavelength detectors.

- AUTOMATION IN CLINICAL CHEMISTRY IN THE EIGHTIES -

- SOME CRUCIAL PROBLEMS -

- NEED OF MANUAL OPERATIONS
- NEED OF SAMPLES PRESELECTION
- REACTION MONITORING TIMES
- DELAY IN STARTING TIME
- ADDITION OF REAGENTS (HOW AND WHEN)
- SPECIMEN THROUGHPUT
- SELECTION OF VOLUMES (SAMPLES AND REAGENTS)
- MULTIPLE WAVELENGTH READINGS
- COMPUTER INTERFACIES FACILITIES, SAMPLE IDENTIFICATION AND AUTOMATIC DATA PROCESSING

Fig.19 Some crucial problems in clinical chemistry automation.

- SOME RECOMMANDATIONS -

- AUTOMATIC IDENTIFICATION AND REPAIR OF TROUBLES
- SUITABILITY FOR EMERGENCY TESTS
- SENSORS FOR SPECIMEN VOLUME
- AUTOMATIC COUNTING OF TEST NUMBER
- RELIABILITY OF THE MEASURING UNIT
- DETECTION OF INTERFERENTS

Fig.20 Some recommendations for future automatic analysers.

As we have just seen, up to now, automation in clinical chemistry has essentially dealt with spectrometric analysis, and probably this will be the case also in the near future. Nevertheless, as we can see in Fig.21, important results have been achieved in other technologies. Because of lack of time, I can only briefly mention this point. All of us well know some excellent automatic instruments for fluorimetry, blood gases analysis, radioimmunology, flame photometry, electrophoresis, high performance liquid chromatography and osmometry. Dry chemistry proved to be an important tool for manual and automatic urine analysis; its application to blood tests is being introduced in laboratories and is presented by some companies as an alternative to wet chemistry automa-

- AUTOMATION IN CLINICAL CHEMISTRY -

- NEWER TECHNOLOGIES AND NON-COLORIMERIC TESTS -

- FLUORIMETRY
- LUMINESCENCE
- DERIVATIVE SPETROSCOPY
- ELECTROCHEMISTRY
- CALORIMETRY
- FLAME PHOTOMETRY
- ELECTROPHORESIS
- IMMOBILIZED ENZYMES
- FLOW INJECTION ANALYSIS
- DRY CHEMISTRY
- HIGH PERFORMANCE LIQUID CHROMATOGRAPHY
- ICP (TRACE METALS)
- RADIOIMMUNO ASSAYS
- OSMOMETRY

Fig.21 Automation of newer technologies and non colorimetric tests.

tion (ref. 14 - 15 - 16). Luminescence (ref.17), calorimetry and electrochemistry offer interesting alternative solutions to colorimetric analysis, at least for some analytes. Some of these techniques have the advantage of high sensibility, linearity within a very wide scale and possibility to be applied to whole blood (ref.18).
Immobilized enzymes found interesting applications especially in continuous flow systems. Non-segmented flow analysis, generally known as Flow Injection Analysis (ref. 19-20), seems to be an interesting alternative to classic segmented continuous flow analysis. By sure other technologies will be automated in next years (ref. 21 - 22). I am rather convinced that automation in clinical chemistry in next years will be characterized by a competition between the classic spectrometric technologies and non-colorimetric ones. Organizative and economic aspects, as already mentioned, as well as reliability of results will play a key role.
To conclude, in my opinion, the fortune of the monster-machines is over. Multichannels will be used for not too large, but well-programmed prophiles in well-defined situations. The future belongs to flexible instruments. Larger attention to the preanalytical steps is also required for automation in clinical laboratory to be more adherent to the user's need (ref. 23 - 24). Technological progress is giving us a great variety of suitable technical solutions to obtain these results. Now, it is up to us to exploit these possibilities: this is the challenge for the future.

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