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Impact of new technology on the future of clinical chemistry

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Abstract. Any discussion of what might be expected to occur in the future with regard to clinical biochemistry must be based upon a sound knowledge of current practice together with a clear understanding of the past. Although practice varies enormously between different countries and cultures there is enough common ground to make an historical approach worthwhile.

HISTORY

The growth, during the early part of the 19th century, of morbid anatomy and histopathology as the scientific base for modern medical practice, was followed not long afterwards, by realisation that visible changes observed in tissues were, themselves, no more than expressions of change in their chemistry. This, in turn, led to the growth of chemical pathology as a distinct academic discipline which relied upon chemical analysis and quantitation as its primary tool rather than upon gross and microscopic anatomy (Refs. 1 to 4).

Early chemical pathologists were often physicians or chemists with an academic bent who were mainly concerned to elucidate the nature and origin of disease in chemical terms rather than with the treatment of individual patients. This fell then, as now, properly within the province of clinicians, mostly physicians but sometimes surgeons, whose help was sought by patients suffering from diverse illnesses. In its formative years chemical pathology was confined mainly to the investigation of urine and tissues obtained at post mortem (Ref. 5). Examinations on blood were limited by the lack of suitable analytical methods. It remained largely an academic subject until the introduction of insulin therapy for diabetes, in 1922, put a premium upon the measurement of glucose in blood (Refs. 6 to 8).

With this development clinical chemistry, as we understand it today, was born and every hospital worthy of the name soon set up a laboratory, albeit an often primitive and poorly staffed one, capable of performing glucose estimations rapidly where and when required. A number of chemical methods had recently been developed which made this possible using small volumes of blood such as could readily be obtained by finger-prick (capillary blood) or venipuncture.

The repertoire of analyses that could be performed on small quantities of blood sufficiently quickly to enable them to be used clinically for the management of individual patients, rather than exlusively to increase understanding and knowledge of disease processes generally, increased relatively slowly so that even as late as 1952 only the largest hospital chemistry laboratories had a menu containing more than 30 items (Ref. 9). Most hospital laboratories confined themselves to less than 10 different types of chemical analysis on blood and rather more on urine, faeces, gastric and other body fluids.

Despite the slow growth in the variety of analyses offered by laboratories during this period there was an exponential growth in the total number of analyses requested (Ref. 10) as clinicians came increasingly to realise how easily they could improve the quality of their practice either by using laboratory data to assist them in making a diagnosis or as a means of monitoring the response to treatment.

The slow rate of growth in the repertoire of tests available, the limited size of the menu coupled with the technical difficulties of mass-producing results - even of the same analyte - served to ensure that clinicians making requests for analyses were, in general, conversant with their clinical indications as well as with their interpretation (Refs 8 to 11). Few hospitals, apart from those in teaching establishments, had medical graduates on their staff whose main or sole function was the pursuit of knowledge through research and development and who could also, by constantly updating their own knowledge of the subject, educate colleagues in other disciplines about ways in which the products of biochemical research could be applied for the benefit of patients.
Hospital biochemistry, which had altered comparatively little in concept or practice during the preceding four decades, underwent a radical and profound change in the early 1960s (Ref. 12). This occurred as a result of three, more or less simultaneous, innovations; the introduction of mechanisation (Ref. 13) and of radioimmunoassay (Ref. 14), and the industrialisation of reagent manufacture i.e. prepacked reagent kits.

Mechanisation

Prior to the invention of the Auto Analyzer in 1957 and its widespread introduction into hospital laboratory practice during the 1960s the number of individual tests that could be carried out in any one laboratory was limited as much by the amount, cost and availability of the skilled labour necessary and able to perform them manually, as by the small size of the analytical menu. The lifting of these constraints by the introduction of mechanisation of manual techniques (often, but incorrectly, referred to as automation) permitted the inexorable and exponential growth in the number of requests for analysis to continue without a corresponding increase in labour (technician) costs. In typical Parkinsonian fashion (Ref. 15) the work expanded to fill the time available for its completion so that the expected, and hoped for. release of skilled analysts from the daily drudgery of producing ever greater numbers of analyses - many of which were irrelevant, unnecessary, uninterpretable or frankly misleading - never took place. The situation which developed - and still exists - can be described succinctly by the phrase "more of the same" rather than variety and progress.

In order to accomodate changes resulting from the expansion of knowledge produced by chemical pathology research - which often masquerades in biomedical circles and the scientific literature as metabolic medicine, internal medicine or endocrinology - more staff were recruited, mostly to carry out the purely technical function of making assays - leaving it to others - usually the requesting physician - to interpret the result as best he could. In this way the prophecy (Ref. 16) made in 1953 by Lord Adrian, Nobel Lauriet, that "the pathologists and biochemists will find that their time is taken up with measurements of uncertain value in which they are not especially interested and the final result may well be that the work is turned over to specially trained technical experts who are the last people to give a dispassionate judgement of the value of what they are doing". This prophecy, made many years before the advent of automation, more or less describes the situation obtaining in most laboratories today where even those clinical biochemists and chemical pathologists who do accept the need for a greater involvement in consultation, education and research, plea "pressure of work" for not doing so.

At first, and still by some, the massive growth in number of analyses performed by each technologist was looked upon as self-evidently beneficial. Unequivocal proof of this has however not been forthcoming; indeed there is more than a hint that the reverse is true namely, that plethora blindness and too great a reliance by clinicians upon analytically correct, but incorrectly interpreted, data can be harmful (Ref. 17). Nevertheless because of the perceived, rather than proven, benefit of an unconfined, user-driven demand for chemical analyses - most often made on blood - clinical chemistry departments not only participated in the general growth in finance experienced by other sectors of the health care industry during the 1960s and 70s but greatly increased their share relative to other specialities. The question now, is whether and how - in a time of no, or little, economic growth and rapidly changing technology - clinical biochemists can change their philosophy and practice in order to maximise their medical and scientific knowledge and their analytical skills for the benefit of patients. Before considering these questions in detail I want briefly to revert to the two other major developments that occurred in clinical chemistry in the early 1960s and which exert so profound an effect upon current practice.

Immunoassay

The repertoire of tests available in hospital clinical chemistry laboratories increased only very slowly until the mid 1950s when it received a fillip by the introduction of assays for a number of different enzyme activities in serum (Ref. 12). Nevertheless many substances of known or potential clinical interest, chiefly hormones, vitamins, drugs and specific proteins, remained refractory to measurement in the clinical environment until the discovery by Yalow and Berson, in 1959, of immunoassay (Ref.14) and its application first to the measurement of insulin and other polypeptide hormones in blood but subsequently to a whole range of compounds. These include small molecular weight hormones, vitamins and drugs, as well as specific proteins and tumour markers. Thus immunoassay not only provided a most powerful tool for biomedical research but gave biochemists an opportunity to enlarge the menu of tests available to clinicians looking after patients. Even so it gained widespread acceptance in hospital clinical chemistry laboratories only after the reagent manufacturing industry began producing prepacked reagent kits which made minimal demands upon technical skills and understanding for their satisfactory performance.

Kits

There are many clinical chemists still practicing their craft who can recall having to make up most, if not all, of their own reagents and standard solutions before embarking upon a clinical assay of even the most elementary kind. Prior to the mid 1950s prepacked reagents were not generally available commercially. This was not as great a hardship as might now appear since almost all clinical chemical tests performed regularly before 1950 relied upon the use of simple, stable reagents. The introduction of an ever greater variety of enzyme assays - many of which employed expensive, unstable or difficult to obtain substrates - and the increasing use of enzymes, antibodies and specific proteins as reagents put a premium upon economy and the desirability of providing all the materials necessary for performing small batches of tests in a single package.

The reagent kit industry, once it had got underway, grew rapidly but, despite the simplification this

made possible in laboratory technology it has not until very recently, had any real impact upon the philosophy of clinical chemistry practice.

MANAGEMENT AND PRACTICE

Centralisation of Laboratory Testing

Modern clinical chemistry has been laboratory based ever since its inception, utilising specialised equipment, reagents and above all technical skills in order to produce quantitative analytical data upon which clinical management decisions can be made. Its growth was associated with a trend towards centralisation in order to make maximum use of scarce resources, including equipment, reagents and above all technical and supervisory skills. This, in addition to introducing the cost benefits of scale, provided an unexpected bonus in the shape of better analytical performance as judged by results obtained in external quality assurance schemes.

Centralisation did, however, carry with it many disadvantages. Amongst these were the lack of constraint on unnecessary testing and the loss of immediacy and relevance of many of the procedures carried out. This, coupled with investments in instruments capable of carrying out a large number of a limited range of tests of low predictive value produced a false sense of economy since even though unit costs were strikingly reduced there was no evidence of corresponding benefit (Ref. 17) unless it was to laboratory managers and/or owners. The increasing geographical remoteness of laboratories and isolation of technologists performing analyses from patients, as well as from the doctors and nurses caring for them, has led to reduced feelings of personal involvement in the outcome of the investigations to such an extent that in some communities medical laboratory technologists have gone on strike in order to obtain financial and/or political advantage, regardless of the inconvenience or harm done to patients. Moreover, although increasing mechanisation and centralisation has been associated with improved analytical precision, it has seemingly done nothing to reduce the number of gross errors (Ref. 18) which though more commonly due to faulty labelling or transcription than technology could, if acted upon unthinkingly by clinicians receiving the reports, have dire or even tragic consequences. The biggest disadvantage of all, however, has been the pre-eminence given to perfection of the analysis - which can be looked upon merely as a tool that becomes useful only in the hands of someone who is fully conversant with its capabilities and limitations i.e. its specificity, precision and predictive value, and the almost complete neglect of the other three pillars upon which good clinical biochemical practice depends, namely consultation, education and research.

Decentralisation of laboratory testing

Given that a clinical chemical analysis is similar to a physical sign in medicine and has no meaning until interpreted against the general clinical background, the ideal place for its performance is adjacent or as near the patient as feasible. This was, until recently, impracticable if not impossible, except in the case of simple semi-quantitative urine and faecal analyses. Meaningful interpetation requires a knowledge of the patient's age, sex and general state of mental and physical health, nutritional state, medication, time of day when the sample was collected, time elapsed since his/her last meal (or medication), phase of the menstrual cycle, presence or absence of concurrent illness as well as a whole host of other variables which, if not recorded at the time the specimen is collected, may make interpretation difficult or impossible. These facts are seldom, if ever, recorded on the request form or in the clinical notes when random samples of blood or other body fluids are collected for despatch to central laboratories. Consequently little importance can be attached to the results obtained unless they are grossly abnormal.

The benefits of bringing laboratory testing closer to the patient than was possible in the past are already evident in some areas of health care. Self calibrating blood gas analysers, capable of being operated by relatively unskilled medical staff, are available in many hospitals and, providing they are properly and adequately serviced, give reliable and useful results where and when they are required. If the results so obtained are at variance with the clinical picture or with the results of other tests, the cause of the discrepancy can be investigated immediately just as the finding of an unexpected tachycardia or hypertension during the physical examination leads to further enquiry and observation. Other quantitative clinical chemical analyses that are already being performed in substantial numbers outside the main laboratory in many hospitals, include blood glucose measurements using solid phase reagents or dedicated glucose analysers, neonatal plasma bilirubin levels using percutaneous reflectance spectrometry and therapeutic drugs in blood using enzyme immunoassays. But this is only the beginning.

More and more manufacturers are designing instruments and reagents that are sufficiently robust, dependable and/or portable to be used in small laboratories, side rooms, outpatient departments or doctors offices. In some circumstances physicians may opt to carry out tests themselves exactly as they would a physical examination; alternatively, and more likely, they will delegate the task to someone who had been specially trained to perform a few simple procedures but has neither the skill nor experience required of a registered technologist. This is, of course, one of the main points of contention; i.e. to whom should such an unskilled individual be accountable and who should be responsible for the quality of his/her work since there is evidence that this can fall to unacceptably low levels quite quickly unless strict and informed supervision is maintained.

It is to this and other questions arising as a result of developments in clinical laboratory science, instrument design, solid phase chemistry, data handling and information technology, that I now wish to turn my attention in an attempt to formulate a policy for the future development and practice of clinical biochemistry.

Future developments

The decentralisation of clinical chemistry and probably most other laboratory procedures, opposition from vested interests notwithstanding, will gradually occur over the next 5 - 10 years as its advantages and feasibility become ever more apparent (Refs. 19-21). This process will, however, do nothing to improve the knowledge base upon which interpretation of the analytical results are based - indeed just the opposite is likely to occur and its correction will require the availability of a Chemical Pathologist whose role will increasingly become that of a specialist investigator who uses chemical analysis as his tools exactly as the radiologist uses x-ray imaging and nuclear medicine specialists uses radio-isotopes. Clinical Chemists will be required to develop and apply analytical procedures to solve specific patient problems and further understanding of metabolic derangements that cause disease rather than serving as laboratory managers. The analysis factories that have grown up in our hospitals will largely disappear to be replaced by specially designated centres carrying out medically, ethically and economically justified screening programs, such as are currently used for detection of certain treatable inborn errors of metabolism. Unnecessary testing will be reduced.

This glimpse into the future should not be construed as advocacy of the closure of hospital clinical biochemistry laboratories - quite the reverse. I believe that they can, and will, be recognised along with other laboratory based clinical science disciplines, i.e. haematology, radiology, nuclear medicine, histopathology, microbiology, physiological measurement and cytogenetics, as constituting the clinical investigation centre of the hospital and its surrounding community (Ref. 23). The way this is achieved will depend upon socioeconomic and political circumstances and will vary from one country to another but will certainly involve as radical a change in the philosophy of medical and surgical practice as in that of laboratory medicine itself.

I would like, and expect, to see the development in Britain and other countries with National Health Services of an organisation based upon that advocated by myself and other clinical biochemists several years ago that recognised the need for different levels of organisation of laboratory service and which led to the establishment of the highly successful Supra-Regional Assay Service (Ref. 26). Because of financial stringency and other reasons neither the regional or area tiers of laboratory organisation originally proposed were implemented.

Briefly, the primary unit of organisation would be the "sub-regional laboratory" providing all but the most esoteric clinical biochemical services - both analytical and consultative - to a population of roughly 1- 2 million people. Each of the 4-8 district hospitals attached to it - and which, in Britain, would cover between them an area of between 1000 - 5000 square miles - would have, as at present, a hospital laboratory staffed by at least two consultants (Ref. 27), one of whom would be a clinician (Chemical Pathologist) the other a (bioanalytical) chemist. Both consultants would be on the board of management of the "sub-regional laboratory" which would be managed by an executive chairman who would be accountable to the Health Authority (or owners). In addition to its local facilities one of the participating District Hospital Laboratories (probably the largest) would house a special analytical laboratory which would perform the screening programs e.g. for phenylketonuria, galactosaemia, neonatal hypothyroidism, maternal α-fetoprotein, for the whole population served. This same laboratory would house the central laboratory computer. This would be used to prepare and store cumulative reports on all patients undergoing investigation anywhere in the region and would be linked on the input side to all laboratories and their satellites and, on the output side, to clinicians whose only equipment requirement would be a telephone line and a video screen (Fig. 1).

Individual hospital laboratories would provide both analytical and consultative clinical services for the district in which they were situated but, in addition, would provide specialist advice and analyses for the region as a whole. In other words, the senior clinical biochemists would act as "generalists" locally but as specialists further afield. They would be available by telephone and/or in person to provide not only specialist advice but also such analytical work as they considered necessary to solve individual patient problems. Thus the individual hospital laboratories within the group would - with their own satellites - be able to deal with all of the "every-day" clinical biochemistry for their own district - which contrary to popular belief is used mainly for monitoring treatment or unthinkingly rather than for diagnosis (Refs 28,29) - as well as providing a specialist diagnostic clinical biochemistry service to a much larger catchment area.

Satellite laboratories housed in small community hospitals, special care units, outpatient clinics, hospital ward side rooms and polyclinics (general practitioners offices) etc. would be staffed by technicians who would be members of the main hospital laboratory by whom they would be supervised. Using dedicated instrumentation they would perform a narrow and specified range of analyses whose results are required quickly for optimum patient management. Specimens upon which analyses are required for purposes other than immediate patient management e.g. for screening, would be sent by transport owned and operated by the laboratory service to the hospital laboratory or even better - the "factory" - for processing by high capital cost, low labour requiring mass-production equipment, the output from which would be linked directly to the central computer. Data generated

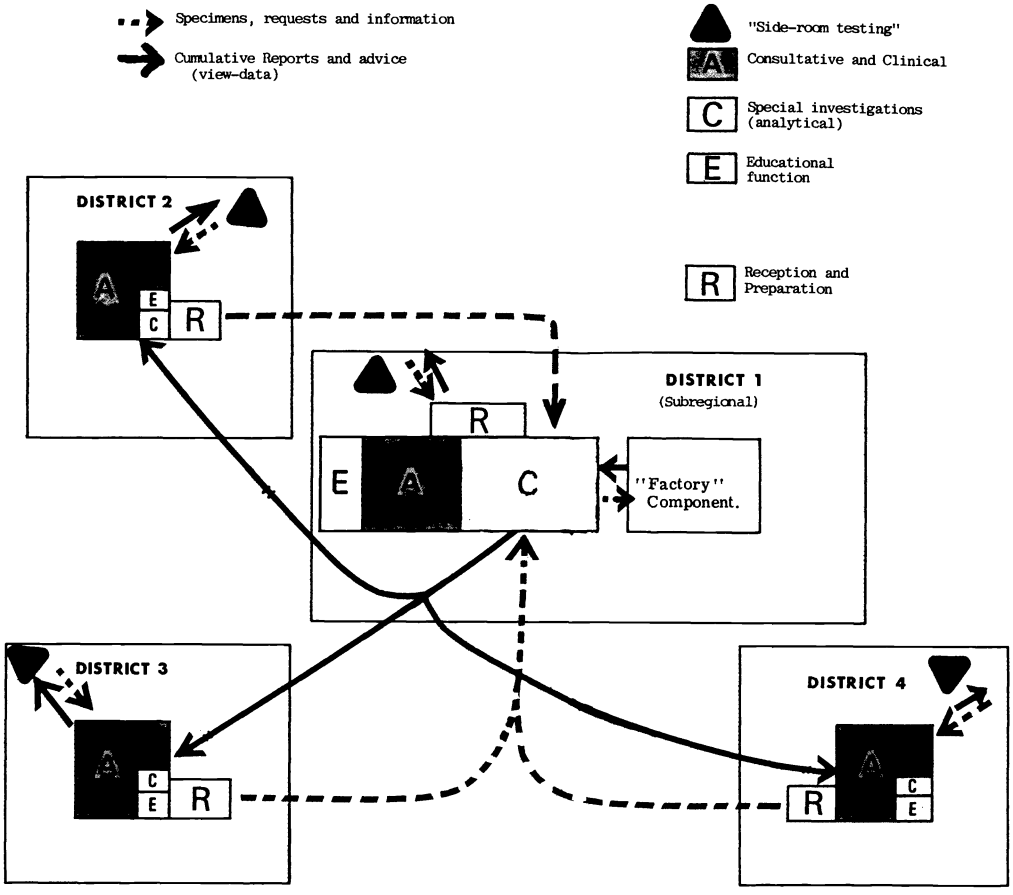

Fig. 1. Scheme for an integrated Clinical Biochemistry Service for a sub-region serving 1-2 million people through four district hospitals. Only the three lower tiers are shown; the supraregional or national tier is omitted. Each district laboratory would be staffed by at least two consultants - a clinician and a chemist (analytical) who would serve on the board of directors of the integrated laboratory.

by peripheral units in respect of individual patients would also be fed into the central computer as and when they were generated and consequently be incorporated into a constantly updated cumulative index to which access could be obtained either immediately by electronic means or more leisurely by hard copy. By ensuring that results are displayed graphically as well as numerically and by incorporating additional information such as the name and amount of drugs each patient is receiving at the time the tests are performed, more clinically useful reports can be generated than is currently possible.

If all this seems unrealistic and/or unachievable it is because of our inate resistance to change - not to any technological or even financial impediment. Advances in laboratory reagent and equipment manufacture, and of computer and information technology, have not only made such change possible but desirable as being the only way the products of biomedical research can be constantly introduced into clinical practice. The implications for clinical biochemists are that they must become more scientific whether it be biological or chemical in their outlook and less concerned with the technology of analysis production which has rightly, in my opinion, become the concern of equipment manufacturers on the one hand and financial managers on the other.

REFERENCES

1. C.A. Herter, Lectures in Chemical Pathology in its relation to practical medicine, Smith Elder and Co., London (1902).

2. H.G. Wells, Chemical Pathology; being a discussion of general pathology from the standpoint of the Chemical Processes involved, Saunders, London (1907).

3. F.C. Fowweather, A handbook of clinical Chemical Pathology, Churchill, London (1929).

4. G.A. Harris, Chemical Methods in Clinical Medicine: their application and interpretation with the technique of the simple tests, Churchill, London (1930).

5. G. Oliver, Bedside Urine Testing including Quantitative Albumin and Sugar, Lewis, London (1884).

6. O.L.V. De Wesselow, The Chemistry of the Blood in Clinical Medicine, Benn, London, (1924).

7. S.P. Stewart and D.M. Dunlop, Clinical Chemistry in Practical Medicine, Livingstone, Edinburgh (1931).

8. J.P. Peters and D. Van Slyke, Quantitative Clinical Chemistry Interpretations Vol. I Balliere Tindall & Cox, London (1930).

9. O. Bodansky, Biochemistry of Disease 2nd Edition, McMillan, New York (1952).

10. J.C. Eaton and G.H. Lathe, Lancet ii, 959-964 (1963).

11. J.D.N. Nabarro, Biochemical Investigations in Diagnosis and Treatment, Lewis, London (1954).

12. V. Marks, Chemical Pathology p. 144-167 in Progress in Medical Laboratory Technology, (F.J. Baker Edit,) Butterworths, London (1962).

13. L.T.Skeggs, Amer. J. Clin. Path. 28; 311-320 (1957).

14. R.S. Yalow and S.A. Berson, Nature 184, 1648-49 (1959).

15. C.N. Parkinson, Parkinson's Law Murray London (1958).

16. E. Adrian, pp i-iv Scientific Basis of Medicine Vol. 1 pI-IV University of London Press (1953).

17. V. Marks, The choice between discretionary and profile testing pp. 259-270 in Centrifugal Analysers in Clinical Chemistry (C.P. Price and K. Spencer Edit.) Praeger, Eastbourne (1980).

18. R.R. McSwinney and D.A. Woodrow, J. Med. Lab. Tech. 26 340-346 (1969).

19. F.L. Mitchell, J. Aut. Chem. 1 179-180 (1979).

20. V. Marks, Br. Med. J. 286 1166-1167 (1983).

21. A.D. McIntyre Scottish Home and Health Department Circular 282 743 (1981).

22. M.L. Wellby, Clin. Biochem. Revs. 4 21-23 (1983).

23. V. Marks, Roy. Coll. Path. Bull. No. 42 2-41 (1983).

24. I.J.L. Goldberg and F.L. Mitchell, Lancet ii 1240-1243 (1970).

25. V. Marks, Inaugural Lecture; University of Surrey 1-22 (1972).

26. F.P. Woodford, pp85-93 in AMNECC Advances in Clinical Chemistry, (M.H. Khayat, M. Montalbetti, G. Cerriotti, P.A. Bonini Edit.) Dolphin, Milan (1982).

27. V. Marks, Lancet ii 284-285 (1966).

28. J.R. Hampton, M.J.G. Harrison, J.R.A. Mitchell, J.S. Prichard, C. Seymour, Br. Med. J. 486-489 (1975).

29. B.G. Wertman, S.V. Sostrin, Z. Pavlova, G.D. Lundberg, JAMA 243 2080-2082 (1980).