The Role of the Clinical Chemistry Service

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SUMMARY

Larger numbers of increasingly diversified laboratory investigations have demanded an improved performance in laboratory services. The implementation of automation has alleviated the analytical problems. The formidable clerical task involving professional staff can be handled conveniently, more accurately and more quickly than by manual methods by electronic data processing systems, which are briefly reviewed. Organisation of the clinical chemistry service in the UK is returning to a centralised system, which has become necessary in the face of escalating expense in buying equipment and the running costs of the Health Service. Serious shortage of specialised personnel is alleviated by the adoption of a rationalised system with the formation of group laboratory services. Application of some of these ideas may help in planning improvement of the clinical chemistry services in South Africa.

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There is a growing demand for laboratory investigations and an urgent need for substantial improvement in performance in order to handle the workloads efficiently.[1] The increasingly scientific approach in patient care has resulted in the development of a wide variety of techniques. Owing to the large numbers of tests being requested, automated analytical procedures have been introduced, many of which generate multiple results on a single specimen.[2] The result is a greater flow of information concerning the condition of the patient. The workflow in a typical laboratory is such that most of the time of the professional staff is spent in routine clerical duties instead of the work for which they were expensively trained.[3] Since most laboratories undertake the same wide range of investigations, many similar routine repetitive unskilled tasks have to be duplicated. The same expensive instrumentation is purchased by all the laboratories when the combined workload of any particular test of a group of laboratories could be handled by a single machine. Similarly, accounts and administration costs are also duplicated.

It is the purpose of this article to examine the requirements in a clinical chemistry service and to consider the facilities presently available in South Africa. Possible future trends are suggested, utilising the facilities and manpower that are currently in the country.

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REQUIREMENTS IN A CLINICAL CHEMISTRY SERVICE

Clinical Chemistry in the Hospital Laboratory

The distribution of work from different sources, such as inpatients, outpatients, other hospitals and private practitioners varies widely. The clinical chemistry service is conveniently divided into several branches.[4] Since it is not possible, nor desirable, for any person to claim expert knowledge throughout the whole subject, someone with specialised knowledge is required in each branch. Much of the equipment required for clinical chemistry is very expensive and cannot be provided for each of the many present laboratories.

Workflow in the Laboratory

Specimens, together with their associated test request forms, are delivered to the laboratory continuously throughout the day, with a peak around midday. The laboratory, operating mainly during normal working hours, is therefore presented with a problem by the late arrival of the bulk of its workload. The specimen and its accompanying test request form are usually allocated an accession number, the requirement being to link the specimen with the form. Blood specimens are centrifuged and prepared for analysis, and worksheets with the relevant data are prepared. The chemical analyses are performed and results are entered onto the worksheets. Quality control samples are checked, although few laboratories are able to carry out an effective system, including statistical quality control. Results for each request may be collated and a report, which is signed by the pathologist, is prepared. A copy of the report may be filed, but few laboratories are able to update records and produce cumulative reports.

Even without a detailed description of these procedures it is obvious that most of the staff's time is being spent in routine calculating and clerical work instead of carrying out chemical analyses. The potential for arithmetical mistakes, transcription errors and incorrectly associating the specimen with the patient is substantial. It is of great consequence that this should be reduced.

FACILITIES AVAILABLE IN SOUTH AFRICA FOR ROUTINE OPERATION

Mechanisation

It has been estimated that the number of specimens passing through most laboratories doubles every 5 years.[5]

The introduction of mechanisation has saved the laboratory from complete submergence in the escalating numbers of specimens received each day for analysis.[6] Experiments have shown that a qualified analyst, when carrying out a manual analysis, will have greater error in his results at the end of a long run than at the beginning. Further, a highly qualified technician is not going to be happy carrying out repetitive work.

The first stage in mechanisation is to provide 'limited function automation', suitable only for smaller laboratories. Large centres serving a major hospital or a group of hospitals have workloads that can only be efficiently handled by more advanced automatic procedures.[7] For the past 15 years continuous flow automatic analysers have achieved great success, where up to 80%[4] of the bulk of the common simple assays are handled. Multiple channel machines are available as a package enabling groups of tests to be carried out from one sampler unit. In general, laboratories have their own ideas on optimum grouping of tests, and find disadvantage in using a rigidly fixed machine. Apart from the economics of carrying out unsolicited tests, factors such as the production of multiple standards and repetition of all tests after a failure on one channel need to be considered.

In the past few years, substantial effort has gone into the commercial development of discrete analysis systems,[3,7,8] which effectively simulate manual methods. These systems operate at much higher speeds than continuous flow systems. About 12 single-channel discrete analysers are currently available. In general, all the systems have been shown to give trouble-free mechanical performance with a high degree of precision. The big advantage of these systems over continuous flow is the greater throughput of most analyses.

A currently popular discrete analysis single-channel system has been evaluated and is suitable for colorimetric[9] and reaction rate[10] analyses. However, it suffers from the major disadvantage of a lack of automatic handling of the samples being introduced to the machine. A modular multichannel automatic biochemical analysis system has been produced by Vickers Limited, Medical Engineering, Basingstoke, UK. This machine can be programmed to analyse 50 to 300 precentrifuged samples of plasma per hour with a higher degree of accuracy and precision in performing the various standard analytical procedures normally carried out by laboratory personnel. Owing to the modular nature of the equipment, up to 20 different blood constituents in each sample can be measured simultaneously, and new analyses may be introduced and other changes made without interfering with the operation of the remaining channels. Blood samples for analysis are collected in disposable vials which are sealed and coded for each patient. The vials are centrifuged and loaded into magazines, which are placed on a magazine platform. Further handling of the specimens and presentation of the results are carried out automatically. The information concerning patient identification and the analytical data are relayed to a teletype for presentation of results, and punch or magnetic tape for computer input can be produced simultaneously.

The Use of a Computer in Clinical Chemistry

Increasing administrative workloads in the laboratory programme are accompanied by a proportionate increase in error.[3] Although the analytical problems have to a great extent been alleviated, the clerical task has become formidable. The evolution of laboratory computer systems abroad has brought out one interesting development: the feature of regular project meetings involving many disciplines, where members of the medical profession have not only discussed matters of principle and detail, but have also had to formally agree on them. It is often said that a greater benefit than the actual operation of a computer is the compelling of an organisation to consider and define its procedures.

Several hospitals abroad have obtained limited funds to purchase a variety of small computers with the intention of developing their own computer programmes (software). The result has been a great multiplication of effort, with no hope of ever achieving full automation. Computer companies are developing software 'turn-key' packages, but variation in the requirements in individual laboratories renders implementation difficult. If this project is to be well organised, the laboratories would have to employ consultants to select the system and also to assist with negotiations and specifications.

Data processing systems have been successfully developed,[11,12] with several basic routines involving the input of raw data of analytical results, interpolation against standards and calculation of concentration of test samples. Input of patient identification data was collated with the results, and reports were printed in tabular form. In 1964, a study of the computer system at University College Hospital, London, where a very high standard is maintained, compared the computer system with manually read, calculated and transcribed results and revealed a significant manual error rate.[3]

In 1965, the concept of fully automatic (on-line) medical systems for data processing was recognised. It was an attempt to avoid the disadvantage of an essentially mechanical system which included too short a mean time between failures. On-line systems[13] have been used in the past 10 years and have their own problems. Much more sophisticated computing was necessary, and the late arrival of specimens in the laboratory caused workload peaking. The result was a carry-over of half of the work file from one day to the next.[13]

ORGANISATION OF THE CLINICAL PATHOLOGY SERVICE IN THE UK

Fundamental to the policy of rationalisation of laboratory services, which is being implemented in the UK by the Department of Health and Social Security,[14] is the concept of creating area laboratories. One reason leading to this policy was the poor standard of work exhibited by some of the smaller laboratories. The result is a more uniform structure which will permit universal application of computers. Merging of laboratories is taking place, not always resulting in closures, since some laboratories specialise in certain analyses, and duplication of expensive instrumentation is obviated. It is interesting that, although

the picture is complicated by commercial interests, a similar trend is evident in the USA[15] and in the Scandinavian countries.[16]

In clinical chemistry several branches are needed, with an expert specialising in each branch of the subject.[4] It is no longer possible, nor desirable, for anyone to claim expert knowledge of the whole subject. Units of functional and/or methodological similarity are preferred, to enable each to develop with a suitable degree of autonomy. Eight branches might be satisfactorily constituted as follows: automation, lipids, enzymology, protein chemistry (including some immunology), steroids, non-steroidal hormones, metabolic studies and toxicology.

A population of about half a million people being served by 3 district general hospitals has been suggested[4] as an optimum size to merit provision of advanced mechanisation, electronic data processing and other necessary specialised units. The branches would be distributed throughout the 3 main centres by local arrangement, but ensuring that staff are evenly spread, and maintaining 3 units of comparable size. Each unit would provide the service for all 3 hospitals, so that a clinical chemistry 'presence' of significant magnitude would be maintained at each hospital. Specimens would be conveyed by an efficient transport system from the hospital where the patient was being treated to the centre where the analyses would be carried out and reported with the use of a computer. Printing of reports over a telephone link would be done in the hospital from which the specimen had originated.

Multichannel automatic machinery and electronic data processing equipment for a grouping of 3 hospitals as described was estimated in 1970 to cost in the region of £120 000 in the UK.[4] These costs may at first seem high; but at present much money is being spent in a relatively unplanned way, and wasteful duplication is inevitable.

POSSIBLE FUTURE TRENDS IN SOUTH AFRICA

Similar problems in the development of clinical pathology laboratory services are encountered in South Africa as anywhere else in the world. The acute shortage of trained and specialised personnel in our country is aggravated by decentralised systems. All laboratories offer a comprehensive service requiring duplicated expensive equipping and administration. The timely introduction of mechanisation has alleviated most analytical problems. Many laboratories bill the patient or a medical aid society and have an additional motivation for automation, which leads to more accurate reporting. Multichannel automatic analysis has been widely criticised, but the emergent opinion is in favour of this type of procedure on a centralised and rationalised basis.[15,16]

As in the London area, nearby hospitals on the Witwatersrand could be grouped in areas. The branches of the clinical chemistry department, distributed throughout 3 centres, would be linked to a computer installed at one hospital of the group. Pooling the clinical chemistry work carried out for 3 hospitals such as the Johannesburg General, Baragwanath and South Rand hospitals, would merit provision of centralised advanced automatic facilities with computer data processing. This would represent about 2 million investigations annually. Installation of the computer would be at one hospital where the work for all automated tests for the 3 centres would be carried out. The remaining branches of the subject would be established at the other hospitals where the relevant experts would be in charge. Each unit would provide the service for all 3 hospitals.

Efficient transport facilities would be required for transit of refrigerated serum samples. After the analyses had been completed, the results, reported by the computer, could be made available on a distant teletype installed at the hospital from which the specimen originated. Peripheral laboratories at each hospital would have a considerable reduction of their workloads, and only basic equipment to deal with urgent 'hot' tests would be required. Greater reliability of results could be achieved and the expert opinion of a consultant would be extended. Extensions of automation in other fields, such as radio-immunoassay, will allow implementation of the same policy.

CONCLUSION

There is an urgent need for standardisation of a uniform structure throughout the country, with universal application of the same system. Regular project meetings of clinical pathologists representing the whole country should compel formal agreement on principle and detail, and action to introduce new systems should be undertaken. An increasing awareness of the need for good management may be expected. Graduate staff more orientated towards physics, mathematics, statistics and chemical engineering will be employed, and laboratories will become engaged in research and developmental projects. Systems engineering, programming and electronics will be provided from external sources. Implementation of advanced types of multichannel automatic analysers will demand maintenance. Mutually planned development with standardisation of purchases throughout the whole country would of necessity lead to better servicing facilities.

Medicine is moving into an era in which it is becoming relatively cheap to accumulate data which are easy to obtain, and such data can wisely be used in diagnosis and treatment.

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The tumour was approached at operation through a long oblique incision along the anterior border of the sternomastoid. A 5 × 5 cm tumour, lying in the fork of the carotid artery, was excised by sharp and blunt dissection, without interrupting blood flow in the carotid system. A further mass then became palpable and visible near the base of the skull. It had the same consistency as the tumour removed from the carotid bifurcation, and was situated in the right vagus nerve. Part of the vagus was sacrificed in removing it. This tumour measured 2 × 3 cm.

In the postoperative period a haematoma developed in the wound. At exploration, active bleeding was found coming from the partially-cut vagus nerve. The vessel was ligated. The patient subsequently manifested evidence of recurrent laryngeal nerve palsy on the right.

The histology of both tumours was the same. There were nests of cells around networks of small bloodvessels. The cells were round to polygonal, with oval, elongated nuclei, some of which were vesicular and some hyperchromatic (Fig. 2). The cytoplasm was abundant and eosinophilic. The features were consistent with non-chromaffin paraganglioma (chemodectoma).

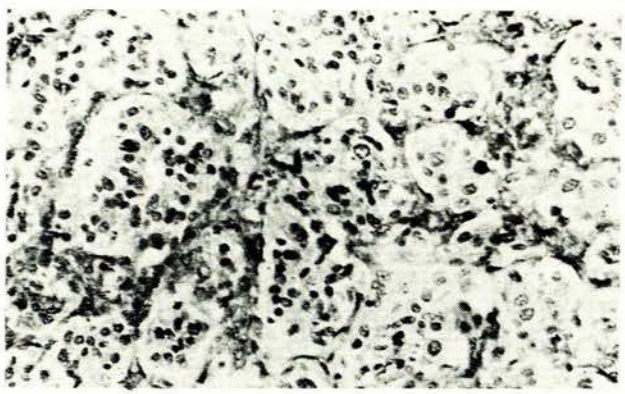

Fig. 2. Representative histology of the tumours, showing typical 'zellballen'.

Five months later the patient complained of a lump on the left side of the neck, adjacent to the angle of the mandible. A left carotid arteriogram showed this to be a carotid body tumour. No further tumours were demonstrated. A 3 × 4 cm tumour was removed from the left carotid bifurcation. Histologically it had the same characteristics as the previous two tumours. The postoperative course was uneventful.

DISCUSSION

The anatomical existence of the carotid body was reported initially by von Haller in 1743.[8] Almost 150 years passed before Marchand (1891)[9] first reported a tumour arising in this organ. Since then reports of chemoreceptor tissue occurring in different sites have appeared at regular intervals.[1,10]

In 1900 Kohn[11] reported his investigations on the morphology and embryology of the carotid body. He coined the term 'paraganglia' to describe a collection of morphologically similar cells which occurred in relationship with either the sympathetic nervous system or a branchial arch artery. The term paraganglion implied that the chief cells of the organ arose from the same cells that form the ganglion cells of the sympathetic nervous system, have an endocrine function similar to that of the adrenal medulla, and are intimately related to the autonomic nervous system. For many years it has been customary to divide paraganglia into two groups, based on their reaction to potassium bichromate. Chromaffin paraganglia exhibit cytoplasmic granules which probably contain catecholamines.[1] They are in close relationship with either adrenal medulla or sympathetic ganglia, secrete pressor substances, and are connected to an efferent nerve. Non-chromaffin paraganglia do not have cytoplasmic granules which stain with potassium bichromate. Nevertheless, catecholamines have been demonstrated in the chief cells of non-chromaffin paraganglia by fluorescent microscopic methods,[1] and these can be secreted.[12] Non-chromaffin paraganglia are usually associated with afferent nerves.[13] Because of these differences, it is increasingly common practice to call non-chromaffin paraganglia 'chemoreceptor bodies'[3] despite the fact that chemoreceptor function has not been demonstrated in all parts of the system.

Anatomy and Distribution

The detailed development of the chemoreceptor system has been studied extensively and has been the subject of debate for some time.[3] The fundamental question has been whether the specific cells of the system are of mesodermal or neural origin. Although this question has not finally been answered, a dual origin from mesoblastic and neural tissue would explain the presence of ganglion cells, nerve fibres and paraganglionic cells in the normal carotid body and also in the normal vagal body.[3]

Chemoreceptor tissue occurs throughout the body, both above and below the diaphragm. These sites have been identified either by standard anatomical dissection, or based on the occurrence of rare primary tumours in sites where chemoreceptor tissue had hitherto not been identified. The common denominator for chemoreceptor tissue occurring above the diaphragm is its association with cranial nerves and their ganglia, as well as with vessels of the embryonic branchial arches. The known sites of occurrence include the carotid body, glomus jugulare,[14] glomus tympanicum, auricular branch of the vagus, aortic body, glomus intravagale, ganglion ciliare, nose, lung, mandible, larynx, trachea, tongue, pineal body, heart, retroperitoneal space, walls of large arteries, pylorus, duodenum and urinary bladder.[1,2]

Histology

Chemoreceptor tissue consists of lobules of parenchymal cells, the lobules being separated from one another by a

variable amount of vascular connective tissue.[15] Within these lobules the cells are arranged in spherical clusters of '*zellballen*', which are delineated by reticulin and cellular fibrous tissue. There are two types of parenchymal cell in the carotid body, the type I or chief cell, and the type II or sustentacular cell. Chief cells exist in three forms, which are termed the light (L), the dark (D) and the pyknotic cells.

Chemoreceptor Tissue at High Altitude

The carotid and aortic bodies have been shown to respond to a decrease in blood pH, a decrease in arterial oxygen tension, an increase in arterial carbon dioxide tension, or an increase in blood temperature.[16] The effects of such a response are to vary the rate, depth and minute volume of respiration, and to affect the tone of the sympathetic nervous system. It was thus theoretically predictable that states of chronic hypoxia would produce continued excess stimulation of the carotid bodies.

Arias-Stella in 1969[17] reported that the carotid bodies of Peruvians living in the High Andes were heavier than those of people living at sea level. This was confirmed in animals from the same regions.[4] This increase in weight was due to hyperplasia, which in guinea pigs and rabbits was due to an increase in the number of light (L) cells. Similar increases in weight have been observed in other states of chronic hypoxaemia, such as chronic bronchitis and emphysema, and also in some anaemias.[15]

The effects of states of extreme oxygen deficiency on the chief cells have been studied under the electron microscope.[15] Chief cells contain granular bodies which probably contain catecholamines. These are discharged into the intercellular spaces during extreme hypoxia. The significance of this is not known.

Since these studies have appeared, there have been reports of the strikingly high incidence of carotid body tumours in people born and living at high altitudes.[2] The obvious question is whether this could be an extreme manifestation of hypoxia-induced hyperplasia of chemoreceptor tissue. However, although hyperplasia may account for some chemodectomata, some at least are true neoplasms, because metastases do occasionally occur.

Multicentricity of Chemodectomata

Multiple chemodectomata have been described arising simultaneously or sequentially in various parts of the chemoreceptor system, and are more commonly found to have a familial tendency.[18] Cases of multicentric chemodectomata which include a vagal body tumour are extremely rare, only 6 cases having previously been reported.[3] Only one of those cases had bilateral carotid body tumours. It is interesting to note in this respect that the second carotid body tumour in our case was initially missed. As the incidence of multicentricity is about 10%, this may be a pointer to the routine use of bilateral carotid angiography in the diagnostic work-up.

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