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ASPECTS OF AUTOMATION IN CLINICAL CHEMISTRY

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DEPARTMENT OF PATHOLOGICAL BIOCHEMISTRY

ROYAL INFIRMARY

GLASGOW

Thesis submitted for the Degree of Doctor of Philosophy in
the Faculty of Medicine, University of Glasgow, Scotland 1983.

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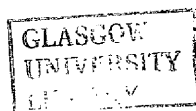
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DECLARATION

The work presented in this thesis was performed solely by the author apart from areas of acknowledged cooperation.

ALAN STEWART McLELLAND

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LIST OF NON-STANDARD ABBREVIATIONS USED

a) UNITS

$\Delta A/\text{min}$	Rate of change of absorbance per minute
cm	centimetres
cps	characters per second
g/l	grams/litre
Kb	kilobyte
mA	milliampere
Mb	megabyte
ml	millilitre
mmol/l	millimole/litre
U/l	International Unit of enzyme activity/litre
$\mu\text{mol/l}$	micromole/litre
μl	microlitre

b) STATISTICS

n	number of points in a group of observations
r	correlation coefficient
SD σ	Standard deviation of a group of observations
SEM	Standard error of mean
σ_x^2, σ_y^2	Variance of x or y
\bar{x}	Mean of a group of observations

c) CRITICAL PATH ANALYSIS (See Table 4)

σ^2	variance associated with mean time t_e
t_e	Expected mean duration of any activity
TE	Earliest expected cumulative mean time to any event
TL	Latest expected cumulative mean time to any event

d) CHEMICAL METHODS AND PROFILES

Alb	Albumin
ALT	Alanine Transaminase
AP	Alkaline Phosphatase
AsT	Aspartate Transaminase
Ca	Calcium
CAP	Profile of tests in Bone Disease
CK	Creatine Kinase
Cl	Chloride
CO ₂	Total carbon dioxide content
LFT	Liver Function Tests
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IgM	Immunoglobulin M
K	Potassium
LDH	Lactate Dehydrogenase
Na	Sodium
PO ₄	Phosphate
TP	Total Protein

e) OTHERS

ACB	Association of Clinical Biochemists
DEC	Digital Equipment Ltd, Maynard, Mass.
GRI	Glasgow Royal Infirmary
ID	Internal Diameter
IL	Instrumentation Laboratories Ltd., Warrington, UK
MRC	Medical Research Council
NCCLS	National Committee for Clinical Laboratory Standards
PID	Patient Identification Data

SHSPC	Scottish Health Service Planning Council
SMA	Sequential Multiple Analyser*
SMAC	Sequential Multiple Analyser and Computer*
VDU	Visual Display Unit
7/120	Seven Channel, 120 sample/h continuous flow analyser, developed in the Department of Biochemistry, Glasgow Royal Infirmary

* Trademark, Technicon Ltd., Houndmills, Basingstoke, UK

SUMMARY

Automation has been employed by laboratories to help them cope with an exponentially rising workload during the last two decades. In this thesis I examine some of the objectives behind applications of automation to both the analytical and clerical processes within the laboratory. I consider, in particular the application of Critical Path Analysis to the problem of achieving a major priority of any laboratory - a fast turnround time.

For the reasons outlined in Chapter 1, in modern clinical biochemistry (chemical pathology) laboratories, staff and equipment are concentrated into fixed sites with large workloads and considerable managerial problems. Control over the diverse and complex sequences of operations performed in dealing with requests for analyses requires an appreciation of the relationship of one activity to another within each sequence. Once the individual activities which contribute directly to the overall turnround time of requests have been identified, attempts can then be made to reduce the duration of elements of the critical path, in the expectation that the total turnround time will then be shortened.

I suggest that Critical Path Analysis, one of a family of related management tools, may be applied to the operations within a clinical biochemistry laboratory. The elements of Critical Path Analysis are described in Chapter 1, and applied to the steps necessary to generate an electrolyte profile.

In Chapter 2, Critical Path Analysis is used to study the inter-relationships between activities performed during analysis of specimens. It is shown that increased sampling rates can directly affect the critical path and some of the work which has resulted in the development

of faster, or more suitable analytical equipment within the author's laboratory is presented. Revised Critical Path networks are then used to demonstrate the effects of implementation of such equipment in the rate limiting areas of analysis. I conclude this Chapter by consideration of automated data acquisition and result calculation, and the amount of time which can be saved by these techniques.

The 'fine tuning' of analytical results is examined in Chapter 3. Some of the problems associated with an overloaded manual reporting system in a large clinical biochemistry laboratory are considered, and the network of activities is described.

Critical Path Analysis is again used to illustrate the effects on turnround time of transferring clerical activities to a computer system, and the major gains to be made by installing computer terminals in ward areas, despite problems imposed by consideration of confidentiality at remote sites, and limitations on the data which can be printed at such sites.

In Chapter 4, attention is drawn to the existence of a finite lower limit to turnround time beyond which no further improvement can be expected, no matter what developments occur in either speed of analysis or efficiency of clerical record handling.

The discussion of Chapter 5 briefly considers the radical changes to the present structure of laboratories which might be necessary to further reduce turnround times in Clinical Biochemistry.

1. INTRODUCTION

"Automation is spreading in two directions which may have many interrelations; comprehensive improvement in the organisation of the laboratory involving data processing, and the development of largely independent devices for analysis".

Neumann and Fisher, 1969

"Automation should be encouraged".

Report of the Royal

Commission on the NHS (1979) para 15.32.

Automation has been defined as the "use of electronic or other mechanical devices to replace human labour" (OED 1972). Like Northam (1981) I shall be using the term "automation" in this, its widest possible sense rather than use the IUPAC definition (1970) and restrict discussion to equipment which embodies feedback controls. In clinical chemistry, in particular, there are two major facets to automation -automation of the analytical processes leading to the production of a result from a patient's specimen, and automation of the clerical activities leading to the return of that result to the requesting clinician.

It was to be expected that automation would alter working practices within laboratories. It will continue to affect the quality of analyses; will provide additional analytical capacity because of higher sampling rates; will, on occasion, radically alter the laboratory's approach to the manner in which it attempts to organise



FIG. 1 A bed-side diagnosis of urine. *17th-century woodcut.*

its workload, and will provide a means of improving the service offered to clinical staff by reducing the time taken to return results to the Ward, Clinic, or practitioner's office.

The aim of this thesis is to examine objectively the extent to which application of automation has improved clinical chemistry in two main areas - overall turnaround time for the more commonly requested analyses, and quality of results - and to examine the role of critical path analysis in obtaining these improvements.

Succeeding sections of this introduction will consider the historical development of clinical chemistry laboratories in the United Kingdom, the demands currently being made on laboratories by clinicians, and the changes in organisation which have been made to try to cope with the increasing amount of work referred to the laboratory.

1.1. Development of Clinical Chemistry laboratories

There is an immense contrast between the practice of clinical chemistry today and many years ago. This is clearly evident from the exterior and interior views of a modern clinical biochemistry laboratory (Plates I and II respectively) and the simple urine testing portrayed in Fig 1 and performed at the bedside by the attending physician.

Attempts to trace the origins and development of the subject however, must go back beyond the 19th century.

It had been known since around 500 AD that insects will approach urine from a patient with diabetes mellitus presumably because of its sugar content (Akernecht, 1944); Paracelsus had developed techniques for quantitative urinalyses during the 16th



PLATE I Exterior of a modern clinical chemistry laboratory



PLATE II Interior view of the author's laboratory

century (Zekert, 1968) and Shakespeare, in Henry IV Part II, wrote a reference to urine testing into a conversation between Falstaff and his page:

FALSTAFF: Sirra, you giant, what says the Doctor to my water?

PAGE: He said, sir, the water itself was a good healthy water, but the party that owned it, he might have more diseases than he knew for.

Blood analysis was less common, although Robert Boyle had demonstrated the existence of chloride in human blood in 1684 (Foster, 1959); William O'Shaunessey had reported the acidosis of cholera in a letter to the Lancet in 1831; Bischoff had demonstrated the presence of carbon dioxide and oxygen in blood in 1837 (Winsten, 1969) and Sir Arthur Baring Garrod had shown raised serum urate concentrations in gout sufferers in 1857 (Lines 1977). Nevertheless, the urinalyses of Fig 1 remained the most important aspect of clinical chemistry until the end of the 19th century. Indeed, William Prout in "Inquiry into the nature and treatment of diabetes, calculus and other affections of the urinary organs" (1821) was able to define a "travel pack" of reagents which "with the aid of a common taper or candle" would enable the user to perform "all the experiments on urine, and urinary productions that are commonly necessary in a practical point of view" (Raine, 1966).

The introduction of the hypodermic syringe in the early 1900s changed the emphasis of clinical chemistry towards blood testing, to the extent that blood analyses currently account for over 90% of the workload of clinical chemistry laboratories (Table 1).

TABLE 1

SCOTTISH CLINICAL CHEMISTRY LABORATORY RETURNS

FISCAL YEAR 1979/80

Division of Workload by Specimen Type

Laboratory	Blood Analyses as % of total	Urine Analyses as % of total	Other Fluids as % of total
Hawkhead (Paisley)	91.6%	8.1%	0.3%
Ballochmyle (Ayrshire)	97.8%	1.3%	0.9%
Falkirk (Stirlingshire)	98.4%	1.2%	0.3%
Aberdeen Royal	99.6%	0.2%	0.2%
Glasgow Royal	92.4%	6.8%	0.8%
Victoria Infirmary (Glasgow)	97.7%	1.9%	0.4%
Western Infirmary (Glasgow)	97.8%	2.2%	<0.1%
Raigmore (Inverness)	95.4%	4.1%	0.5%
Edinburgh Royal	98.9%	0.9%	0.2%
Ninewells (Dundee)	97.2%	2.8%	<0.1%

A combination of factors including the switch to a more easily available fluid; the necessity to pre-process blood specimens by centrifugation before analysis, the requirement for protein removal in certain methods and the variety of bulky equipment required to perform tests led to analyses being performed away from the patient's bedside and inside the permanent clinical laboratories which had been developing during the middle and late nineteenth century. Examples include a lectureship in Chemical Pathology for J.W.L. Thudichum at St Thomas's hospital in London in 1865 (Lines 1977) and Henry Bence-Jones report in 1848 of his discovery of a new protein in his laboratory at St Georges Hospital.

An ever increasing workload and a repertoire which by 1924 already included serum bilirubin, calcium, chloride, phosphate, glucose, creatinine and urea, caused laboratory staff to look to manufacturers of scientific instruments to improve and expand their capacity and range. The selenium barrier layer photocell was introduced in the United States in the 1930s (Varley, 1966) and this offered the potential for more accurate colorimetry, compared with the Duboscq type of visual colorimeter or Lovibond comparator, but at a price sufficient to ensure that not more than one or two would be purchased for any hospital.

Thus by the middle of the 20th century the trend was established for analyses to be performed in the hospital laboratory rather than at the patient's bedside.

The physical displacement of the laboratory worker away from the patient created a problem which has been amplified over the years and still exists today - the need for some form of delivery system to

transport specimens to the laboratory and return results to the wards, and the major time delays which such a system automatically introduces into the request-analysis-report cycle. The consequences of this need for a distribution system will be considered more fully in Section 2.2.1.

1.1.1 Centralisation of laboratory resources

The trend towards centralisation has continued throughout the 20th Century and for similar reasons. Arguments for centralisation (Whitby, 1967) include making the best use of comparatively small numbers of trained staff (Total ordinary membership of the Association of Clinical Biochemists was 1500 in 1981 - Worthington, (1982)); meeting the needs of junior staff for adequate training; making the best use of costly analytical equipment (In the early 1970s the first analyser costing over £100,000 was introduced in the UK (Bick et al, 1972)); coordinating service and research functions, and the capital cost of constructing an adequate laboratory. For example, Hospital Building Note 15 (1973) provides for 214.5 square metres of primary space for the Biochemistry components of a District General Hospital and this provision is generally considered grossly inadequate. Current safety regulations covering the provision of piped gases, fume cupboards (Howie, 1978) and other essential services will further increase the cost of the basic laboratory (Westbury, 1979).

There are as yet no signs that the tendency towards centralisation will diminish and at regular intervals fresh proposals arise in support of centralisation, arguing economies of scale (Whitby 1967, Marks, 1972, Camm, 1980). It has been suggested that clinical chemistry laboratories can be among the most expensive areas in a

hospital (Josephson 1972). A major influence of automation on clinical chemistry departments, however, has been to reduce the labour-intensive, and therefore costly, aspects of laboratory work. It is generally held that around 80% of laboratory costs are staff costs (Lathe 1969), and it is certainly true that biochemistry laboratories have succeeded in holding staffing to, at worst, a linear increase in the face of an exponentially increasing workload (Fig 2). Even where expensive equipment alone is considered, the equipment costs of radiology and radiotherapy departments are considerably higher than those of clinical biochemistry and some pathology equipment such as scanning electron microscopes, which are used in the study of relatively few samples, cost approximately the same as a multi-channel analyser in biochemistry.

Centralisation is not without drawbacks, however. Whitby (1967) noted that the major adverse implication of centralisation was a potentially increased time for an investigation through delays both in the collection of specimens and delivery of reports. There is also some loss of contact between laboratory staff and clinicians, and there may be inability to meet the special requirements of hospitals and units at some distance from the main laboratory. Despite this, the concept of centralisation has been generally favoured because a centralised laboratory is better able to adjust to changes in the basic factors affecting any clinical chemistry laboratory - workload, repertoire, arrival times of specimens and requesting patterns.

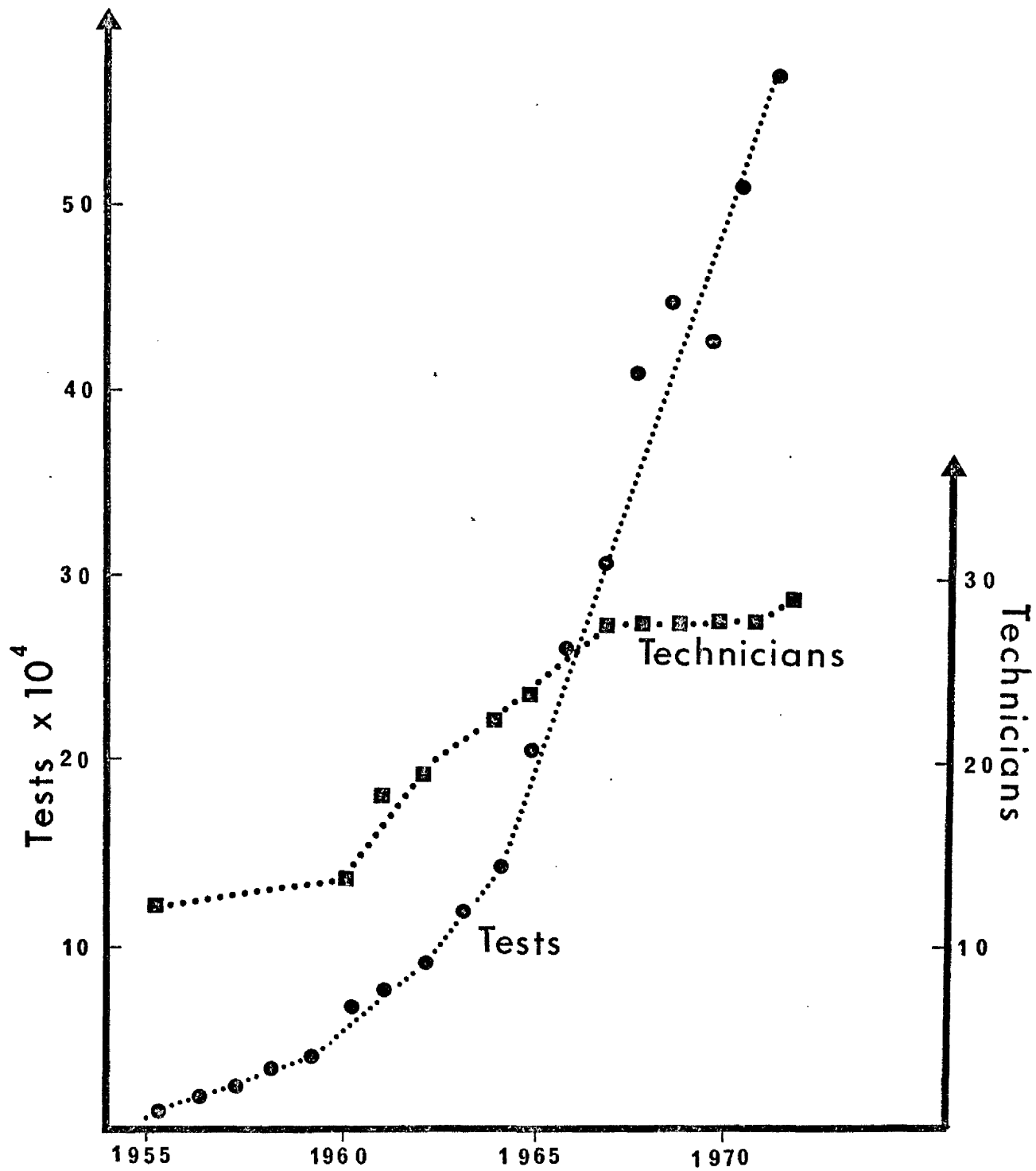


Figure 2

GRI Annual Totals (Analyses & Staff)

1.1.2 Workload

The dependence of the practice of medicine on objective quantitative measurements has been increasing over the years. One consequence has been the dramatic increase in the numbers of analyses which clinicians have requested of biochemistry departments throughout the 20th century (Nelson, 1969, Lathe and Mitchell 1966, Whitby 1967).

Two examples which typify the growth in the numbers of analyses requested come from Whitby in 1967 who showed that the workload in the Royal Infirmary, Edinburgh had risen exponentially from about 1,400 in 1923 to 407,000 in 1966, interrupted only by the war years, and from the Royal Infirmary, Glasgow where the number of analyses performed went from around 10,000 in 1950 to over half a million in 1971. This is illustrated in Figure 2. Clinical biochemistry laboratories in teaching hospitals are currently likely to be carrying out about 5,000 analyses each day with somewhat smaller numbers at weekends.

The reasons for the increase include clinical dissatisfaction with other diagnostic methods, the ability of a laboratory result to reflect quickly a rapidly changing clinical situation, and, above all, an increased awareness of the value of chemistry not only in diagnosis but, even more so, in the monitoring of therapy (Watts 1973).

This development has been encouraged by clinical chemists who now have a significant part to play in medical training at both undergraduate and postgraduate level and who have always taken an active role in interpretation of results, and in developing research into the nature of disease processes.

1.1.3 Repertoire

The repertoire of the clinical laboratory has also evolved over the years as analytical techniques have improved, and the range of test available has greatly increased. It is currently possible to request of a clinical biochemistry laboratory of the order of 500 different analyses (Marks 1972) of which about 250-300 might be performed locally, and the rest referred to specialist centres. A sample repertoire of a major biochemistry laboratory is listed in Table 2. Requesting is not uniform across the full list, however, and Table 3 gives a clearer indication of the workload for each identifiable analytical sub-section of the laboratory expressed as a percentage of the total analyses. From this it can be seen that around sixteen individual analyses in the first four groups account for over 65% of the total workload of the department. The remainder of this thesis will concentrate primarily, but not exclusively on the management of this small group of analyses, not because they are the most important clinically of the tests offered, but because they involve the largest numbers of requests and hence contribute the most significant management problem.

It also happens that a large number of clinical management decisions are based in part on this restricted group of profiles. Decisions on alterations to intravenous fluid regimes, transfer of patients into coronary care units, the need for renal dialysis and the fitness of patients to undergo surgery, all depend to some extent on this limited group of sixteen or so tests, and their rapid analysis and return of results in time for the ward round when these decisions will be taken.

TABLE 2

LISTING OF ALL ANALYSES PERFORMED BY OR THROUGH THE
DEPARTMENT OF BIOCHEMISTRY, GLASGOW ROYAL INFIRMARY - DECEMBER 1980

17-oxosteroids
17-alpha-hydroxyprogesterone
2,3, Diphosphoglycerate
3-methyl histidine
acetoacetate
acetylator phenotype
acid phosphatase (prostatic)
adrenocorticotrophin
alanine transaminase
albumin
aldolase
alkaline phosphatase
aldosterone
alpha-amino nitrogen
alpha 1 acid glycoprotein
alphafetoprotein
alpha 1 antitrypsin
alpha 2 macroglobulin
aluminium
amino acids
ammonium
amylase
androstenedione

Table 2 (contd)

Angiotensin II
antidiuretic hormone
apo-lipoprotein A-1
Apo-lipoprotein B
arsenic
ascorbate
aspartate transaminase
barbiturates
base excess
Bence-Jones protein
beta-hydroxybutyrate
Beta 2 microglobulin
beta quantification
beta lipoprotein
bicarbonate
bilirubin (total)
bilirubin (direct)
blood gases
bone screen
bromide
bromsulphthalein
C-reactive protein
cadmium
caeruloplasmin
calcium
calcitonin
calculi
carboxyhaemoglobin
carotene

Table 2 (contd)

Carcinoembryonic antigen
catecholamines
chloride
chlormethiazole
chorionic gonadotrophin
cholinesterase + phenotyping
cholesterol
chromium
CO₂ content
CO₂ tension
complement C3
copper
coproporphyrin
Cortisol
creatinine
creatine kinase
creatine kinase B ISO
creatine
cryoglobulin
cyanide
cystine
dehydroepiandrosterone
dehydroepiandrosterone sulphate
digoxin
drug screen
drugs (other)
ethanol
faecal occult blood
faecal fat

Table 2 (contd)

ferritin
follicle stimulating hormone
folate
free fatty acid
free thyroxine index
gamma GT
gastrin
globulins
glucose
glutathione reductase
glutathione peroxidase
glucose-6 phosphate dehydrogenase
gold
growth hormone
haematocrit
haemosiderin
haemoglobin
haptoglobin
HDL-cholesterol
hydroxyproline
hydrogen ion
immunoglobulin A
immunoglobulin G
Immunoglobulin M
immunoelectrophoresis
insulin
iron-binding capacity
iron
LDH isoenzymes

Table 2 (contd)

Lactate dehydrogenase

lactate

LDL-cholesterol

lead

lecithin

lipoprotein X

lipotrophin (MSH)

lipid electrophoresis

lithium

luteinising hormone

magnesium

manganese

melanogen

mercury

methaqualone

methaemalbumin

metadrenaline

methotrexate

methaemoglobin

myoglobin

nickel

nitrogen

oestriol

oestradiol

oestrogen

orosomuroid

osmolality

oxalate

oxygen saturation

Table 2 (contd)

oxygen tension

P 50

packed cell volume

pancreatic polypeptide

paraquat

paracetamol screen

paracetamol

parathyroid hormone

pH

phenytoin

phenobarbitone

phosphatase. Acid (Prostatic)

phosphate

placental lactogen

porphyrins

porphobilinogen

potassium

prednisolone

prealbumin

pregnancy test

primidone

prolactin

progesterone

protein (total)

protein electrophoresis

pyruvate

pyridoxine

Table 2 (contd)

pyruvate kinase

renin

Residual albumin binding capacity

retinol binding protein

reverse T3

riboflavin

salicylate

sex hormone binding globulin

silver

sodium

specific gravity

sphingomyelin

sulphonamides

sulphaemoglobin

testosterone

theophylline

thiamine

thiocyanate

thyroxine binding globulin

thyroid stimulating hormone

thyroglobulin

thyroxine

titratable acidity

transferrin

transketolase (erythro)

trimethoprim

trichloroacetic acid

triiodothyronine

triglycerides

Table 2 (contd)

urate

urea

uroporphyrin

urobilin

urobilinogen

valproate

vanillyl mandelic acid

Vitamin E

Vitamin D3 (25-OHCC)

Vitamin C

Vitamin B12

Vitamin B6

Vitamin B2

Vitamin B1

Vitamin A

Vitamin C (leucocyte)

VLDL-cholesterol

Warfarin

xylose

zinc

TABLE 3

GLASGOW ROYAL INFIRMARY AND ASSOCIATED HOSPITALS
BIOCHEMISTRY WORKLOAD 1980 BY LABORATORY SUB-SECTIONS.

Section	No. of individual analyses performed (thousands)	Percentage of total analyses
Electrolytes (Na,K,Cl,Co ₂ ,Urea,Creatinine)	419	34.0%
Liver Function Tests (AsT,AlT,Bilirubin,AP)	150	12.2%
Cardiac Enzymes (AsT,AlT,LDH,CK)	45	3.7%
Calcium,Phosphate,Proteins (Ca,PO ₄ ,TP,Alb)	188	15.3%
Specific Proteins	12	1.0%
Thyroid	50	4.0%
Other Endocrinology	134	10.9%
Other enzymes	23	1.9%
Lipids	21	1.7%
Trace Metals	27	2.2%
Manual Analyses	23	1.9%
Paediatric/Neonatal	80	6.5%
Others	58	4.7%
OVERALL TOTAL	<u>1,230</u>	<u>100.0%</u>

While a department's reputation will often depend on technically complex, labour intensive specialist assays which require both interpretive and analytical skill, and often relate to new and challenging areas of medicine like aluminium levels in dialysis encephalopathy or parathormone estimation on specimens from neck-vein catheterisations, these analyses are expected to accompany an efficient "routine" service and it is with the efficient operation of this basic, fundamental service that this thesis is mainly concerned.

The number of request forms received during 1980 was 281,000 or around 1000 requests for analyses per working day throughout the year. The majority of these requests (600-700/day) involved (not always exclusively) the first four test groups of Table 3.

1.1.4 Distribution of specimens

Having shown the increase in the numbers and types of analyses which the laboratory is expected to perform, it is necessary to consider in more detail the constraints on laboratory operation imposed by this workload.

One of the most obvious constraints relates to peaks in the workload for any group of analyses. Table 3 shows the number of analyses performed by each section of the author's laboratory during 1980, and from this it is possible to compute that the average number of samples to be processed for the electrolyte group on any working day is around 240 on the basis of a 7 to 1 test/request ratio for this group of tests. Thus given an eight hour working day, the sampling rate of any prospective analyser apparently need only be around 30-40

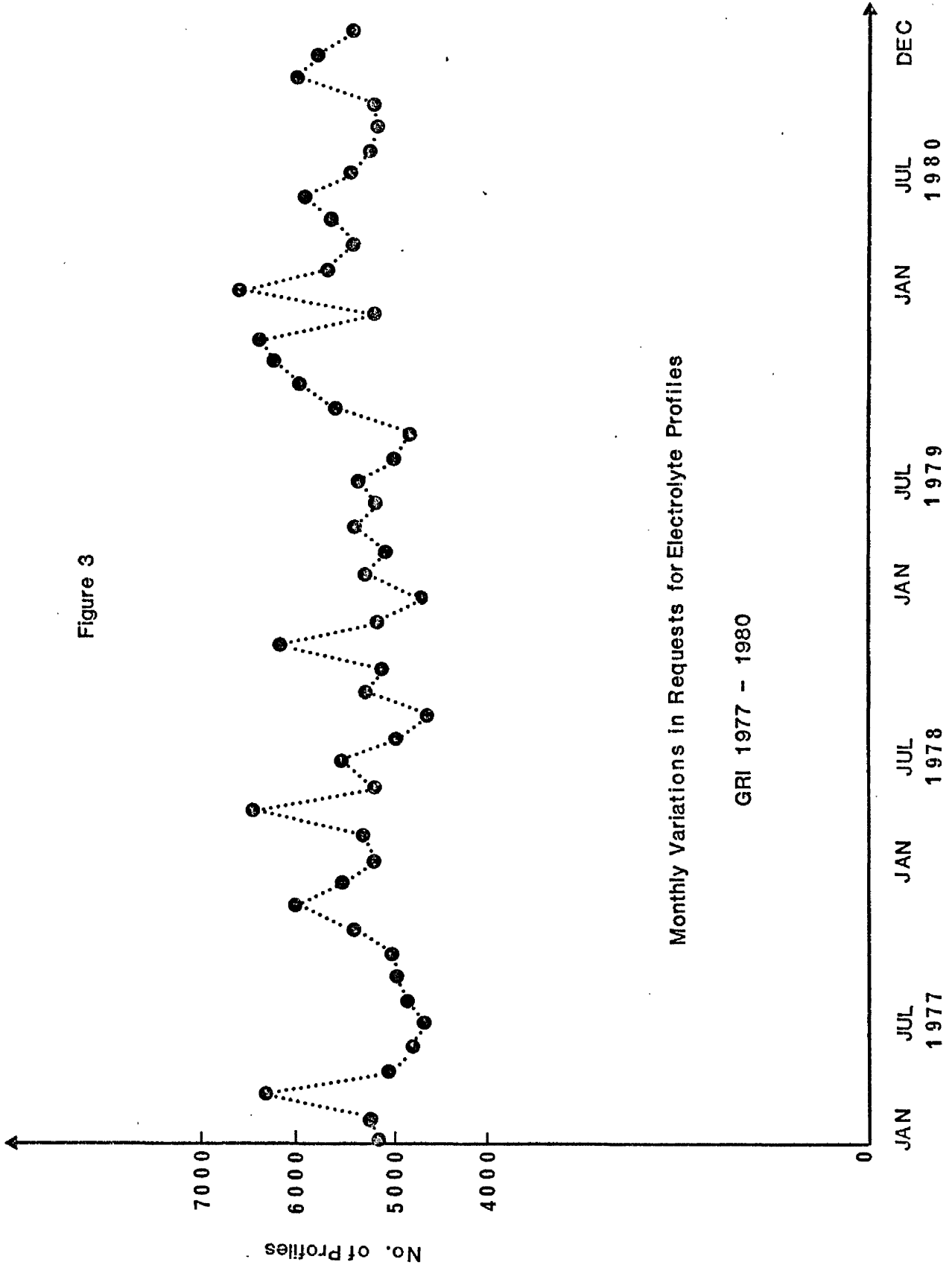
samples per hour to cope with this load. This oversimplified calculation does not, however, allow for setting up the analyser, cleaning and simple maintenance.

Laboratories must also plan for the various kinds of peaks in demand, and the variation in distribution of requests for analyses must be considered. Fig 3 shows the monthly variation in requests for this group - it is clear for example, that the winter months make more demand on the service than does the summer holiday period. The upward trend in the number of requests can also be seen from Fig 3, amounting to an average annual growth rate of around 5% pa. Fig 4 shows the daily variation in electrolytes and liver function tests during February 1982, again demonstrating the peak demand caused mainly by particular clinics being held on specific days of the week.

In Fig 5 the typical hourly distribution of specimens for electrolyte analysis on arrival at the specimen reception area is shown. These are classified according to source. It is clear that 41% of this work arrives in the afternoon between 2 and 5 pm. On the busiest days of the week from Fig 4 this will amount to over 180 specimens for this group alone. It is also clear from Fig 5 that these samples are mainly of out-patient origin, and that, if they are not dealt with on the day of arrival, they will delay the more urgent in-patient samples which constitute the bulk of the early morning requests reaching the laboratory.

Consideration of these simple factors taken with the lost analytical time through the need for preventative maintenance on the equipment, the necessity to run calibrants, quality control samples and drift standards and a 5% pa growth rate gives a predicted requirement

Figure 3



Monthly Variations in Requests for Electrolyte Profiles

GRI 1977 - 1980

Figure 4

Daily Variation in Requests for Electrolytes and Liver Function Tests

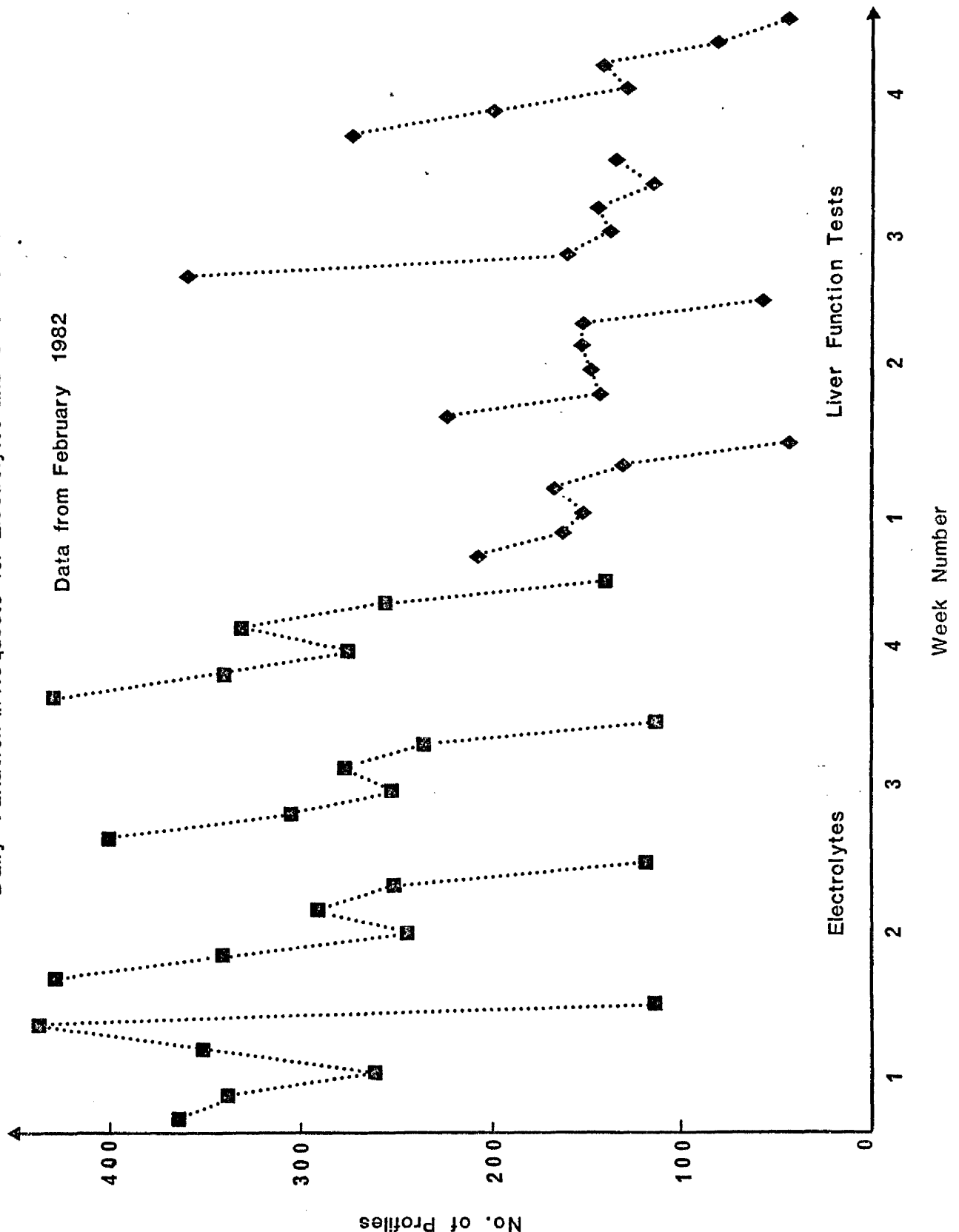
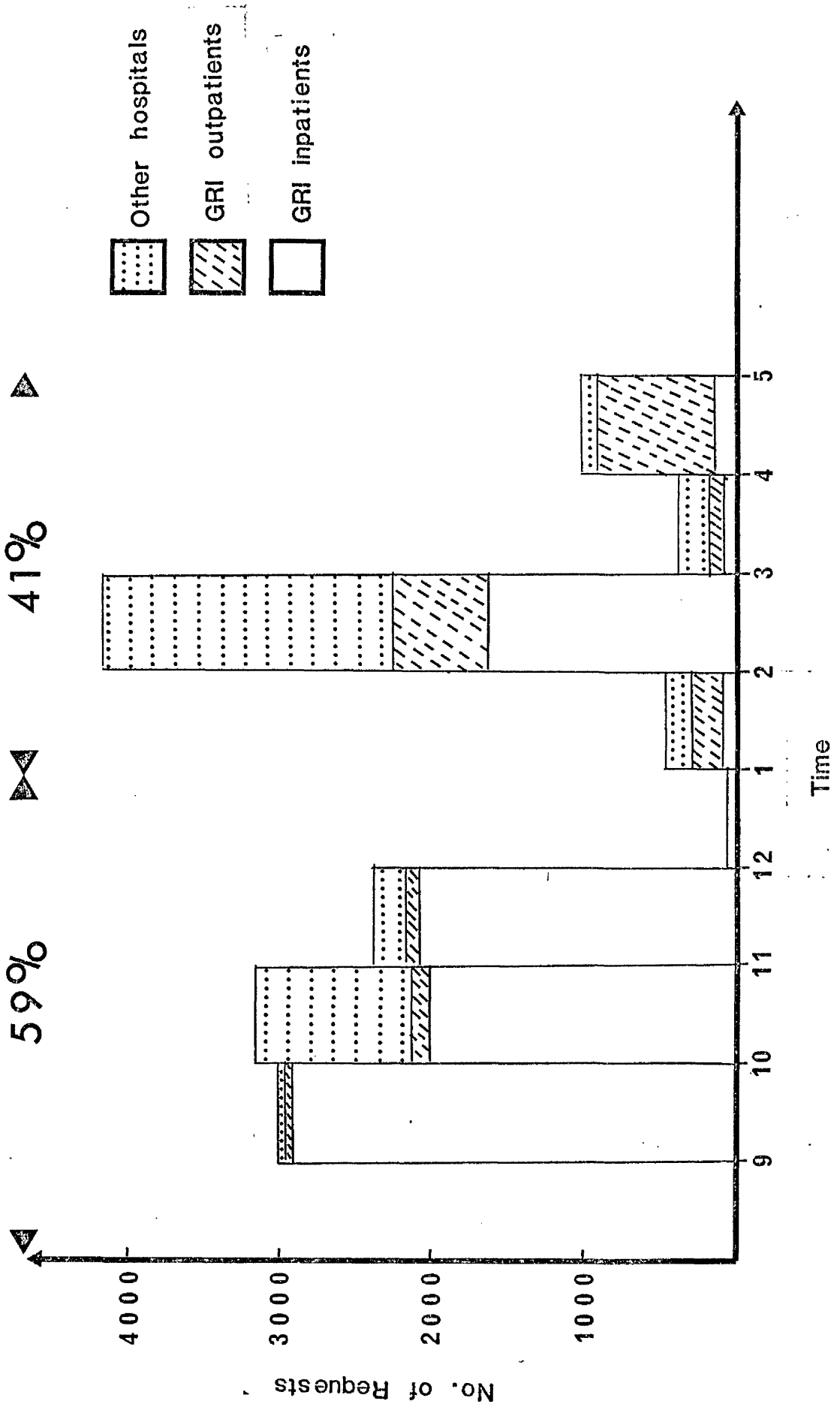


Figure 5

Arrival Times of 14934 Electrolyte Requests GRI Jan -Mar 1979



for electrolyte processing in 1987 of around 140 samples/h. Clearly the laboratory must expect instrument manufacturers to provide present-day analysers capable of performing at similar sampling rates in order to provide a service over the expected seven year working life of the equipment. The effect of the types of instruments available on the ability of the laboratory to respond to clinical requests, and on the structure of the laboratory's internal organisation will be considered in the next section. However, before leaving this section, it should be mentioned that an excessive sampling rate can be an embarrassment to a laboratory. The reagent consumption of a large 300/h multichannel analyser can be such that the day's workload is processed as one, or perhaps two very large batches so that gains in shortened analysis times can be more than offset by extended waiting time before analysis.

1.1.5 Effects of Automation on Requesting Patterns

Based initially on workload along the lines of the arguments in Sections 1.1.2 to 1.1.4 a laboratory will acquire analytical instruments appropriate to its needs. This equipment is likely, however, to pull together a number of analyses for two main reasons -the analyses form functional groups of tests such as the electrolyte and renal function group, cardiac enzyme profile, gonadotrophins, or thyroid group, and it is usually possible for an instrument manufacturer to link a number of tests together into a multi-channel analyser using the same process control system and thus offer a more cost-effective package than the alternative automation of single methods (Clarke, 1978, Andrews, 1972). Additionally, laboratory operation is simplified by grouping a number of channels together and staff costs can be

reduced (Hindricks, 1975) thus improving the apparent productivity of the laboratory, based on the number of tests produced by the laboratory divided by the total number of technical staff. (Nelson, 1969). Some manufacturers have extended this to fifteen to twenty test profiles, but these have their own drawbacks clinically, including the concealment of important results within the large non-selective profiles. The form which reports should taken will be further discussed in Section 1.16 where the clinical requirements of the basic service are considered in more detail.

This in turn, will mean that the clinician who makes his requests from the automated section of the laboratory's repertoire will ensure a fast turnaround of results, but if he associates this with a request from a slower, or non-automated section there is a risk that the completed results may well be delayed because the reporting system operates at the rate of the slowest analysis. This in turn will have an effect on the requesting patterns which develop. It can be argued that faster turnaround will generate its own demand to some extent - for example when gravimetric sodium and potassium estimations required 1 to 2 days before results were available, the analyses were often of academic interest to a clinician, and so demand was contained because of the laboratory's inability to return results within the time required.

Introduction of flame photometers which gave a more accurate result in minutes contributed to the increase in workload. Similarly, the relatively recent concept of providing on site glucose analysers in diabetic clinics has led to an increased demand for this type of service.

Laboratories tend to automate requests and request groups which already comprise the largest sections of the workload, and there is a risk that improved response in those areas will lead to greater use of the service and a type of positive feedback may develop to the detriment of the other tests which are requested less frequently.

Methods of overcoming some of the potential constraints related to the requesting of unusual groupings of tests, or the slower, more time-consuming sections of the repertoire will be considered in detail in Section 3.4.4, but for the moment, it is necessary to recognise that laboratory organisation must allow all combinations of tests to be requested, with fastest possible turnaround irrespective of requesting patterns.

1.1.6 Clinical Expectations of a laboratory service

Before considering laboratory organisation, it is instructive to consider the expectations of the clinical staff and what they see as their ideal requirements for laboratory requests. A study among clinical staff in the Western District of Glasgow (Ormerod et al 1976) identified extended turnaround time for routine analyses as a major source of dissatisfaction among clinicians, with one third of those returning questionnaires unhappy at laboratory performance in this area, and a smaller, but still substantial minority (~15%) concerned even about turnaround of emergency analyses. Inadequate communications in reporting abnormal results by telephone, and lack of interpretation of results was also indicated, but this latter data was not unfortunately correlated with the provision of clinical information on request forms. A majority of clinicians found the system of ordering

large profiles helpful, but a preference for ordering analyses by functional groups (eg liver function tests, lipid profiles), was expressed by a majority of users, with a marked (60%) disinclination to order individual analyses.

Cumulative reporting was also requested, at some stage, by at least one third of the clinical staff, and this aspect will be discussed in Section 3.4.3.

Attempts to satisfy these criteria, and in particular to meet the twin aims of improving turnaround times while basing the analytical equipment on the need to perform functional groupings of tests, will have a considerable bearing on all aspects of laboratory organisation, in particular the specimen reception and distribution system (Section 2.3), the manpower requirements, the number and variety of data acquisition devices (Section 2.5) and the provisions for report production (Chapter 3).

1.1.7 Summary

In Section 1.1 it has been shown that, in response to increasing workload, laboratories have remained centralised. This makes best use of resources, although at the expense of introducing a delay between specimen collection, analysis and the delivery of a report. This delay is mainly due to the distance between the clinician and the laboratory - which requires a delivery system. Laboratories have automated their common analyses in response to clinical demand for faster turnaround, and geared this automation to the peak demands for each analytical group although it has been suggested that combinations of common and uncommon requests can pose problems for the laboratory. Evidence has also been presented to show that

clinicians favour small functional groups of analyses over either single tests or large profiles and are dissatisfied with the turnaround times which laboratories can achieve.

1.2. A simple Method of assessing the impact of automation on the laboratory

The first page of the introduction indicated that automation would have an effect on both the analytical processes and the ways in which the laboratory was organised to report results. The objective of this and succeeding sections in the Introduction is to describe methods which permit objective assessment of these effects, and, in particular, to concentrate on the application of network analysis techniques to laboratory organisation, since it is by this technique that all subsequent improvements in analytical sampling rates (Chapter 2) and automation of reporting systems (Chapter 3) will be measured.

It has been shown in Section 1.1, that, for historical reasons, clinical laboratories became physically removed from the source of a request for analysis - the patient's bedside, the general practitioner's surgery or the clinic. Thus the familiar cycle of requesting - specimen transportation - analysis, and report delivery was created, in which the laboratory is regarded as a box into which requests and specimens are placed, and out of which come reports. (Fig 6).

The next level of sophistication labels the events within the box and shows the logical sequence of these events necessary to produce the report (Figure 7). From this it is clear that the overall turn-round time of any analysis is the sum of the times taken for a number of intermediary events, some of which proceed stepwise in a linear fashion (eg the specimen reception processes) and others of which are performed in parallel (eg the separate worksheet construction and analytical activities at each separate work area of the laboratory).

THE REQUEST-RESULT-REPORT CYCLE

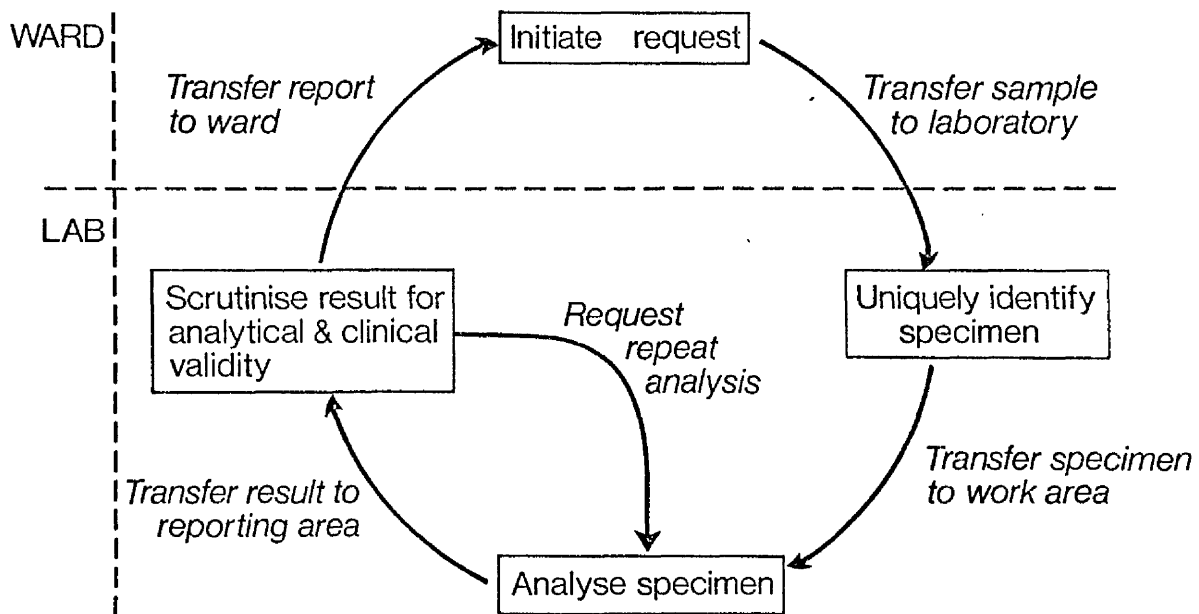


FIGURE 6 Schematic diagram of report production in a clinical chemistry laboratory

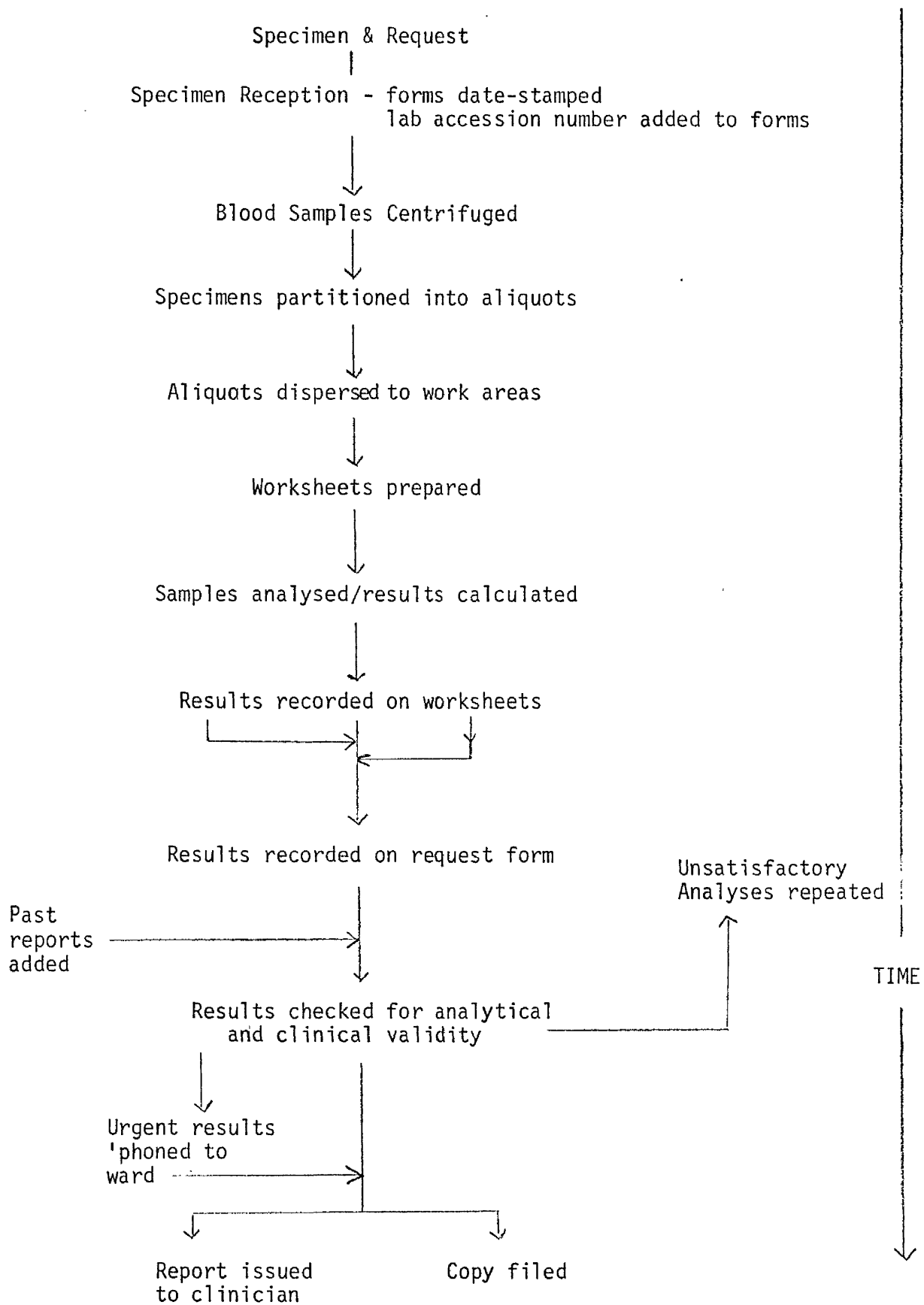


FIGURE 7 Sequencing of operations within a Clinical Chemistry laboratory

To study the processes further it is useful to employ some form of management system which will allow us to identify the time-critical areas of the sequence and hence permit evaluation of the effects of any adjustments which attempt to optimise the sequence. In this sense, clinical laboratory management is no different from building projects, production systems or assembly lines, and should be amenable to some form of network technique. These have been available since the late 1950s (Payne, 1966) and were originally used in the Polaris project by the American Navy, but there seem to have been few attempts to apply these to clinical laboratories (Spiegel, 1980, Boer, 1972). A number of different approaches to long-term planning have been suggested, such as PERT (Program Evaluation Review Technique); CPM (Critical Path Method); PRISM (Program Reliability Information System for Management); IMPACT (Integrated Management Planning and Control Technique) and SCANS (Scheduling and Control by Automated Network Systems) (Starr, 1964). All of the above share the concept of a critical path - that is the event or sequence of events which is rate-limiting in the flow chart of the system.

1.2.1 Elements of Critical Path Analysis

The objective of attempting to use critical path methods in studying the various operations within a clinical chemistry laboratory is to define the rate-limiting activities within the laboratory and thus focus attention on the areas which, if improved, would shorten the total turnaround time in line with the clinical requirements identified in Section 1.1.6.

In essence, critical path methods add a time dimension to the sequence of events which have already been elucidated. Each of the activities to be accomplished is shown as an arrow, and the completion of an activity is called an event and is shown as a circle (Table 4). The method traditionally requires that three estimates be made to permit calculation of the expected elapsed time for each activity. These are an optimistic estimate (a) a pessimistic estimate, (b) and an estimate of what is most likely, (m). The expected elapsed time, (t_e), is then calculated as

$$t_e = K_1(a+b) + K_2(m) \dots\dots\dots 1$$

where K_1 and K_2 are derived weighting constants, frequently taken as $K_1 = 1/6$ and $K_2 = 2/3$ (Starr, 1964). Further, an estimate of the variance σ^2 associated with the t_e for each activity is necessary, since the sum of the variances of the independent activities in a system will provide the variance of the total sequence and permit estimates to be made of the likelihood of deviating from the target time. The formula for the variance of an elapsed time estimate is given by

$$\sigma^2 = [K_3 (b-a)]^2 \dots\dots\dots 2$$

where K_3 is also a derived weight and is generally taken as $1/6$ (Starr 1964).

1.2.2 Application of Critical Path Analysis to Laboratory

Workflow

To illustrate this process we can consider a section of laboratory workflow relating to the production of computer-based cumulative electrolyte reports in the authors laboratory in 1975 (Fig 8).

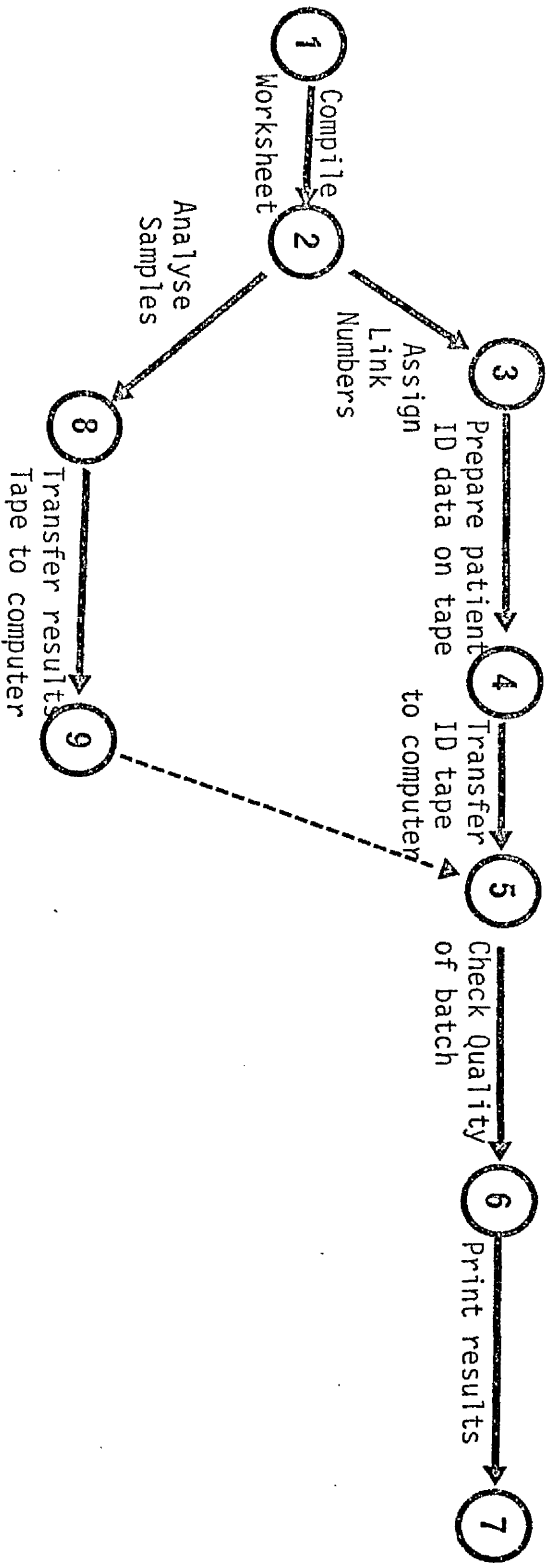


FIGURE 8 GRI Electrolyte Report Production (1975) - Basic Network

TABLE 4

ELEMENTS OF CRITICAL PATH ANALYSIS




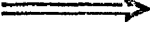
Symbol	Name	Interpretation
	Activity	Specifies a particular operation to be performed and demonstrates the relationships between events.
	Node/event node	Symbolises the completion of an activity
T_e	Cumulative Mean Time	Measures the earliest expected cumulative mean time taken to get to any node in the network along the particular activity sequence shown. It is associated with the Node symbol
t_e	Expected Elapsed Time	This time measurement is the mean time taken to complete any one activity and is associated with the activity arrow
	Dummy Activity	This shows a logical connection between two nodes, but has no physical existence, and a t_e of zero.
σ_e^2	Variance	The variance is a measure of the likely spread of times for a single activity. Variances are additive and can be used to measure the 95% confidence interval of the likely time to completion of any section of the network.

TABLE 4 (contd)

Symbol	Name	Interpretation
	Critical activity	An activity whose duration is critical to the overall time to completion of the network
T_L	Latest Cumulative time	The difference $T_L - T_E$ at any node specifies the slack in the network at that point

The dotted line between nodes 9 and 5 is used to re-connect two parallel streams of activity (in this case clerical activities through nodes 2,3,4, and 5 and analyses through 2,8,9 and 5) which must both be completed before the next activity (check Quality of Batch) can begin. It is known as a dummy activity as it has no physical existence, and a t_e of zero.

1.2.2.1 Duration of Activities - Timing Studies

An immediate difference between this application of critical path analysis and the use of similar methods in project management is that where the method is used to identify the time-critical areas of an existing network, it is possible to measure the elapsed timings of each activity, rather than use estimates as one would to construct a network analysis of a proposed building project, for example.

The formulae for expected elapsed time, t_e , and its variance, σ^2 , given in equations 1 and 2 for completeness, are therefore replaced by the straightforward, and rather more familiar statistical equations for the mean and variance of the group of observations, where each observation (X_i) represents one measurement of the actual duration of any named activity.

The formulae then become:

$$t_e = \sum x/n \quad \dots \dots \dots 1a$$

$$\sigma^2 = \sum (x_i - \bar{x})^2 / (n - 1) \quad \dots \dots \dots 2a$$

where t_e and σ^2 have the same meaning as before ,

X_i is an individual time measurement for the activity

$\sum x$ is the sum of all individual timings.

\bar{x} is the mean elapsed time and is equal to t_e .

and n is the number of timing measurements for the activity.

The differences between the pairs of formulae are interesting. If equation 1 is re-written, incorporating the traditional values for the weighting constants, we obtain.

$$t_e = 1/6 (a + b + 4 m) \dots\dots\dots 1b$$

and it can be clearly seen that this is a simple attempt to weight the value of t_e towards the most likely estimate m , while permitting slight modification by the optimistic and pessimistic estimates. In that sense, t_e is more of a median estimate than a mean, being subject only to slight bias by the extreme values which can be considered to lie at each end of the probable distribution of expected times, and it is arguable that the median, rather than the mean time obtained from the timing measurements used in formula 1a would therefore be more appropriate.

In practice, however, there is a problem with this concept. It concerns the calculation of the variance, since the variance estimate from equation 2 is used strictly as a variance of a Gaussian distribution in statistics. That is, all variances may be added to provide a measure of the total variance of a sequence of activities, and the square root of any variance is used to define the 67% and 95% confidence intervals for completion of the activity. Thus it is necessary that the Gaussian distribution statistical formula of equation 2 be used to calculate the variance from measured timings.

1.2.2.2 Example of timing studies within a network

Figure 9 shows the basic network of Fig 8 plus observed mean times t_e associated with each activity within the basic network.

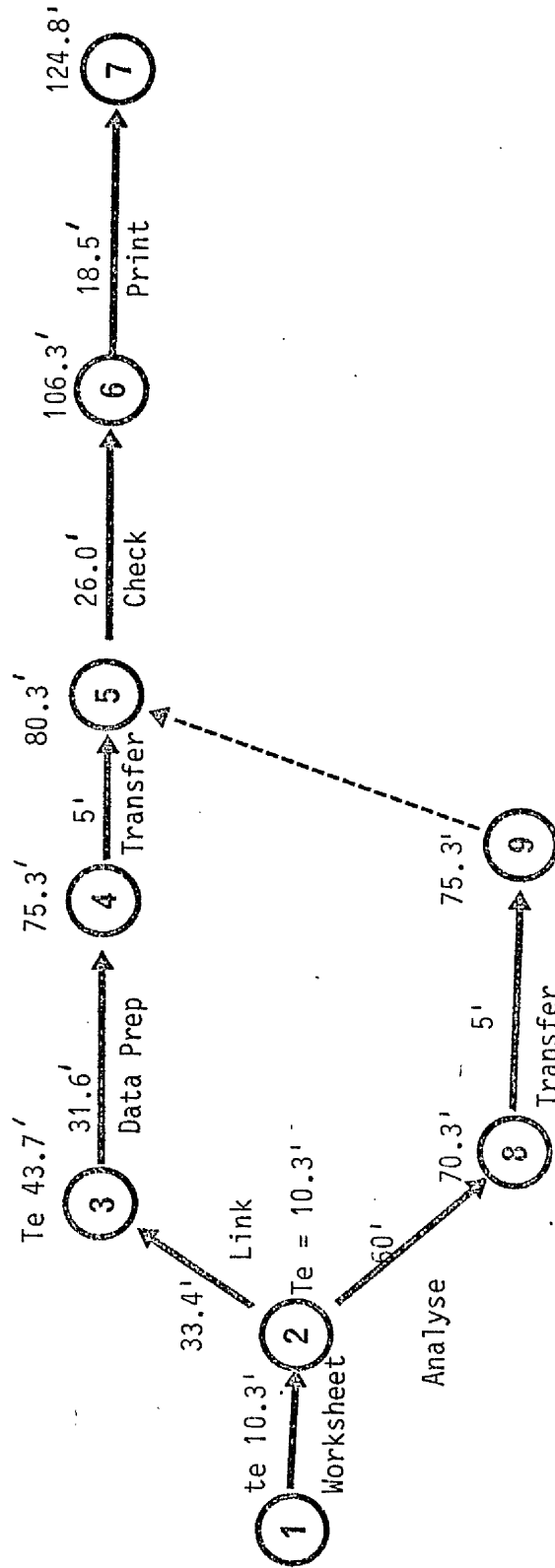


FIGURE 9 GRI Electrolyte Report Production (1975) - Timing Study

Cumulative mean time along each path is now determined at each node by adding together the previous time estimates, and this cumulative time T_E is shown directly above, or to the right of the event circles. It will be noted that the two routes to junction node 5 give different cumulative sums for the two branches, but that, when this conditions arises, we carry forward the larger total in calculating the elapsed time to completion of the project. With this estimated mean time for job completion we can now move backwards through the network, subtracting from each T_E value the observed timings t_e which immediately precede it, and associating the result, T_L , with the previous node. Calculations associated with Fig 9 are tabulated in Table 5.

It will be noted in Table 5 that where the two branches converge at node 2, (Fig 9) the two values of T_L obtained by subtraction of the expected elapsed times for assignment of link numbers (33.4) and for analysis (60') from the T_L at nodes 3 and 8 respectively are not equal, and that the smaller of the two T_L values has been accepted.

The difference $T_L - T_E$ can now be obtained for each event node and is shown in Column 4 of Table 5. This difference is called the 'slack' or 'slack time' and is a measure of the amount of slippage which can be permitted for each activity. That is, activities on that branch can be allowed to slip by the amount of slack indicated at the event node without affecting the overall time to completion of the network.

TABLE 5

CALCULATIONS ASSOCIATED WITH THE CPA NETWORK OF FIGURE 8.

Node	T_E (mins)	T_L (mins)	Slack ($T_L - T_E$)	Cumulative Variance
1	0	0	0	-
2	10.3	10.3	0	5
3	43.7	43.7	0	30
4	75.3	75.3	0	65
5	80.3	80.3	0	67
6	106.3	106.3	0	94
7	124.8	124.8	0	119
8	70.3	75.3	5	-
9	75.3	80.3	5	-

The critical path has no slack and, from the data in Table 5 it is clear that in this instance the critical path on Fig 9 lies through nodes 1 to 7 inclusive.

Any slippage along the critical path will clearly be reflected in an increased time to completion of the network. There is however, a small slack of five minutes on the analytical branch (Nodes 2,8,9) implying that this section can take up to five minutes longer to complete without affecting the total project time.

1.2.2.3 Inferences from critical path networks

From even the simple network example in Fig 9 a number of conclusions can be drawn. Firstly, there would appear to be little point in expediting the analytical processes since they are not on the critical path. However, there is also little point in improving the data prep operations 2 to 5 in isolation. In this situation the analytical processes 2,8,9 would almost immediately become rate-limiting, since, as soon as more than the five minute slack is removed from the section 2 to 5, a new critical path through nodes 2,8,9 and 5 will be created.

Thirdly, overall performance, in this instance, is more likely to be affected either by the purchase of a faster line printer (affects activities 5 to 6 and 6 to 7 - both on the critical path) or by improving the speed of checking the summary list (Step 5 to 6).

The system outlined above uses time as the fundamental dimension of the manager's objectives. It is understood however, that no two days will be the same, and even individual batches will vary in their completion times depending on availability of samples, instrument malfunctions, and other factors. It would be useful, then, to have

some idea, based on a number of timings, of the spread of network completion times, and this is where the variance estimates can be used. The variance of each activity was calculated from the basic timing studies by formula 2a of section 1.2.2.1. As previously stated, variances are additive and the data from Table 5 shows that the cumulative variance along the critical path is 119 min².

The standard deviation (S.D.) is taken as the square root of the variance, and confidence intervals based on the hypothesis that the distribution of the completion times will be Gaussian can be calculated in the usual manner (Snedecor 1956) resulting in a 95% probability that the reporting processes will be completed between 103 and 146 minutes after the start time (mean + 2 S.D.s).

The example in Figure 9 has illustrated an attempt to identify where the critical path lay and to identify areas where improvements were most likely to be effective. Critical path analysis can also assist in that, having identified substantial slack in the system, it might be possible to shift resources from the areas with most slack to the critical path. As an example, suppose improved analytical automation allowed a new electrolyte analyser to be installed which operated at double the throughput rate of the existing instrument thus reducing the activity "analyse samples" (nodes 2 and 8) from the 60 minutes of Fig 9 to a new low of 30 minutes and a variance of 10. Clearly the critical path has not altered since this new effort would have been expended on a non-critical branch. The slack in this branch, however, would now increase from the previous 5 minutes to 35 minutes. Thus it might be possible to allocate part of the data

preparation tasks of assigning identification numbers or data preparation itself to staff seconded from analysis and to expedite the production of reports by direct effect on the critical path.

1.2.2.4 Summary of use of critical path methods

Critical path methods allow the effects of projected alterations in work flow to be examined and their consequences predicted and provide a tool for better resource allocation to the time-critical areas of laboratory organisation. It should also be noted that better control over a network may reduce the variance estimates along the critical path. The effect of this is to leave the expected project completion time unchanged, but to reduce the risk of deviating substantially from the target time.

1.2.3. Assessment of the effects of automation on the quality of results

The effects of introducing automation are not purely restricted to shortening the time necessary for analysis. Automation will affect the quality of results in terms of precision and accuracy and it is the purpose of this section to identify the methods available to evaluate these effects.

The question of what constitutes acceptable precision has often been raised among clinical chemists. In general, it is assumed that values within certain limits are probably normal (the reference range) while those outside the limits probably indicate illness. While the level at which the transition takes place can be adjusted to improve the predictive value of a test (Galen and Gambino 1975; Vecchio, 1966) and while it is well documented that a large number of non-disease reasons such as age, gender, diet, drugs, use of tourniquets, genetic factors and diurnal and circadian rhythms can contribute greatly to physiological variation (Harris, 1974; Statland et al, 1973, 1974; Pickup et al, 1977; McPherson et al, 1978; Morrison et al, 1979; Harris and Brown, 1979), poor analytical precision will also contribute considerably to the probability of mis-classifying an individual since the distribution of results is a function of both analytical and physiological variability.

Tonks (1963) proposed the rule that the error should be smaller than one quarter of the physiological reference range and Ackland and Lipton (1971) tabulated the probability that a sample from a 'normal' subject would be classified abnormal due to analytical

error. That one could achieve a reduction in misclassification of subjects through the improvement of analytical precision was described by Massart et al (1978).

If the effect of improving precision are to the patient's benefit how then can precision be monitored, and what evidence exists to demonstrate improvements in precision due to the introduction of automation?

Precision has been defined as "the concordance of a series of measurements of the same quantity" and methods of measuring precision normally involve the calculation of the variance and standard deviation of a group of analytical results obtained from sampling the same material a number of times (Vogel, 1961). A number of publications have examined the evaluation of the precision of automated instruments (Broughton et al, 1969 and 1974, NCCLS, 1975; McLelland et al 1978) with the recognition that assessment of precision and accuracy is the most important part of an evaluation (Broughton et al, 1974) and that the precision estimates should not be based on analysing a number of successive identical specimens, but must incorporate the effect of drift and carryover.

Accuracy has been defined as the 'concordance between a determination and its true or most probably value (Vogel, 1961) and has been recognised as 'probably the least accessible of the criteria by which equipment can be judged' (Broughton et al, 1974). In practice, instrument evaluators concern themselves with a comparison between the results obtained from the instrument and the value either assigned to the material under test or established over a period on a comparable analyser. Whitehead and Woodford (1981) found that the comparison

between this consensus value, that is the mean value of all results for a particular analyte and method in fact showed a surprisingly close relationship to the definitive values assigned by the best available reference method.

There have been a number of attempts to assess the performance of laboratories based primarily on their performance in external quality assessment schemes and using performance indices like Variance Index (VI) and Running Overall Mean Variance Index Score (ROMVIS) designed to test the accuracy of analysis by the extent of its bias from the consensus mean for all participating UK laboratories using the same method (Whitehead et al, 1973; Whitehead, 1977).

One of the most authoritative studies of factors influencing quality of result was the report of a joint working party nominated by the Royal College of Pathologists, the Association of Clinical Biochemists and the Institute of Medical Laboratory Sciences, and sponsored by the Nuffield Provincial Hospital Trust (Nuffield, 1980) which investigated both accuracy and precision through the use of returns from the UK National External Quality Assessment Schemes.

The report concluded that there was a significant positive correlation between performance and a number of factors associated with laboratory size including workload, number of requests per annum and capital cost of equipment. It is also noted that those laboratories among the poorest 33% in the scheme did twice as many methods by manual means than did the best third of laboratories, implying that precision of manual methods is poorer than that of automated ones. This is in keeping with the report of the ACB analytical methods working party (1979) which showed that automated multichannel methods gave much

better mean precision figures than did manual methods. Other evidence also suggests that while manual analysis may be more precise than automated analysis when performed by a skilled analyst with a low workload, precision deteriorates, primarily due to operator tedium (Robinson, 1967). The automated analyser in contrast continues to perform uniformly throughout the day.

1.3 Discussion

This introduction has briefly outlined the impact which automation has made and will continue to make, in Clinical Biochemistry. Automation has allowed laboratories to cope with exponentially-increasing workloads, to improve accuracy and precision of results and to contain costs to some extent. Automation of analytical equipment has also enabled analyses to be performed faster, but in order to shorten the turnaround times of the entire system from specimen withdrawal to report delivery, it is necessary to identify the logical sequence of events, both within and outside the laboratory and examine the rate-limiting steps in the cycle. Critical path analysis has been suggested as a useful tool which will permit the study of workflow within the laboratory and both predict and measure the effects of resource reallocation or new resource deployment within the network.

Chapters 2 and 3 of this thesis will examine a number of approaches to automation of the analytical and clerical aspects of the laboratory, and will use critical path analysis to examine the effectiveness of these developments, insofar as they help to reduce turnaround time.

Additional effects of automation on quality of results will also be considered.

2. AUTOMATION OF ANALYTICAL AND RECEPTION PROCESSES WITHIN THE LABORATORY

This chapter will consider application of automation to the analytical and requesting aspects of laboratory organisation. While it has been shown earlier that it is not satisfactory to consider the effects of analytical automation in isolation from the other laboratory procedures, the generation of a result or a number of results from a sample forms a natural break-point in the discussion in that the procedures up to that point are in the main analytical and those which follow are managerial and clerical (Rappaport, 1969).

2.1. Critical Path Analysis up to and including results

Before comment can be made on the effectiveness of introduction of automation in this area, it is necessary to establish the time taken to complete each of the operations in the upper section of Figure 7.

2.1.1 Materials and Methods

In 1976, each of the major activities involved in analysing the group of four enzymes AsT, ALT, LDH and CK, which comprise the 'Cardiac enzyme' profile in the author's laboratory were identified, and their duration measured on a number of separate occasions. The profile at that time was performed on 3 LKB 8600 reaction rate analysers (Plate III) with one analyser measuring both LDH and CK.

The operation and limitations of these instruments are discussed in Section 2.4.2.2

For the purposes of calculating elapsed times, it is assumed that the sequence LDH first, then CK was adhered to, although in practice there were days when the running order was reversed.



PLATE III LKB 8600 Reaction Rate analyser

Further, all elapsed time estimates have used 'working hours', that is, laboratory activities are expected to cease at 1700 hrs and resume at 0900 hrs the following morning without the intervening sixteen hours being considered.

All Network Analysis data was processed on a DEC PDP 11/44 computer using a variant of the BASIC program 'Network' written by the author and listed in Table 6.

2.1.2 Results

Figure 10 represents a network diagram of the activity sequence outlined in 2.1.1, and Table 7 contains the times for 24 samples, at the major event nodes in Figure 10.

Table 8 shows the calculations derived from the 'Network' program using the data from Table 7, and figure 11 shows the effect of replacing some of the activity names of Figure 10 by their elapsed times from Table 7, and removing intermediate steps of short duration.

Some small differences in the use of critical path analysis for project planning and for laboratory organisational studies arise from Table 7. These are due to the necessity to superimpose a sequence of events on operations which occur at an absolute time of day. For example, the specimens for subjects 6 and 7 in Table 7, having missed the mid-morning collections from the wards, ostensibly spent 3 hours in transit between ward and laboratory. This is reflected in a very large variance estimate for steps 1 to 2 in Figure 10, identifying considerable variation in elapsed time between the withdrawal of a specimen and its delivery to the central collection point. Again, a number of activities had variable waiting times prior to commencement,

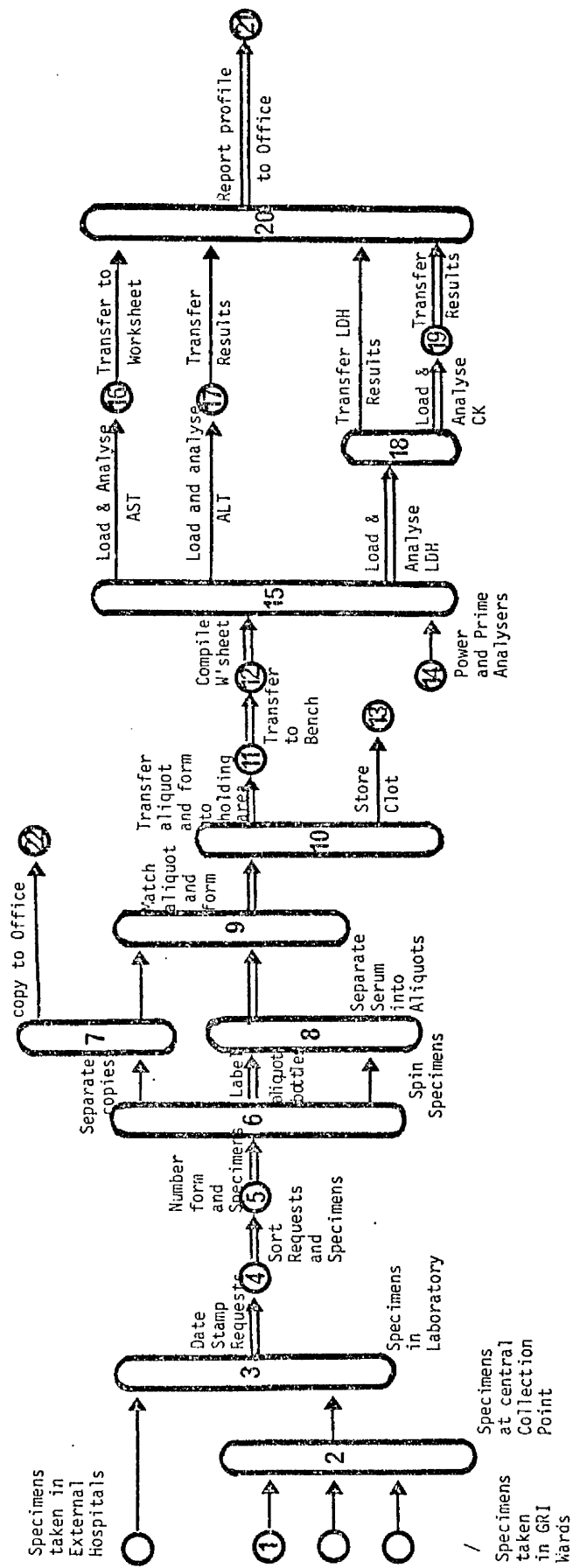


FIGURE 10 Basic Network Diagram for analysis of cardiac enzyme profiles, Glasgow Royal Infirmary, 1976

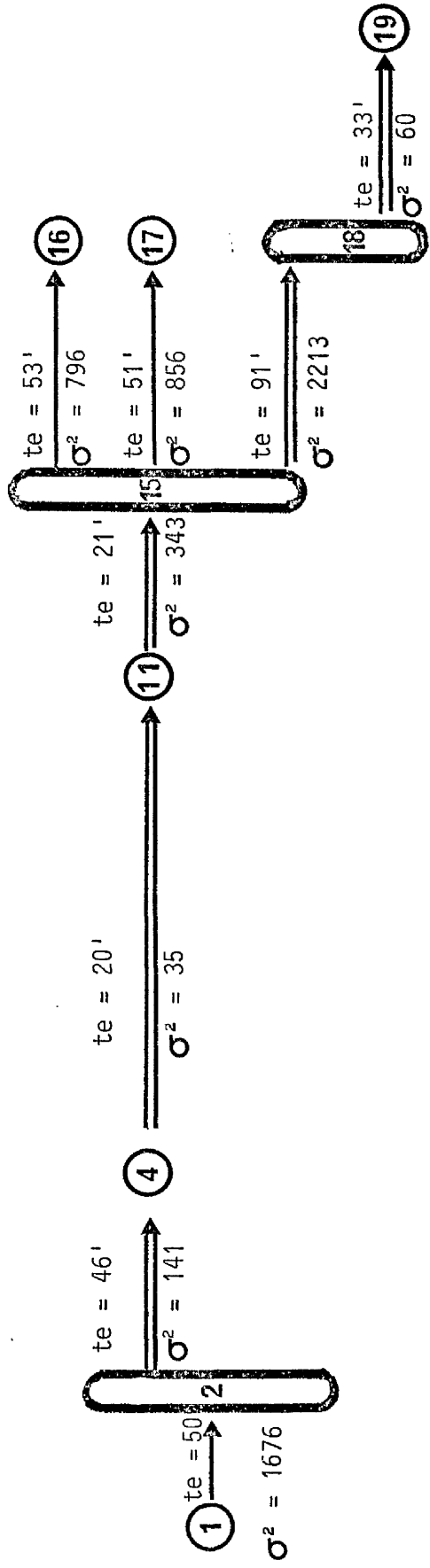


FIGURE 11 Timing Study of CPA network associated with cardiac enzyme profile analysis - Glasgow Royal Infirmary 1976 (Nodes numbered as Fig 10, Data from Table 7)

TABLE 6

LISTING OF BASIC PROGRAM 'NETWORK'

```

100 PRINT "CRITICAL PATH ANALYSIS - ACTIVITY TIMINGS"
110 DIM #2,X(500,20) \ OPEN "DP1:NETFIL" AS FILE #2
111 PRINT "INPUT NO OF COLUMNS "; \ INPUT #0:C
112 PRINT "INPUT NO OF ROWS "; \ INPUT #0:R
113 READ Z
115 PRINT \ PRINT "DO YOU WISH TO ENTER DATA (Y/N) "; \ INPUT A$
116 IF A$<>"Y" THEN IF A$<>"N" THEN 115
117 IF A$="Y" THEN GOSUB 2000
118 GOSUB 800
124 FOR J=1 TO Z
125 READ J1,J2
127 S1=0 \ S2=0 \ S3=0
130 FOR I=1 TO R
140 K=X(I,J1) \ GOSUB 1000 \ X1=K
145 K=X(I,J2) \ GOSUB 1000 \ Y1=K
150 IF X1<>0 THEN IF Y1<>0 THEN 160
155 GO TO 190
160 IF Y1<X1 THEN Y1=Y1+480
170 D=Y1-X1
180 S1=S1+1 \ S2=S2+D \ S3=S3+D^2
190 NEXT I
200 PRINT TAB(20); \ PRINT "CPA RESULTS FOR COL";J2;"MINUS COL";J1
210 PRINT TAB(20); \ PRINT "NO OF NON-ZERO TIMINGS =" ;S1
220 M=S2/S1 \ V=(S3-S1*M^2)/(S1-1) \ S=SQR(V)
230 PRINT TAB(20); \ PRINT "MEAN ELAPSED TIME FOR ACTIVITY =" ;M;"MINUTES"
240 PRINT TAB(20); \ PRINT "VARIANCE ESTIMATE =" ;V;"SQ. MIN"
250 PRINT TAB(20); \ PRINT "-----"
260 NEXT J
270 STOP
500 REM PAIRS OF COL NOS TO BE COMPARED
505 REM THIS IS THE NO OF DATA PAIRS \ DATA 9
510 DATA 1,2,2,3,3,4,4,5,5,6,5,7,5,8,8,9,1,9
800 REM PRINT TABLE OF DATA
810 FOR I=1 TO R
815 PRINT USING " ####",I;
820 FOR J=1 TO C-1
825 PRINT USING " ####",X(I,J);
830 NEXT J
840 PRINT USING " ####",X(I,C)
850 NEXT I
855 PRINT \ PRINT \ PRINT
860 RETURN
1000 REM CONVERT TIME TO ELAPSED MINUTE COUNT - M=MINS, H=HRS
1010 H=INT(K/100) \ M=K/100-INT(K/100) \ M=M*100 \ K=M+60*H \ RETURN
1999 STOP
2000 FOR I=1 TO R \ FOR J=1 TO C \ PRINT I;J; \ INPUT X(I,J) \ NEXT J \ NEXT I
2010 RETURN

```

TABLE 7

REPRESENTATIVE TIMING STUDIES OF CARDIAC ENZYME ANALYSES 1976

No. Specimens Taken	Time at Collection Point	Time at Reception	Time at Holding Point	Time at Bench	Time at ALT Available	AST Available	LDH Available	CK Available	
									Point
1	07.35	08.30	09.15	09.45	10.00	11.22	11.13	11.41	12.13
2	07.45	08.30	09.16	09.45	10.00	11.26	11.16	11.44	12.15
3	08.00	08.30	09.26	09.45	10.00	11.30	11.18	11.45	12.15
4	09.00	09.30	10.15	10.30	11.00	11.50	11.55	11.48	12.20
5	10.42	10.50	11.12	11.30	11.35	12.10	12.20	12.02	12.33
6	11.00	13.10	14.03	14.20	14.30	16.04	16.10	16.37	16.05
7	11.12	13.10	14.12	14.25	14.30	16.10	16.10	16.42	16.06
8	13.00	13.10	14.10	14.25	14.30	16.09	16.10	16.45	16.10
9	14.05	-	16.02	16.30	10.00	10.20	10.15	11.15	12.05
10	08.00	08.30	09.23	09.40	10.00	10.22	10.18	11.30	12.10
11	08.00	08.30	09.10	09.40	10.00	10.30	10.27	11.35	12.15
12	09.00	09.30	10.21	10.45	11.10	11.30	11.30	11.38	12.20
13	10.45	10.55	11.35	11.50	12.00	12.30	12.30	16.10	16.40
14	11.15	13.15	14.19	14.40	14.45	15.15	15.10	16.14	16.45
15	08.00	08.35	09.12	09.30	09.45	11.04	11.10	11.40	12.10
16	09.00	09.40	10.09	10.20	11.00	11.40	11.45	11.55	12.20
17	10.30	10.50	11.14	11.30	11.40	11.55	12.10	12.03	12.30
18	14.00	-	14.40	15.10	16.00	16.15	16.30	16.35	16.50
19	07.30	08.30	09.25	09.45	10.00	10.40	11.10	11.45	12.30
20	12.00	13.10	14.04	14.20	14.30	14.45	15.00	16.40	16.10
21	08.00	08.30	09.21	09.35	10.00	11.00	11.00	11.30	12.10
22	08.15	08.30	09.15	09.35	10.00	11.00	11.00	11.35	12.15
23	11.00	13.15	13.49	14.15	14.30	15.15	15.00	16.30	16.50
24	16.00	-	16.40	17.00	09.30	10.20	10.50	12.35	12.05

TABLE 8
CARDIAC ENZYME NETWORK RESULTS
USING DATA FROM TABLE 7

CPA RESULTS FOR COL 2 MINUS COL 1
NO OF NON-ZERO TIMINGS = 21
MEAN ELAPSED TIME FOR ACTIVITY = 50.0476 MINUTES
VARIANCE ESTIMATE = 1675.65 SQ. MIN

CPA RESULTS FOR COL 3 MINUS COL 2
NO OF NON-ZERO TIMINGS = 21
MEAN ELAPSED TIME FOR ACTIVITY = 46 MINUTES
VARIANCE ESTIMATE = 140.899 SQ. MIN

CPA RESULTS FOR COL 4 MINUS COL 3
NO OF NON-ZERO TIMINGS = 24
MEAN ELAPSED TIME FOR ACTIVITY = 20.0833 MINUTES
VARIANCE ESTIMATE = 34.6884 SQ. MIN

CPA RESULTS FOR COL 5 MINUS COL 4
NO OF NON-ZERO TIMINGS = 24
MEAN ELAPSED TIME FOR ACTIVITY = 21.0417 MINUTES
VARIANCE ESTIMATE = 343.433 SQ. MIN

CPA RESULTS FOR COL 6 MINUS COL 5
NO OF NON-ZERO TIMINGS = 24
MEAN ELAPSED TIME FOR ACTIVITY = 50.2917 MINUTES
VARIANCE ESTIMATE = 856.737 SQ. MIN

CPA RESULTS FOR COL 7 MINUS COL 5
NO OF NON-ZERO TIMINGS = 24
MEAN ELAPSED TIME FOR ACTIVITY = 53.4167 MINUTES
VARIANCE ESTIMATE = 796.168 SQ. MIN

CPA RESULTS FOR COL 8 MINUS COL 5
NO OF NON-ZERO TIMINGS = 24
MEAN ELAPSED TIME FOR ACTIVITY = 91.5 MINUTES
VARIANCE ESTIMATE = 2213.74 SQ. MIN

CPA RESULTS FOR COL 9 MINUS COL 8
NO OF NON-ZERO TIMINGS = 24
MEAN ELAPSED TIME FOR ACTIVITY = 33.0833 MINUTES
VARIANCE ESTIMATE = 59.8189 SQ. MIN

CPA RESULTS FOR COL 9 MINUS COL 1
NO OF NON-ZERO TIMINGS = 24
MEAN ELAPSED TIME FOR ACTIVITY = 257.958 MINUTES
VARIANCE ESTIMATE = 4699.09 SQ. MIN

principally at nodes 2, 3, 11 and 15 of Figure 10. These are not treated separately, but are reflected in extended t_e s for the main sections of the network portrayed in Figure 11.

It can be concluded from Figure 11 that of a total elapsed time of over 4 hours for analysis of any cardiac enzyme profile, around 90 minutes were spent in bringing the sample to the laboratory; 20 minutes in sample preparation, and the remaining two to two and a half hours in bench level analytical and clerical activities.

2.1.3 Discussion

The findings in Section 2.1.2 provided general support for the argument that turnaround time is hampered by the remoteness of the laboratory from the wards, and suggested also that the analytical procedures required to be reviewed. In particular, a single, method oriented analyser used sequentially for both the LDH and CK assays clearly contributed greatly to the overall elapsed time, as did the batching of cardiac enzyme samples into two runs towards the end of the morning and of the afternoon. This is reflected in the extensive and extremely variable t_e for the step from having aliquots available in reception to completion of the profile (nodes 11 to 19 of Figures 10 and 11).

Figure 11 also provides an instance of the difficulty of separating out a section of the laboratory activities for study as an independent system. It would seem that, since all three analysers used for cardiac enzyme profiling are capable of running any of the four analyses, the slack observable at nodes 16 and 17 that is, at the completion of the AsT and Alt assays could be utilised for CK analysis, thus shortening the overall turnaround time. In practice this proved

unworkable since these analysers were required to analyse samples from the Liver Function Test (LFT) group of Table 3. This directly contributed to the comparatively lengthy and variable analysis time for both AsT and AlT as part of the cardiac enzyme profile, since the enzyme samples were grouped together and assayed in a batch, separately from the bulk workload of AsT and AlT arising from LFT requests.

2.2 Initial requesting and specimen delivery

From the data in Table 7 it is clear that delivery of specimens to the laboratory is a major element of the network depicted in Figure 10.

Figure 10 is based on withdrawal of a specimen from a patient as the starting point in the network. In practice, the process starts with the clinician filling a request form or forms for the patient, usually during the previous evening. While this is not important to the timings of the network, the content of the request(s) and the manner in which the data is presented to the laboratory may have a significant effect on the turnaround time of the patient report, and this will be discussed further in sections 2.2.2 et seq. Also, while it is legitimate for the laboratory to consider analysis of the bulk workload in terms of 'working hours' (Section 2.1.1) the sixteen hour overnight time delay can have important consequences for patient care. Reports for over one third of the subjects in Table 7, for example, either explicitly or implicitly incorporate an overnight delay before return of results, since an analysis completed after 1600 hrs on any day has no guarantee of being reported that evening.

Again, from Figure 5, an appreciable proportion of specimens, particularly those from external hospitals, do not reach the department until at least 1500 hrs and are unlikely to be both analysed and reported before evening.

This problem of transportation of specimen and results to and from peripheral hospitals, clinics and health centres, must be briefly discussed at this point.

2.2.1. Specimen Transportation

From Figure 11 specimen transportation even within a hospital, may cause considerable delays. For an external hospital served by a centralised laboratory the situation can be much worse. Here the concept of a network is appropriate since the system is governed by the fixed time and relatively fixed duration activities of the van serving the remote units. Details of such a service are shown in Table 9.

A van service will tend to be 'time critical' in two areas -delivery of specimen and return of completed report. While this latter factor will be discussed further in Chapter 3 it is evident that an electrolyte specimen may be withdrawn from a patient in Lightburn Hospital at 0730, reach the laboratory at 1115 and generate a report by lunchtime. From Table 9, that report will not reach the hospital, far less the individual ward concerned until 4 pm that afternoon.

In general it is clear that the greater the geographic separation of the laboratory from the patient, the more prolonged the time delay before the specimen can be analysed.

Biochemistry services in the Eastern District of Glasgow have occasionally been provided locally for Duke Street Hospital (1950-59), Belvidere Hospital (1960-68), and the Royal Maternity Hospital but the first two laboratories were closed because it was deemed more economic for the main laboratory to do the work, albeit by incurring a substantial increase in turnaround time. Advocates of centralisation (Whitby, 1967, Marks, 1972, Camm, 1980) have recognised this as a likely consequence of continuing centralisation of laboratory services, but have been unable to suggest effective methods of tackling this problem other than by retaining a capacity for urgent analyses on-site.

TABLE 9

GREATER GLASGOW HEALTH BOARD

EASTERN DISTRICT

DISTRICT LABORATORY SPECIMEN VAN COLLECTION SERVICE

Proposed Timing:

<u>a.m.</u>	<u>p.m.</u>		<u>Collection Points</u>
09.10		Arr.	Centre for Rheumatic Diseases
09.25		"	Glasgow Royal Maternity Hospital
09.35		"	Glasgow Royal Infirmary
10.00		"	Duke Street Hospital
10.20		"	Belvidere Hospital
10.35		"	Lightburn Hospital
10.50		"	Glasgow Royal Infirmary
11.15		"	Ruchill Hospital (if required)
11.30		"	Centre for Rheumatic Diseases
11.40		"	Glasgow Royal Infirmary
	13.00	"	Duke Street Hospital
	13.20	"	Belvidere Hospital
	13.25	"	Lightburn Hospital
	13.50	"	Glasgow Royal Infirmary
	14.10	"	Ruchill Hospital (if required)
	14.30	"	Glasgow Royal Infirmary
	14.40	"	Duke Street Hospital
	15.00	"	Belvidere Hospital
	15.15	"	Glasgow Royal Maternity Hospital
	15.30	"	Centre for Rheumatic Diseases
	15.40	"	Glasgow Royal Infirmary
	16.00	"	Lightburn Hospital
	16.20	"	Glasgow Royal Infirmary

Curiously, there is a realistic limit to the time overheads in that a distance of over 100 miles is likely to be given appropriate transportation by air or possibly train whereas for shorter distances the overheads increase roughly linearly. Urban motorway development can ease some of the problems and help provide a more reliable and consistent service for transporting specimens.

Within a hospital, pneumatic tubes for specimen delivery have been tried, but an organisational study in 1963 concluded that "a well organised messenger service is more efficient, costs nothing to install, and operates at one-third of the cost of a pneumatic tube system" (Nelson, 1969).

2.2.2 Initial Requesting - Material, Methods and Results

Two aspects of initial requesting were considered - unique patient identification and composition of request forms.

Cumulative reporting (Section 3) requires linkage between current and previous results and efficiency of the linkage will depend on the quality of the patient identification data (PID) supplied with each request form (Flynn, 1969). Various numbers, unique to the patient have been tried, but all have been shown to possess limitations (Reekie, 1977; Simpson, 1973) and local numbers, assigned by the hospital or district records offices are still commonly used, and can be supplied on adhesive labels, or on embossed plates which can imprint PID directly on to request forms in the manner of credit card printers. Attempts to link results to analyses and reports using this unique number must require close to 100% use of such numbers on the request forms.

A short survey was carried out in 1975 in the authors laboratory into the use or provision of this number by the clinicians. The study differentiated between printed data and hand-written since the latter might be expected to be of dubious value. The results are presented in Table 10, which shows that around 60% of routine requests reaching the laboratory carried full PID with a further small percentage of hand-written hospital numbers. On the first request for each patient, however, the figure drops to around 25%, since at the time that biochemistry is first requested on a new admission, the registration documents have not been made available.

This contrasts markedly with several major hospitals with computer-based record systems where the provision of unique case reference numbers is approximately 100% (Fleck, A; Flynn, F.V. personal communications).

The corollary to this is that the author's department was required to introduce a type of computer reporting system which did not depend on the hospital number (Chapter 3).

Request forms may significantly affect turnaround, particularly since the laboratory until 1981 operated a mainly manual reporting system. In the author's laboratory over 75% of the workload was requested on two separate forms - the 'A' and 'B' forms in Plate IV - initially to separate the fast, urgent 'A' analyses from the slower turnaround, less urgent 'B' group, and subsequently to differentiate the 'A' forms which required data preparation at a computer terminal from the 'B' forms which did not.

TABLE 10

PROVISION OF HOSPITAL NUMBER ON A SAMPLE OF 4,640 ROUTINE REQUEST FORMS REACHING THE DEPARTMENT OF
 BIOCHEMISTRY, GLASGOW ROYAL INFIRMARY, NOVEMBER, 1975

	Total no. of Request forms	No. with full patient ID (Addressograph or Bradma)	No. with handwritten hospital number
Electrolyte and associated tests	2,064	1,368 (66%)	52 (3%)
Other Analyses	2,576	1,436 (56%)	92 (4%)

This arrangements of requests, although convenient for the laboratory, meant that clinicians were commonly required to fill two forms for the same patient on the same date, and meant also that data preparation staff were required to enter these into the computer as separate requests when 'B' form tests became computer-reported; clearly an inefficient process.

The single request form - the 'X' form in Plate IV - had been planned since 1978, but was not implemented until mid-November, 1981, one month after the 'B' group of reports were finally printed by computer.

The study of implementation concentrated on two aspects of the form - the anticipated reduction in the number of forms reaching the department, and the potential for substantial increase in the numbers of analyses requested, particularly the association of electrolytes with the former 'B' group requests (LFT's, enzymes etc) since it was now convenient to request these together on one form.

The numbers of forms arriving in the department over the period August 1981 to March 1982 is shown in Table 11 together with the corresponding figures from fiscal year 80/81. It is clear that widespread use of the 'X' request form had reduced the number of forms arriving in the department by around 25% by early 1982. This represents a measurable time saving for data preparation of over 2 hours/day assessed on the basis of 200 less request forms per day at 40 sec/request.

The effect on requesting patterns was assessed by a computer program written by the author, and designed to analyse the number of requests in the first week of each monthly archive data file, and to

TABLE 11

NUMBER OF ROUTINE REQUESTS ARRIVING IN DEPARTMENT AUG 81-MAR 82

Month	1980/81	1981/82	% Increase
August	23486	25731	+ 9.5%
September	26660	27240	+ 2.1%
October	30047	28870	- 4.0%
November	27237	28462	+ 4.4%
December	28642	28993	+ 1.2%
January	28210	21279	- 24.6%
February	28549	20652	- 27.7%
March	32627	26053	- 20.2%

compute the percentages of each of the major types of 'B' group requesting patterns within the file. The program listing is included as Appendix I. The program output is summarised in Table 12.

Table 12 expresses the major request groups on the 'B' request form either as LFT (liver function tests); CAP (Bone profile), Protein (Total protein, albumin, globulins) and Enzymes (Cardiac Enzyme Profile) and shows the relative popularity of the various combinations of these groups, expressed as a percentage of all 'B' group requests written to the archive file on the first full week of each month. The November data represents the situation prior to introduction of the 'X' form, and the combinations are marked from top to bottom in order of popularity while the 'A' and 'B' forms were still being employed, and before it became simple a) to request multiple-test combinations on a single form, and b) to request electrolyte profiles together with 'B' group requests.

Table 12 shows that, contrary to the fears expressed by staff prior to the release of the 'X' form, there was little evidence of major alterations in the requesting patterns. In particular, there is no evidence that the multi-organ screening combinations such as LFT, CAP, Enzymes and LFT, Protein, Enzymes have become more prevalent since the 'X' form was introduced. Similarly, there is no clear evidence that electrolytes and 'B' group analyses are being requested together any more often than they were when requesting involved two separate forms, although there is some suggestion of a tendency to request a higher proportion of electrolytes with the two largest combinations. Whether or not these particular figures continue to rise remains to be seen.

TABLE 12

'B' Group Requesting Patterns - November 1981 to February 1982

Test Combination	NOVEMBER		DECEMBER		JANUARY		FEBRUARY	
	% of 'B' Group	% with 'A'	% of 'B'	% with 'A'	% of 'B'	% with 'A'	% of 'B'	% with 'A'
LFT, CAP	33%	83%	31%	84%	28%	88%	26%	87%
LFT, PROTEIN	18%	65%	14%	67%	19%	66%	19%	71%
PROTEIN ONLY	11%	38%	13%	45%	11%	39%	9%	30%
LFT, CAP, ENZYMES	8%	74%	9%	84%	8%	88%	6%	87%
LFT ONLY	8%	67%	9%	76%	7%	72%	11%	70%
CAP ONLY	8%	48%	11%	40%	11%	59%	12%	63%
LFT, ENZYMES	4%	67%	3%	71%	3%	64%	3%	77%
LFT, PROTEIN, ENZYMES	3%	64%	3%	92%	3%	72%	4%	68%
ENZYMES ONLY	2%	46%	3%	47%	2%	24%	2%	38%
ENZYMES, PROTEINS	2%	24%	2%	65%	3%	56%	2%	27%
CAP, ENZYMES	1%	59%	2%	36%	3%	60%	2%	68%
OVERALL PERCENTAGE OF 'B' REQUESTS WITH SIMULTANEOUSLY-REQUESTED ELECTROLYTES		65.4%		67.4%		63.8%		67.4%

2.2.3 Discussion

The pattern of requesting can have some effect on laboratory efficiency and is arguably influenced by the laboratory staff and the forms and analytical automation which they decide to employ. Requesting procedures tend to be modified solely on the initiative of the laboratory, and are designed to suit the laboratory's needs for more efficient, less time-consuming data preparation, for example. Attempts have been made to provide machine readable PID on request forms either as punched holes or by use of optical character recognition (Whitehead et al, 1968, Rappoport, 1969, Vitek et al 1974) but these have not been totally successful because much of the information provided on request forms is extremely variable (eg date of request, current diagnosis, time received, request number), and has almost always had to be manually entered into computers. Also, pre-coding of PID in machine-readable forms was only possible in hospitals like the Queen Elizabeth Hospital in Birmingham, which had no significant casualty workload (DHSS, 1975).

The other major alternative is the linkage of the hospital patient administration computer with the service department machine so that service departments have access to the patient master index, thus association of unique case reference numbers with requests becomes more effective.

In contrast, the delivery of specimens to the laboratory is a continued source of problems and delays which are, in the main, outside laboratory control. Although archive analysis of laboratory computer data files can be used, as in Figure 5, to demonstrate and monitor unsatisfactory distribution of specimen arrival times, the only

effective way of controlling and improving specimen delivery times would appear to be the employment by the laboratory of their own phlebotomists. It then becomes possible for clinical staff to requisition analyses through ward-based visual display terminals (VDUs) or even by modified telephone (Rappoport, 1978) and have the printed list of requisitions, sorted by ward, available within the laboratory as required.

Before considering reception activities, one further point arising from the timescale so far discussed, requires attention. It would seem that clinicians request a considerable fraction of the laboratory's workload while the laboratory staff are unavailable to answer questions of detail on appropriate form type, containers, minimum necessary specimen volumes and the like. Up to date data must be made available at this time, and an enquiry program written by the author to provide such data is available at the Ward Terminals to the Biochemistry computer 24 h/day as an alternative to the frequently outdated information on printed lists.

2.3 Specimen Reception

Specimen reception for cardiac enzymes occupied only some twenty minutes of the network diagram of Figure 10 and so no major benefit will be obtained from intensive attempts to reduce this time. It is, moreover, a problem which will diminish if additional resources are made available but the fundamental importance of specimen reception perhaps requires some further discussion. While some analysers, notably the Vickers M300, can aspirate serum from the vessel into which the blood was originally dispensed by the requesting clinician, in most laboratories a centrifugation step, followed by a partitioning of serum or plasma into aliquots, each in its own sample bottle, is required, and the elapsed time of the specimen reception processes becomes a function of the number of staff in the reception area, the number and capacity of the centrifuges available to them and the number of analytical areas and functional groups of tests within the laboratory. It is possible to introduce some forms of sample streaming at this stage, giving priority to particular groups of tests, and within that to individual specimens from acute areas of the hospital or Health District, but the use of successive decision criteria by junior grades of staff who normally operate the reception area is likely to slow down the reception process.

Automation of the reception procedures has been neglected, or at best, been partially achieved through advances in instrument design which have allowed steps such as specimen separation and sample partitioning to be deleted. A range of instruments which employ ion-selective electrodes can measure partial pressures of oxygen and carbon dioxide, sodium, potassium, and glucose concentrations in whole

blood, obviating the centrifugation step, and some analysers will aspirate sample from the original specimen containers, removing the partitioning step but delaying further analysis on the specimen.

Specimen reception is often regarded as the most tedious and in some respects menial task within the laboratory, to be entrusted to the most junior grades of staff. Quite clearly from Figure 10 however, it is of central importance in laboratory workflow because it is the first step in the critical path within the laboratory - every laboratory staff member is from time to time reminded, usually unpleasantly, that delays in reception reverberate through the complete analytical and reporting system. The sample which emerges from the reception area is fundamentally different from the specimen which arrived by the messenger in that its patient identification data is now secondary, having been copied from the original specimen and/or request form. The primary and unique means of sample identification is now the laboratory accession number rather than any information supplied with the request, since more than one request for any individual may be being processed at any given time.

In this transition in identification lies the origin of the majority of patient/sample identification problems which will arise in a variety of forms from here to, and even beyond the point where a report is returned to the initiator of the request.

2.3.1 Patient/Sample Identification

Approaches to positive patient/sample identification have arisen through instrument manufacturer's attempts to avoid identification errors during analysis and have concentrated, in the main, on the change of prime identification characteristic from laboratory

accession number to the analytical sequence number assigned during worksheet production at each work area (Figure 10, nodes 12 and 13). The sequence number is not unique, and adequate identification is dependent on the manual loading of the analyser sampling module in the correct order. Common mistakes at this point are the interchanging of two samples, or a displacement of the sequence by one position across part of a batch of samples (Whitehead 1967). Good laboratory practice and careful attention to detail can minimise the risk of these occurrences, but will not eliminate them.

To remove this second change in result identifier, a number of instruments in common use now read the accession number or equivalent directly from the sample container as sampling is taking place. Among these instruments one can list the Technicon IDEE option for SMA 6, 12, and 18/60s, the Vickers SP120 data acquisition system, (Plate V), and the Technicon SMAC analyser, (Plate VI). All of these have a detector system which reads a coded tag attached to the sample or its carrier block and thus eliminates the possibility of a sequencing error in analysis (Plate VII). They do not, however, eliminate the possibility of mis-assignment of the tag to the aliquot, and they do not fully overcome the problem of the transfer of the patient's identity from the initial specimen container to the aliquot.

Attempts have been made to tackle this area also. In the middle 1960s, a Technicon system was available to provide a tag which was affixed to the specimen container, was machine readable, and carried the same identification number as the prepunched request form (Constandse 1966; Whitehead, et al, 1968; Chalmers, 1969). The tag could be read by the ID unit attached to the T-40 sampler (Whitehead,

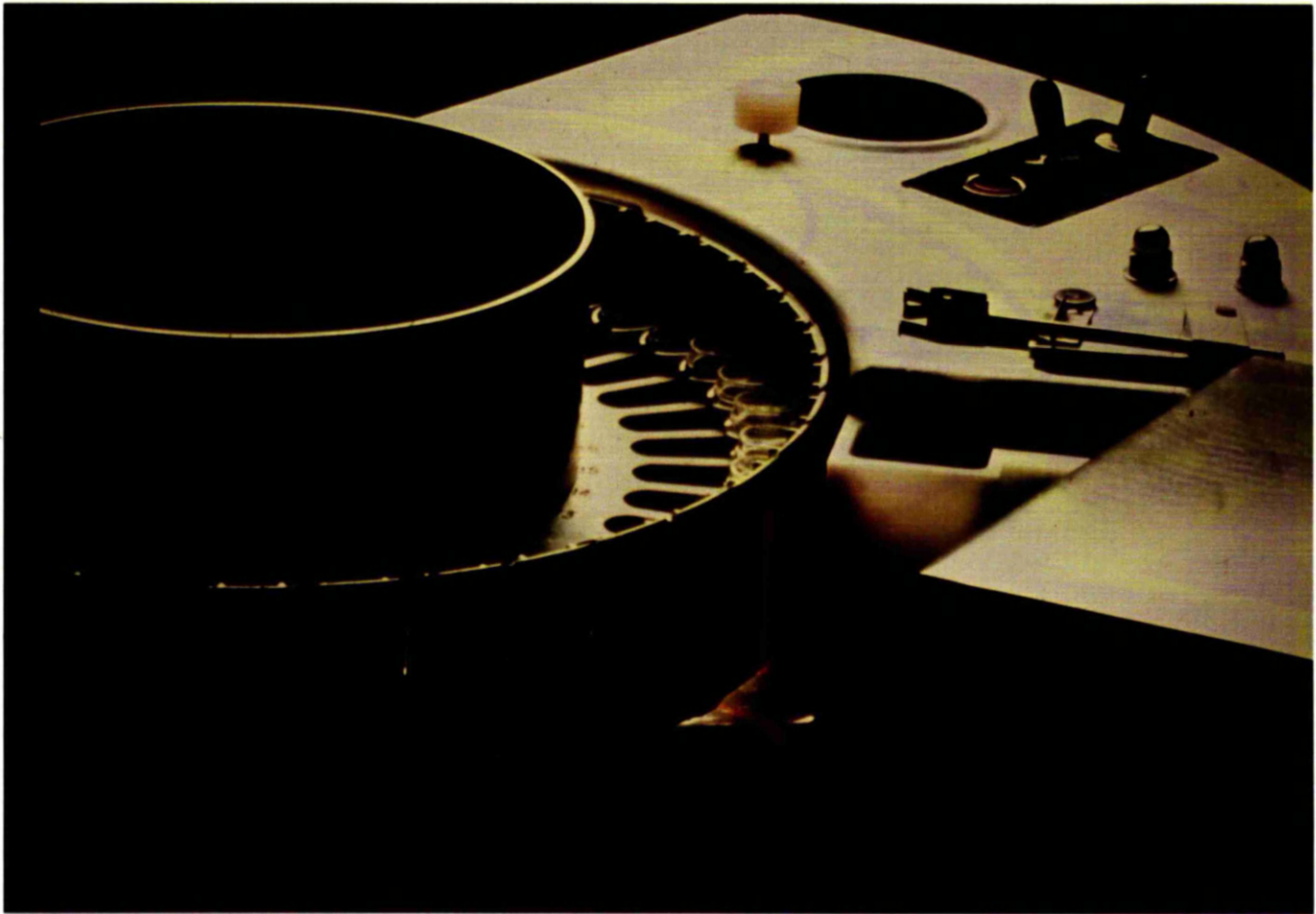


PLATE V Vickers SP120 Laser specimen identification system
(Photograph by Courtesy of Vickers Ltd, Medical Engineering
Basingstoke, UK).

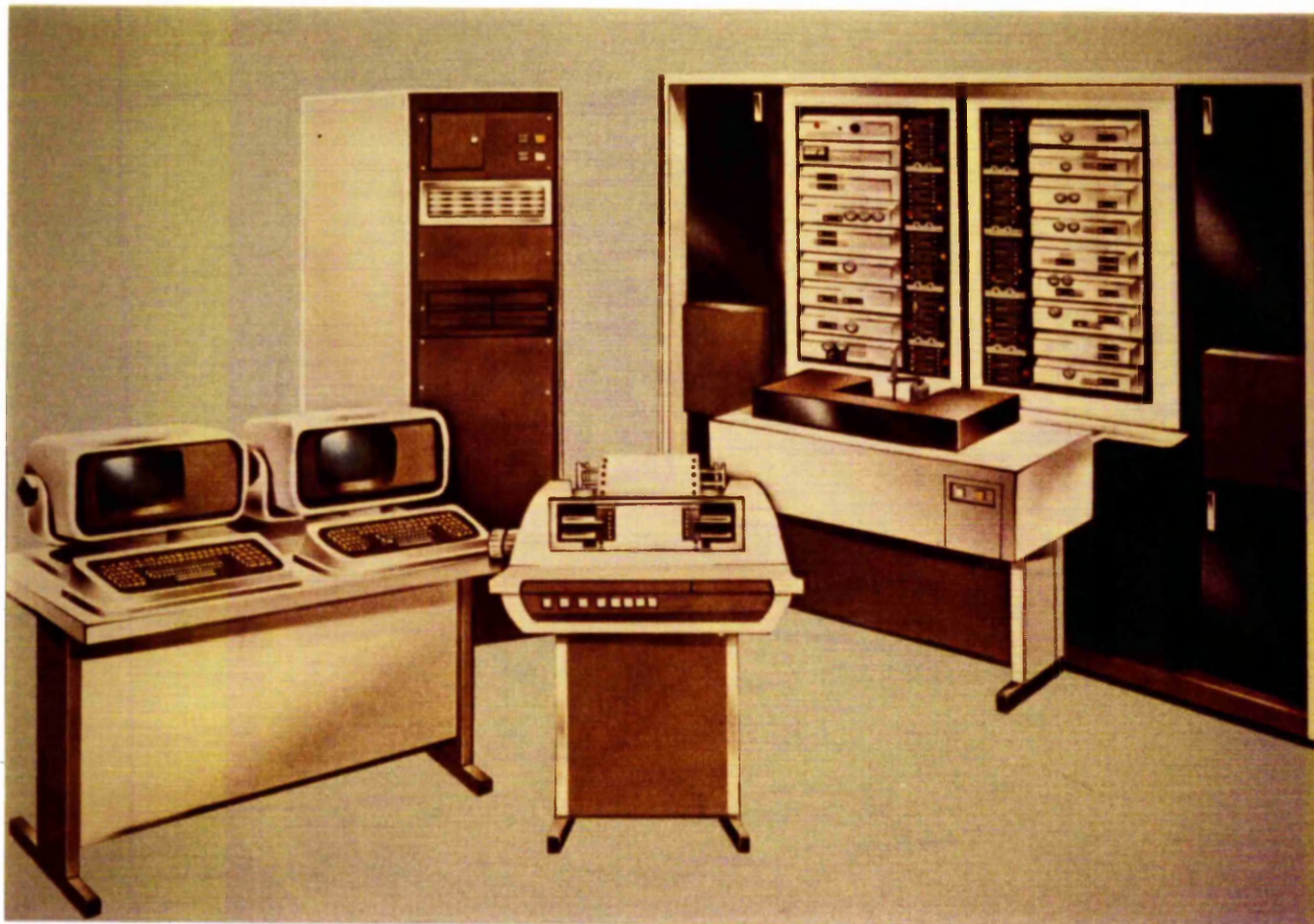


PLATE VI Technicon SMAC 11 Multi-channel parallel continuous flow analyser (photograph by courtesy of Technicon Ltd, Basingstoke, UK)

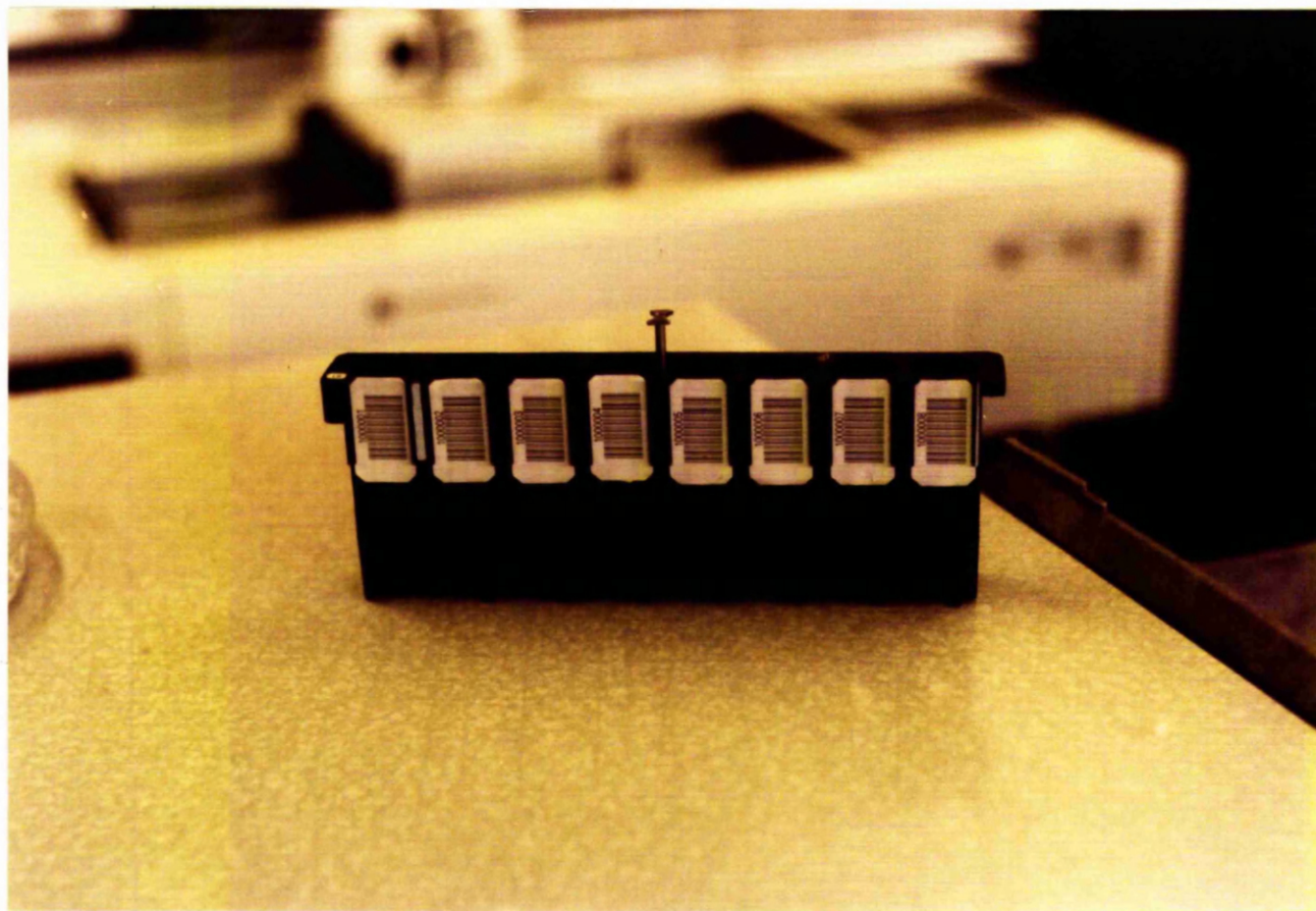


PLATE VII Carrier block for Technicon SMAC 11 showing bar-code labels

1967) and the card by an IBM reader attached to the laboratory processor (Constandse, 1966). However it was still necessary to input some or all of the patient information manually into the processor, so that the risk of mis-identification was still present. Moreover, this system was dependent both on adequate documentation, including provision of the cards and tags on admission before any laboratory request was initiated, and transfer of the tags to the sample aliquots after centrifugation. Also, where the analyses were not automated, the request cards were used to generate a worksheet which then required that the analyses be performed in sequence as before with the attendant risks.

A major attempt to circumvent these problems was made by Vickers Ltd with their M300 analyser towards the end of the 1960s. The Vickers sample vial was coded by pushing in foil flags on the reading surface, and was used as specimen container which could then be centrifuged and loaded on to the sample rack of the M300 so that the identification number was read directly by the analyser and associated with the results from that specimen. No provision was made, however, for recovery of the containers after analysis and subsequent tests required the use of a standard worksheet system.

Since the needs of the laboratory and the hospital for patient identification are different - the hospital need only identify the patient, while the laboratory may have more than one specimen for analysis from the individual patient during one day - an ideal system would involve the attachment to the specimen bottle of a machine-readable identification number which would also appear on the request form. A self-contained, processor controlled sampling unit could then

centrifuge specimen containers, read the PID and create the necessary number of serum aliquots, each carrying the laboratory accession number assigned to the specimen in machine readable form - a bar-code label, for example. The accession number would also be attached to the specimen bottle and a table of incoming specimen numbers, date and time of receipt, and associated laboratory numbers could be held in the processor and accessed as required. The bar-code label on the aliquot bottles could then be read by automatic samplers on the analytical equipment so that the transfer of identification could be as error-free as possible.

A variant of this scheme is currently employed at the Youngstown Hospital Association as a development of the system described by Constandse, in 1966, where a telephoned request for analyses results in the production of machine-readable tags carrying the laboratory identification number. These are then given to the phlebotomists before the specimens are taken (Rappoport, 1978). This should also help to remove the earliest problem in the chain of potential errors in patient/sample identification - the initial collection of the specimen into an incorrectly-labelled container.

2.3.2 Request Data Preparation - objectives and problems

The amount of patient-data which needs to be transcribed into a reporting processor will vary considerably between laboratories, depending on the format of the final report and whether or not it is normally attached to the original request form (Challand et al, 1979). In the author's laboratory, for example, computer reporting of electrolytes has gone from single reports on adhesive labels with manual

cumulation and a three-line patient identification entry (1973-77) to full cumulation on a report form separate from the original request and with a ten-line identification set.

The aim of PID entry is to generate a report which carries enough information to ensure (a) that the correct analyses have been performed, (b) that results are returned to the correct patient's case-notes, (c) that the results can be interpreted in the light of the clinical data, (d) that correct linkage with the previous results for the same patient has been achieved where a cumulative report is required.

Undoubtedly the most difficult objective to fulfill is the last one. The inadequate provision of unique identification, the high percentage of handwritten requests and external problems such as change of name and/or address between admissions ensure that few cumulative reporting systems achieve one hundred percent success. The most satisfactory systems are those which allow a visual match of previous likely candidates with the current request. Thus most laboratories use a visual display terminal (Abson et al, 1972a; Morgan et al, 1980; Naylor et al 1979).

The benefits and drawbacks of two potential methods of linking current and previous reports were studied and the findings are presented below.

2.3.2.1 Materials and Methods

a) **Manual Card System**

Prior to the implementation of the file handling package in the author's laboratory, a manual card system had provided the link between current and past reports. Each card (Figure 12) carried the

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FIGURE 12 Patient ID Record Card Format

unique, laboratory-assigned link number used to identify the patient's file within the processor. As was shown in Figures 8 and 9 interrogation of the card file and the allocation of the link number was a time-consuming process. Note that Figure 8 shows manual worksheet compilation, rather than the sequence prepare data - generate worksheet from computer - analyse specimens, which would clearly prolong the turnaround time. Hirst et al (1979) and Flynn (1978) reported similar findings.

This card system in routine use from 1975 to 1980 posed a number of problems; these are summarised in Table 13. To demonstrate the effects of the fourth disadvantage (Table 13)- full identification to be typed for each request - an analysis was performed to assess the number of patients on file with more than one electrolyte profile; the results are shown in Table 14.

b) **Visual Matching**

In October, 1980, data preparation began using the RMS-11 file handling package; use of the card system was discontinued in 1981. The revised timings for the electrolyte report production network of Figure 9 are depicted in Figure 13. Assignment of the link number is now an integral part of PID entry hence nodes 3 and 4 of Figure 9 have been deleted. The revised timings for the analytical activities are discussed in Section 2.4.

2.3.2.2 Results

From Table 14, it is clear that, while 62% of patients had no follow-up request within the next eight weeks (this related to the algorithm then in force for culling patient files from the data base) the other 38% of patients accounted for over 80% of the electrolyte

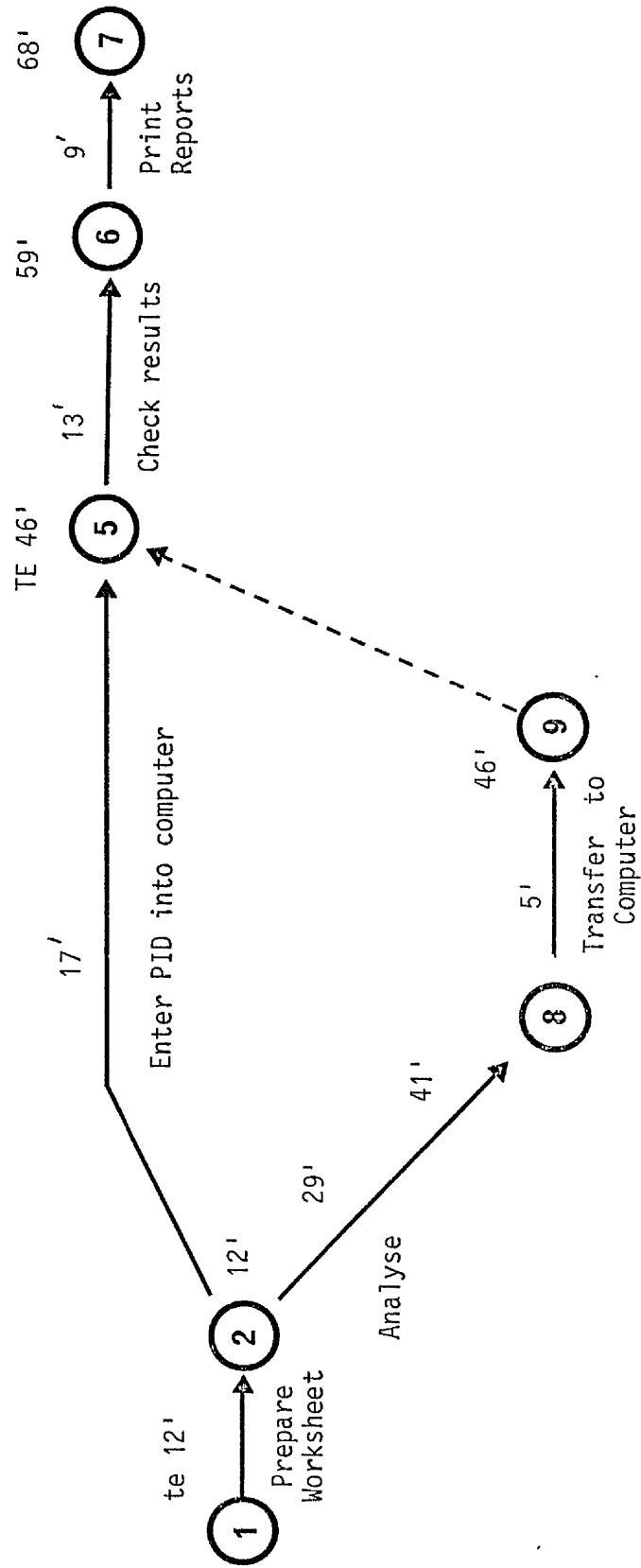


FIGURE 13 GRI Electrolyte Report Production 1981 - Timing Study

TABLE 13

ADVANTAGES AND DISADVANTAGES OF A MANUAL CARD-BASED PATIENT ID SYSTEM

Advantages

- 1) Independent of processor failure

Disadvantages

- 1) Unsuitable for more than one operator
- 2) Requires 5-6 hours of clerical staff time per working day
- 3) Causes, on average, a 33 minute delay on the critical path of report production (Figures 8 and 9, Nodes 2 to 3)
- 4) Requires full patient identification to be typed for each request.
- 5) Imposes a limit of around 450 on the total number of request forms which can be processed within one working day.

TABLE 14

No. of Electrolyte Profiles on file per patient - Glasgow Royal Infirmary

August/September 1977

<u>profiles per patient</u>	<u>No of patients</u>	<u>% total patients</u>	<u>No. of profiles</u>	<u>% profiles</u>
1	3310	62.3%	3310	19.5%
2	784	14.8%	1568	9.3%
3	339	6.4%	1017	6.0%
4	176	3.4%	704	4.2%
5	159	2.9%	795	4.7%
6	105	2.0%	630	3.7%
7	74	1.4%	578	3.1%
8	48	0.9%	384	2.3%
9	43	0.8%	387	2.3%
10	32	0.6%	320	1.9%
11	30		330	
12	27		324	
13	25		325	
14	3		42	
15	14	2.3%	210	9.6%
16	6		96	
17	4		68	
18	2		36	
19	7		133	
20	3		60	
21-30	29		722	
31-40	22		751	
41-50	25		618	
51-60	11		604	
61-70	14	2.3%	913	33.4%
71-80	9		663	
81-90	8		699	
91-100	-		-	
> 100	4		700	
TOTAL	5313		16927	

profiles on file towards the end of 1977, thus a majority of daily routine electrolyte requests were on patients previously known to the system. Further, there existed at least four patients, whose primary identification data had each been typed at least 100 times.

The estimated elapsed time of 17 minutes for data preparation in Figure 13 relates to the maximum batch size of 33 patient samples and gives a mean of 31 seconds per patient, but this figure also reflects the transfer of personnel resources from the card system to data preparation. A more accurate figure for each PID entry would be 40-50 seconds, but invariably the whole batch of 33 was timed and this was normally shared between two staff members (although not necessarily equally). The mean figure stated for the elapsed time for the batch also included waiting time where forms had been delivered to the VDUs while the staff were otherwise occupied.

2.3.2.3 Discussion

The results in Section 2.3.2.2 and Fig 13 demonstrate that improved methods of patient data preparation using commercial file handling software, together with improved analytical capability (further discussed in Section 2.4), can cut almost one hour from the intra-laboratory activities involved in processing routine patient electrolytes. In particular, a major limitation in the speed of data preparation has been removed, and has allowed the activity to profit from a re-distribution of manpower resources. The only major disadvantage of on-line data preparation is that it is wholly dependent on the departmental computer, but on the few occasions when that has either failed or been closed down for preventative maintenance, the

system of operation has allowed up to six terminals to be utilised to further reduce the time taken to enter a batch of patient results once the processor has been restored to full function.

In passing, it should be noted that the markedly skewed distribution of requests per patient invalidates the use of Gaussian statistics to describe the findings, in contrast with a similar study by Holland in 1969.

2.4 Automation of sample analysis

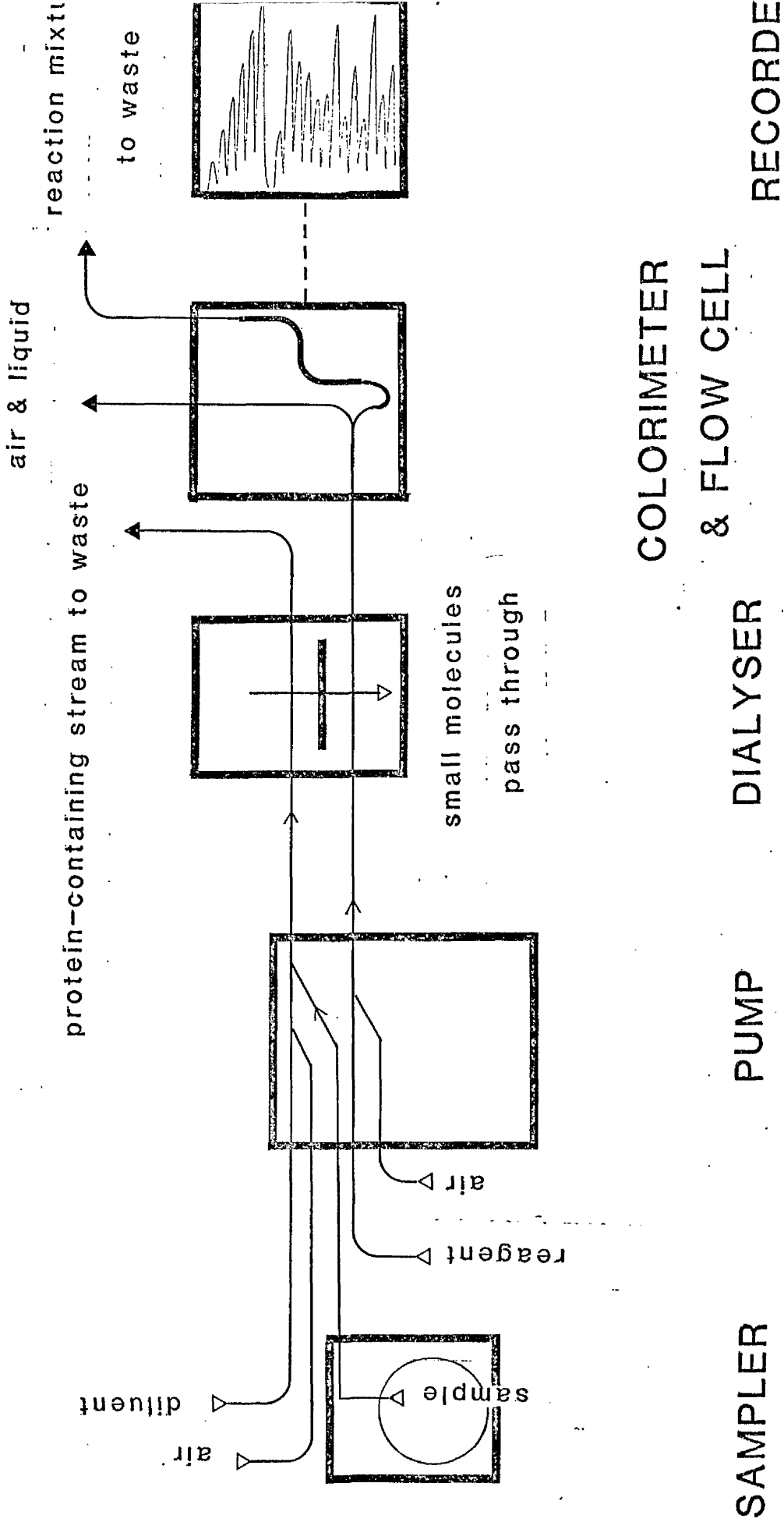
The results in Section 2.1.2 (Fig 11) indicated that for cardiac enzyme analysis in GRI in 1976, over 50% of the time up to the point at which a report was available was taken up by work at the laboratory bench. The remainder of this Chapter will focus on that area of the overall turnaround where most work has been done in improving throughput -the analytical equipment. There are three major types of analyser -continuous flow, discrete and centrifugal.

2.4.1. Continuous flow Analysis

The concepts of continuous flow analysis were first stated by Skeggs in 1957. He described the basic principles of continuous-flow analysis, the design of the sampler, pump, dialyser, heating bath and colorimeter and their application to analysis of urea nitrogen at sampling rates of 20 to 40 samples per hour. A block diagram of a typical continuous flow analyser is shown in Figure 14. Skeggs also considered the rate-limiting steps in continuous flow analysis and listed these as dialysis (and in particular the lag time for the cellophane membrane to adjust to the new equilibrium), carryover of chromogen from one reaction mixture to the next within his 600 ul flow cell, and the stability and regularity of the bubbles injected into the fluidic system. Skeggs also claimed superiority of results from his automatic analyser over the then current manual methods of analysis and better reliability in the longer term. Since that time this claim has been well substantiated (Thiers and Oglesby, 1964; Neill and Doggart, 1969).

Figure 14

Block diagram of modules in a continuous-flow analyser



Over the next ten years the variety of detectors to which this uniquely flexible sample proportioning and delivery system could be linked by clinical chemists was increased to include atomic absorption spectrophotometers (Klein et al, 1966), flame photometers (Levine and Larrabee, 1966), fluorimeters (Breen and Marshall, 1966) and intermediate modules like the digester for protein-bound iodine. It was however not until the wide-spread introduction of type C dialysis membranes, tubular flow cells and a more precise sampler, the Sampler II, that single-channel methods began to reach throughput rates of 60/h (in the mid-1960s 40/h was still the common sampling rate (Levine and Larrabee, 1966; Mabry et al, 1966)). Multi-channel analysers were being manufactured during this period with an eight-channel SMA (Sequential Multiple Analyser) system in 1963 and an SMA-12 in 1965 (Skeggs and Hochstrasser 1966) operating at 30/h, with the 60/h versions becoming available in the UK in 1968/69 (Neill and Doggart, 1969).

The late 1960s and early 70s also saw clinical chemists who, throughout this period had encountered steeply rising workloads (Figure 2), develop an interest in how fast continuous flow analysis could be made to perform.

The consequences of attempting to run the analysers at higher speed were well known. Because of leakage of material from one segment of the reaction mixture to another, continuous flow systems had always

shown a distortion of the perfect square wave pattern which might have been expected. (Figure 15(i) and (ii)). While it was not necessary that the 'steady state' or plateau be achieved, (Fig 15 iii) it was necessary that all samples reach the same percentage of this ultimate plateau height so that results could be calculated from the standard materials within the batch. Reduction in sampling times cause sensitivity and precision problems and reduction in wash time caused the chromogenic material from samples of high analyte concentration to tail back across the wash segments into the sample segments of the next sample in the batch and produce the characteristic loss of peak definition for the second peak known as carryover (Figure 15(iv)).

This period saw a succession of papers published on the theoretical kinetics of continuous flow analysis (Thiers et al, 1967; Neumann and Fischer, 1969; Walker et al, 1970; Begg 1971; Fleck et al 1971; Thiers et al, 1971; Walker et al, 1971) aimed at investigating the causes of carryover in terms of the properties of the liquids in the stream, and at identifying the phases of the final, typical Auto Analyser peak and describing these mathematically in the belief that application of carryover correction formulae to the analogue signal would resolve the merged peaks of Figure 15(iv) and permit higher throughput (Strickler et al 1970; Thiers et al 1970).

The approach to these problems in the authors laboratory centred around the physical limitations of the modules of the analytical system depicted in Figure 14.

Carryover



Fluid

Flow

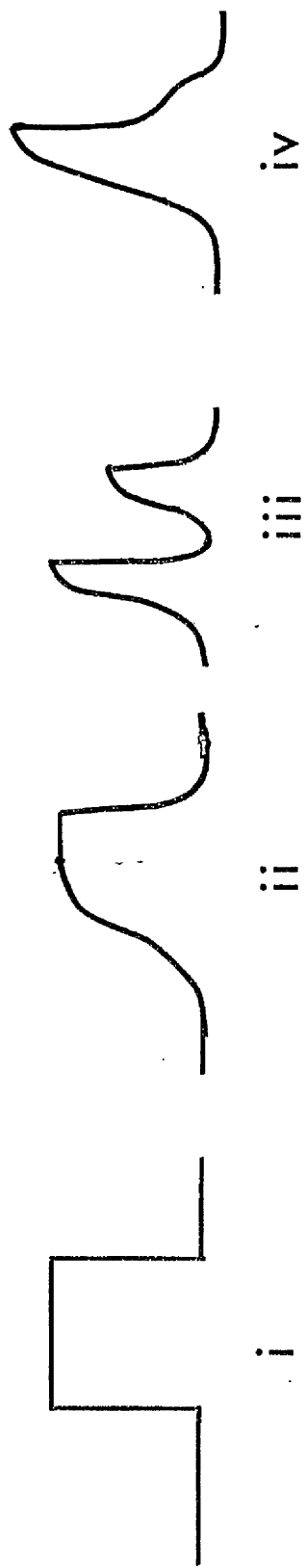
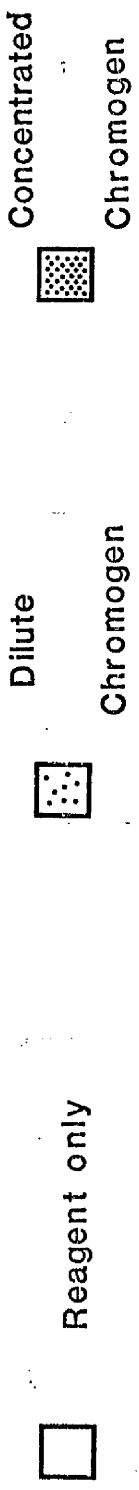


Figure 15

Effect of continuous flow on detector signal

2.4.1.1 Sampler

The function of a sampler is to extract a fixed volume of material from a sequence of cups. The precision with which the sample volume is withdrawn depends on the length of time for which the sample probe remains within the sample volume. A number of factors influence this precision, including the proportioning pump (since the sample aspiration rate, which is assumed to be constant, will vary with inferior pump performance) and the velocity of the probe arm (since a slow probe arm will accentuate differences in sample volume between cups filled to different levels). A major factor, however will be the accuracy of the timing device used to control the sampler.

Studies by Young et al, 1968, and Friedman, 1970 had reported imprecision figures for different Autoanalyser cams at the common sampling rates but had neither related these directly to analytical results, nor investigated the effect on sampling rates of greater than 70/h. Since the department was interested in sampling rates of over 100 samples/h a project was begun with the Group Pathology Laboratory in Warwick to determine the degree of imprecision attributable to sampling variation at high speed and the remedies available.

2.4.1.1.1 Materials and Methods

A standard Technicon Sampler II is driven by a 10 r p h motor linked to a rotating cam. Since one revolution of the cam takes six minutes, a number of lobes are provided on each cam, corresponding to the number of sampling cycles within a 6 minute period. The

geometry of the cam, the successive lobes of which hold closed a microswitch on the sampler linked to the probe mechanism, is critical in controlling the sampling time and hence the volume of sample taken. Eccentricity of the cam, or of the spindle driving the cam, or unequal lengths of the contact-closing chords of the cam lobes will affect the sampling precision.

Variation in sample timing was measured in two ways. First, an advance Electronics time/counter was connected to the microswitch of the sampler to measure contact closure time directly. Secondly, to simulate more exactly the movement of the sampler probe into the cups, the wash receptacle of the sampler was filled with mercury, as was a beaker which replaced the sample cup. Wires from both mercury pools, and from the probe were led to the timer and the actual sampling time measured.

2.4.1.1.2 Results

The results are summarised in columns 2 to 5 in Table 15. Each cam tested showed statistically significant differences between lobes at the 0.1% level for both contact closure and mercury contact methods using analysis of variance. As an example the sample and wash times for each lobe of the 100 samples/h cam are summarised in Table 16. From this it is clear that each lobe is more precise by at least one order of magnitude than the cam.

TABLE 15

MEASURED SAMPLING TIMES OF VARIOUS CAMS ON A TECHNICON SAMPLER II

Sampling Rate	Theoretical Times Sample, Wash	2			3			4			5			6		
		\bar{x}	SD	CV	\bar{x}	SD	CV	\bar{x}	SD	CV	\bar{x}	SD	CV	\bar{x}	SD	CV
40/h	60s 30s	62.7	0.35	0.6%	27.2	0.17	0.6%	63.0	0.53	0.6%	27.1	0.41	1.5%	58.4	0.015	0.03%
50/h	48s 24s	57.2	0.2	0.4%	20.8	0.12	0.6%							47.3	0.042	0.09%
60/h	40s 20s	42.9	0.13	0.3%	17.1	0.2	1.2%	42.9	0.30	0.7%	17.1	0.12	0.7%	39.4	0.012	0.03%
70/h	34.3s 17.15s	37.3	0.25	0.7%	14.1	0.3	2.1%									
80/h	30s 15s	31.4	0.37	1.2%	13.7	0.3	2.2%	31.3	0.33	1.1%	13.8	0.17	1.2%	29.7	0.009	0.03%
90/h	26.7s 13.35s	27.8	0.44	1.6%	12.3	0.41	3.3%									
100/h	24s 12s	25.5	0.71	2.8%	10.6	0.81	7.6%	25.4	0.65	2.5%	10.8	0.48	4.4%	24.0	0.007	0.03%
120/h	20s 10s													20.0	0.009	0.05%
240/h	10 s 5s													10.0	0.006	0.06%
480/h	5 s 2.5s													5.1	0.002	0.04%

All timings based on 8 replicates per lobe ie 8 revolutions per cam

All cams used a stated 2:1 sample/wash ratio

TABLE 16

Mean sample and wash times for each lobe of a 100/h cam,
using the contact closure method of
timing

Cam lobe	Sampling time			Wash time		
	Mean	SD	CV...	Mean	SD	CV
1	26.0	0.04	0.15%	10.1	0.03	0.3%
2	26.3	0.05	0.19%	10.0	0.07	0.7%
3	24.3	0.02	0.08%	11.6	0.04	0.3%
4	24.5	0.02	0.08%	12.3	0.02	0.2%
5	25.8	0.03	0.11%	10.2	0.01	0.1%
6	25.2	0.02	0.08%	10.7	0.01	0.1%
7	26.3	0.01	0.04%	9.3	0.01	0.1%
8	25.3	0.03	0.12%	10.3	0.02	0.2%
9	25.1	0.04	0.16%	10.8	0.03	0.3%
10	26.2	0.04	0.15%	10.3	0.05	0.5%
OVERALL	25.5	0.71	2.8%	10.6	0.81	7.6%

All results based on 8 replicate timings per lobe

2.4.1.1.3 Discussion

The theoretical effect that these badly cut lobes might be expected to produce are indicated by Figure 16. From Table 16 the expected range of sampling times between longest and shortest is 2.8s, that is, four times the overall standard deviation. From Figure 16, the closer one approaches steady state, the less difference a 2.8s range will make to the final height of the Autoanalyser trace, but at 100 samples/h where one can expect to be at less than 90% of plateau value, the effect on precision should be noticeable. The practical consequences of this effect at high sampling rates is shown in Figure 17, where data from an 80/h albumin analysis using the immunoprecipitation technique of Wegfahrt et al (1970) is graphed. On an extended run of replicates it is noticeable, despite the overall downward drift in the system, that every 8th peak is low.

This low peak corresponded exactly to the combination of a particularly badly-cut lobe and an unusually long wash segment on the 80/hr cam used in the timing study of Table 15. The effect of excluding data from the suspect lobe is shown in Table 17. The results indicate a mean difference due to cam error of 2 g/l or 5%. The same cam was then sent to colleagues in Warwick where it was used in the measurement of calcium by Technicon method N3b and of sodium using a Technicon Mk IV flame photometer. Both methods, despite reaching a higher percentage of the steady-state reading than the albumin method

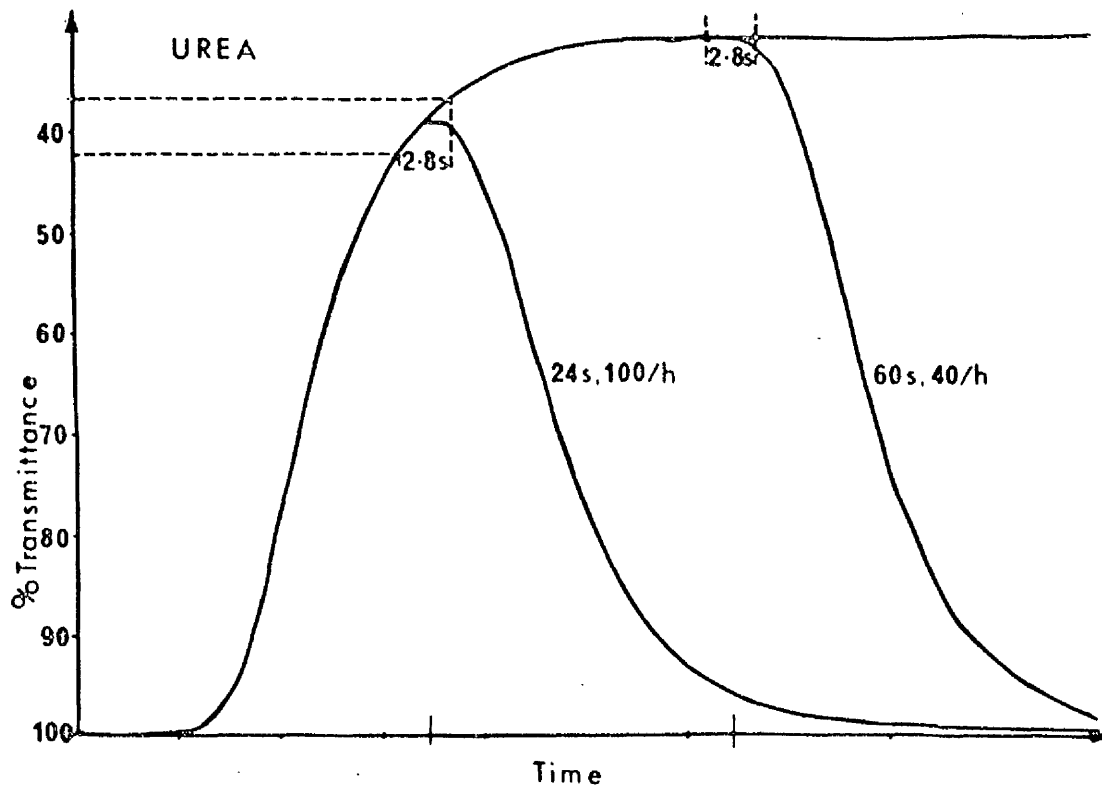


FIGURE 16 The effect of sampler timing on analytical results. The curves are redrawn from a chart record of the urea method, aspirating the same specimen (a) continuously, (b) at 40 samples/h and (c) at 100 samples/h

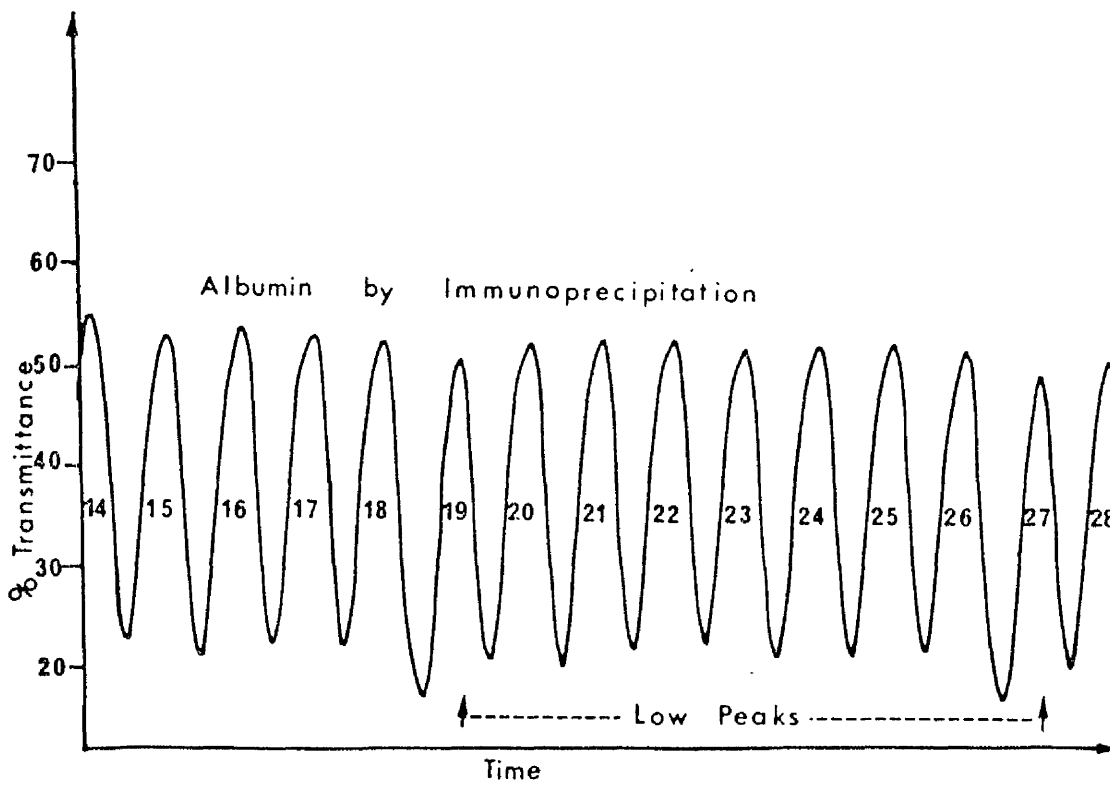


FIGURE 17 Albumin by Immunoprecipitation.
 The trace shows a pooled serum aspirated at 80 samples/h
 A short lobe on the cam (Table 17) generates a low
 peak on every eighth replicate.

TABLE 17

Albumin by immunoprecipitation

Effect of one badly-cut lobe on an 80/h cam

Group	Content	No	Mean g/l	SD g/l	CV
1	All results	30	38.9	0.9	2.4%
2	All results excluding suspect lobe	26	39.2	0.5	1.4%
3	Suspect lobe results	4	26.9	0.4	1.0%

Group 3 v Group 1, $t = 4.34$ $p < 0.001$

Group 3 v Group 2, $t = 8.73$ $p < 0.001$

showed a high correlation between sampling time and result ($p < 0.01$) and a significant variation in results due to differences between lobes.

It was concluded that the Technicon cams were unreliable at throughput rates greater than 60/h and that a better method of triggering the sampler must be sought. Other samplers were considered, but examination by Owen and Stevens (personal communication) had shown that a range of commercial samplers exhibited unsatisfactory precision at sampling times of less than 30 sec.

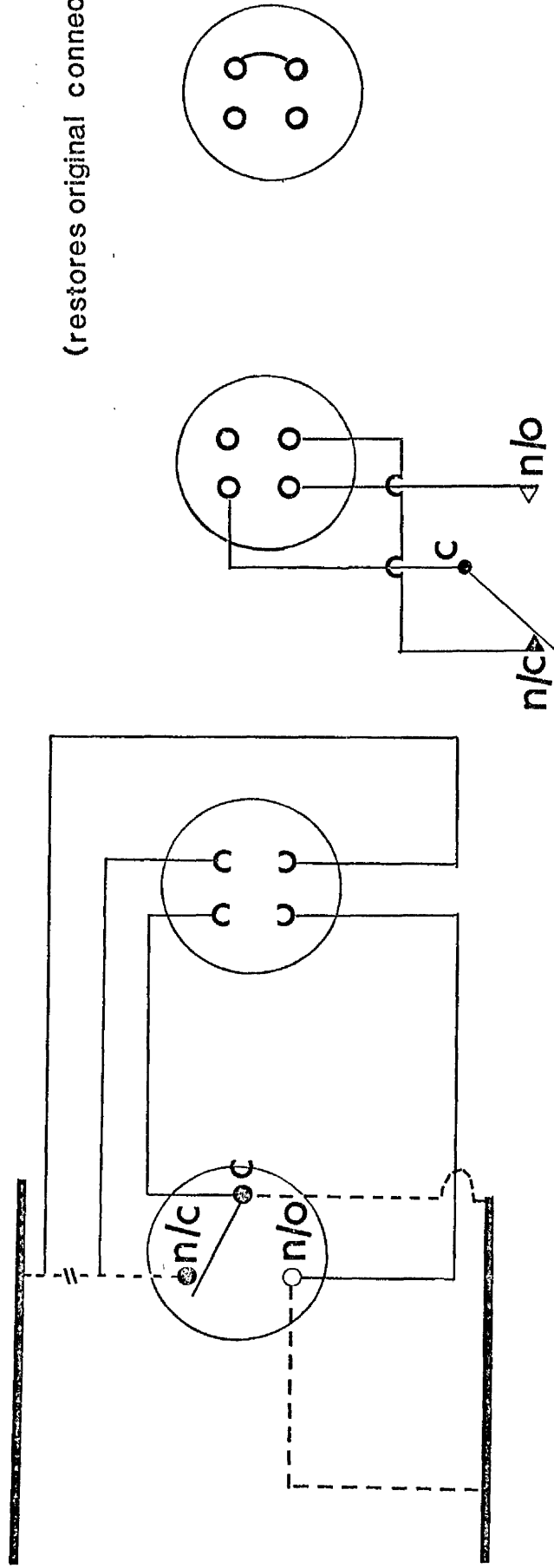
Young et al, 1970 recommended replacement of the 10 rph motor by a 1 rpm motor and gear train using a cam with a single notch, for improved precision at 60 samples/h and it is clear from Table 16 that each lobe of the cam performs reproducibly and with a very much smaller standard deviation than the complete cam. Other authors replaced the cam by a synchronous motor (Evenson and Olsen, 1972) but it was felt that the demonstrable precision of electronic timing might offer a way of improving the performance even of a high-speed analyser at moderate costs, and allow better flexibility of sample/wash ratio than the original cams. Accordingly, a prototype electronic timer was constructed to this department's specification (Decade Process Timer DRT 24 - Shennanton Electronics Ltd, Church Street, Kirkcowan, Wigtownshire) and fitted to a Technicon sampler II by a method similar to that used by Johnson (1969). (figure 18). The performance of the combined sampler II and timer were evaluated in the same way as the

SAMPLER

TIMER

LINK PLUG

(restores original connections)



Original wiring

Additional wiring

Break

n/o Normally open

n/c Normally closed

C Common

Figure 18

Linkage of Process Timer to Technicon Sampler II

original unit, using the contact closure method only, since the results from Table 15 were similar in both methods, indicating that play in the probe transport mechanism does not cause significant variation in timing. The results are shown in column 6 of Table 15 and indicate that such a timer is more precise, not only than the complete cam, but also than any single lobe of any cam. Moreover the precision of the unit improved as the sampling time decreased, and the sample and wash times could be varied independently by one-second increments over the range from 0-99 seconds. The results of the timing study were later published by McLelland, Fleck, Wagstaff, and Robinson, (1975).

2.4.1.2 Pumps

The prime function of the pump module in a continuous flow system is to provide the driving force to move the fluids along the tubing. It must pump evenly and consistently so that sample, reagents, and air may be properly proportioned within the continuous flow system.

Standard proportioning pumps operate by completely occluding tubing of various internal diameters so that the volumes delivered by the pump rollers squeezing the fluids to the delivery end of the pump will be proportional to the square of the internal diameter of the pump tubing.

Sample integrity, during dialysis for instance, depends on exactly comparable flow rates on each side of the dialyser membrane, but it is clear that the resistance or back pressure from the analytical modules beyond a dialyser will be different since the protein-rich stream goes directly to waste at atmospheric pressure. It

was therefore thought valuable to devise a testing procedure to evaluate reproducibility of volume delivery under load and to estimate the contribution of each analytical module to the back pressure on the pump, particularly since the possibility of back flow or 'pulsing' in the system had already been described (Neumann and Fischer, 1969) and it had been predicted that the consequences of this type of artificial lengthening would include an increase in the carryover characteristics of the system (Fleck et al, 1971). Moreover, the elasticity of the air bubbles used to segment the reagent stream and so scour the walls of the tubing to minimise the transfer of material from one segment of the stream to the next might be expected to cause pulsation at bubble addition and removal points and in response to the excessive pressure build up within the analytical modules.

2.4.1.2.1 Materials and Methods

The simple circuit devised to compare the effects of a number of different continuous flow modules is shown in Figure 19, with the unit under test introduced as the Unit A in the circuit. A junction in the diluent stream led to a vertical section of tubing calibrated in centimetres. Opening the clamp B allowed the water from the circuit to rise up the tubing, and when equilibrium was achieved the head of fluid was taken as the back pressure of the system on the pump.

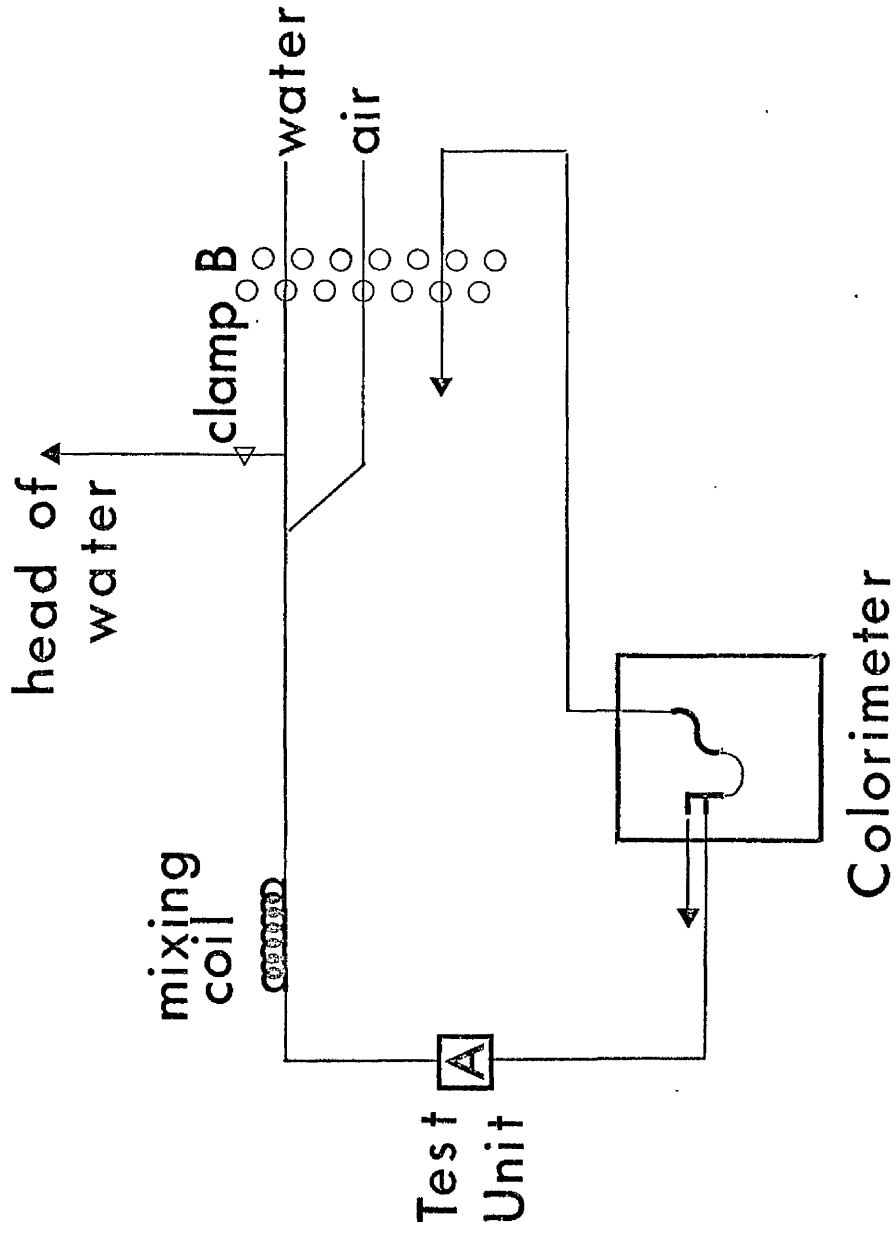


Figure 19

Estimation of Back Pressure

2.4.1.2.2 Results and Discussion

The results for a number of standard continuous flow modules are indicated in Table 18, showing that the primary cause of back pressure among the components of the system is the tubing length within the module. The test circuit also proved useful in examining variations in back pressure during the pumping cycle, and also at varying pump speeds. It was noted that there was a consistent variation of 2.8 cm of water during the pumping cycle and that this was at a minimum as each roller lifted from the tubing and allowed a small amount of pressure drop. As expected, increasing the pump speed increased the back pressure on the system approximately linearly with pump motor rheostat setting; (Table 18) and both length and fluid velocity effects are consistent with a retardation of the passage of the air-segmented stream through the circuit caused by friction against the tubing walls - the surface effects considered by Chaney (1968).

The effect of air segmentation itself was also studied through this circuit and it was found that the introduction of air bubbles, which are crucial in minimising carryover within the continuous flow system added greatly to the measurable back pressure (Table 18). This finding confirmed some of the work of Chaney (1968).

Finally, the fluid load indicated by the findings in Table 18 were used directly to provide a back-pressure equivalent to a double-coil heating bath in testing the reproducibility of delivery both with

TABLE 18

Back pressure measurements attributable to AutoAnalyser Modules, alterations in pump speed, and air segmentation of the fluid line, using the circuit of Fig 19

Pump	Unit 'A'	Air Segmentation	Head of Water (cm)
Technicon Pump I	-	No	4.6
"	-	Yes	16.5
"	40' coil	No	16.6
"	40' coil	Yes	83.1
"	single mixing coil	Yes	29.5
"	Heating bath (double 40' coil)	No	28.6
"	Heating bath "	Yes	144.0
"	Dialyzer module	No	33.2
"	Dialyzer module	Yes	138.3
Quickfit & Quartz	Delivery rate		
(using 0.1 cm ID	1.33 ml/min	Yes	47.0
tubing and a	1.99 ml/min	Yes	72.0
constant load of	2.65 ml/min	Yes	94.2
one 40' coil plus	3.31 ml/min	Yes	108.0
air segmentation)	3.96 ml/min	Yes	124.6
	4.6 ml/min	Yes	138.5
	5.2 ml/min	Yes	149.5
	5.85 ml/min	Yes	168.9
	6.45 ml/min	Yes	180.0

and without air-segmentation of a variety of tubing sizes on a number of pumps thought suitable for incorporation into continuous flow systems of the period (Fleck et al, 1972).

2.4.1.3 Dialysis

One of the advantages of continuous flow systems over discrete analysis is on-line dialysis, which removes potentially interfering macromolecules and cellular debris from the reaction mixture. Continuous flow analysis has traditionally used concurrent dialysis where at most only 50% of the analyte will diffuse through the semi-permeable membrane separating the dialysis plate. Skeggs noted in his original paper in 1957 that the flow rates should be matched as evenly as possible lest differential pressures on either side of the flexible membrane distend it and produce inequalities in proportioning of the fluids. The equation governing transfer of material across the dialyser is that of Fick's First Law

$$k = \frac{A t D (C_1 - C_2)}{\delta x}$$

where k = total amount across dialyser in moles

A = Area of diffusion in cm²

t = time of dialysis in seconds

d = diffusion coefficient in cm²s⁻¹

c₁ = concentration of analyte in donor stream (mole cc⁻¹)

c_2 = concentration of analyte in recipient stream

δ_x = thickness of the dialyser membrane in cm.

Since increasing the sampling rate will reduce the effective maximal concentration of analyte in the donor stream, C_1 , a loss of sensitivity can be expected. To increase sensitivity, a combination of lower flow rate (to prolong dialysis time) and increased temperature, (since the diffusion coefficient varies directly with temperature) may be considered. Later work by Torrance (1978) directly related to the construction of a high-capacity electrolyte analyser in the author's laboratory confirmed these conclusions experimentally.

2.4.1.4. Flow cell/Photometry

One of the main identifiable causes of carryover within the early continuous-flow system was the dead space within the debubbler unit of the Technicon colorimeter (Habig et al, 1969; Walker et al, 1970; Fleck et al, 1971), since removal of the air bubbles allows the segments of the reaction stream to mix together, prior to being drawn through the flow cell. Habig and colleagues (1969) experimentally eliminated the need for debubbling by monitoring flowcell conductance and deactivating the output signal when it was evident that a bubble was present in the flow cell. Neeley and coworkers (1974) achieved the same end using an electronic circuit which compared signals on the basis of their duration and constancy and passed to the recorder only those signals which excluded the presence of bubbles. By this means

they were able to report a continuous flow glucose method running at 150 samples/h. This technique has been used to advantage in the Technicon SMAC and Rank Hilger Chemispek analysers.

2.4.1.5 Fluidics

The distorting effect of strong alkali on the rise curve of continuous flow analyses had also long been recognised (Fleck et al, 1971) and by the early 1970s it was clear that the total path length of the system was important in producing carryover (Begg, 1971). Further work by Torrance (1978) summarised the additional fluidic effects, such as the length of the sample tube and dialyser size, which increase carryover within the system.

Where a debubbler is used, a small dead volume and fast flow rate through the flow cell were also reported to reduce carryover. (Habig et al; 1970, Tweedie, 1973).

It was demonstrated (Pennock et al, 1973) that consideration of such factors could be used to increase sampling rates to above 70/h for common methods.

2.4.1.6 Curve Regeneration

Arising from initial considerations of the kinetics of continuous flow analysis (Thiers et al, 1967; Walker et al, 1970, 1971) Walker advanced the principle that the deformation of the perfect 'square wave' caused by carryover in continuous flow analysis could be partially corrected mathematically from knowledge of the final

peak shape (Walker, 1971), and that, in particular, the height to which the recorder pen would have risen if the sample had been aspirated to equilibrium could be predicted by means of equation

$$E = h + b \, dh/dt$$

where E is the equilibrium plateau height

h is the height of the pen above baseline

dh/dt is the rate of rise or fall of the pen in unit time

and b is a constant, dependent on the analytical system.

This process he called curve regeneration.

Improvements in technology, and in particular the shorter dialysers and small dead-space debubbler systems available with the second generation of Autoanalysers together with optimisation of the methods had enabled sampling of around 100/h to be considered by the early 1970s. Walker considered that the correction algorithm, applied in "real-time" would increase sampling rates by about 50% since the shape of the peaks at the higher rate with curve regeneration were similar to the type of peak achieved at around 100/h without curve regeneration. The algorithm was then produced as a logic circuit in a commercially available independent unit. The circuit was published by Walker and coworkers in 1972 as an alternative to the bubble-gating circuitry of Habig et al (1969) and an instrument also became commercially available in the UK (Weir electronics Ltd, Bognor Regis, Sussex, England) in 1972.

This device introduced between the colorimeter and recorder, would perform the calculations indicated and restore the shape of the peaks towards their square wave form by removing that part of the distortion attributed to the exponential factor (Thiers et al, 1967; Walker et al, 1970). On practical application to AutoAnalyser I systems in the author's laboratory it gave demonstrable improvement in performance at around 60/h and allowed sampling rates to be increased with no loss in precision compared to the slower speed. The carryover characteristics which caused poor precision and loss of peak identity (Figure 14 (iv)) were virtually eliminated (figure 20) and the percentage of plateau equilibrium achieved at sampling rates of 100/h rose from 89% to 100% (Table 19)

This ability to correct directly for carryover is the major factor which permits the higher throughput. The findings from this work were later published (Carlyle, McLelland and Fleck, 1973) and curve regeneration remained a topic of interest until the late 1970s (Jacklyn et al 1978). It is noteworthy that some of the less desirable characteristics of the older Autoanalyser I systems seemed at that stage a positive advantage. The debubbler of the older system which had been criticised and indeed deleted from the analyser by Habig et al (1969) and Neeley et al (1974) had the merit of smoothing the rise curves from each sample, and thus improving regeneration, while experience with the improved debubblers of the Autoanalyser II and SMA-6/60 type gave much less satisfactory results.

TABLE 19

PERCENTAGE OF STEADY STATE EQUILIBRIUM ACHIEVED

AT VARIOUS SAMPLING RATES

<u>Sampling Rate</u>	<u>Unregenerated</u>	<u>Regenerated</u>
40/hr	100%	100%
60/hr	98%	100%
80/hr	93%	100%
100/hr	89%	100%

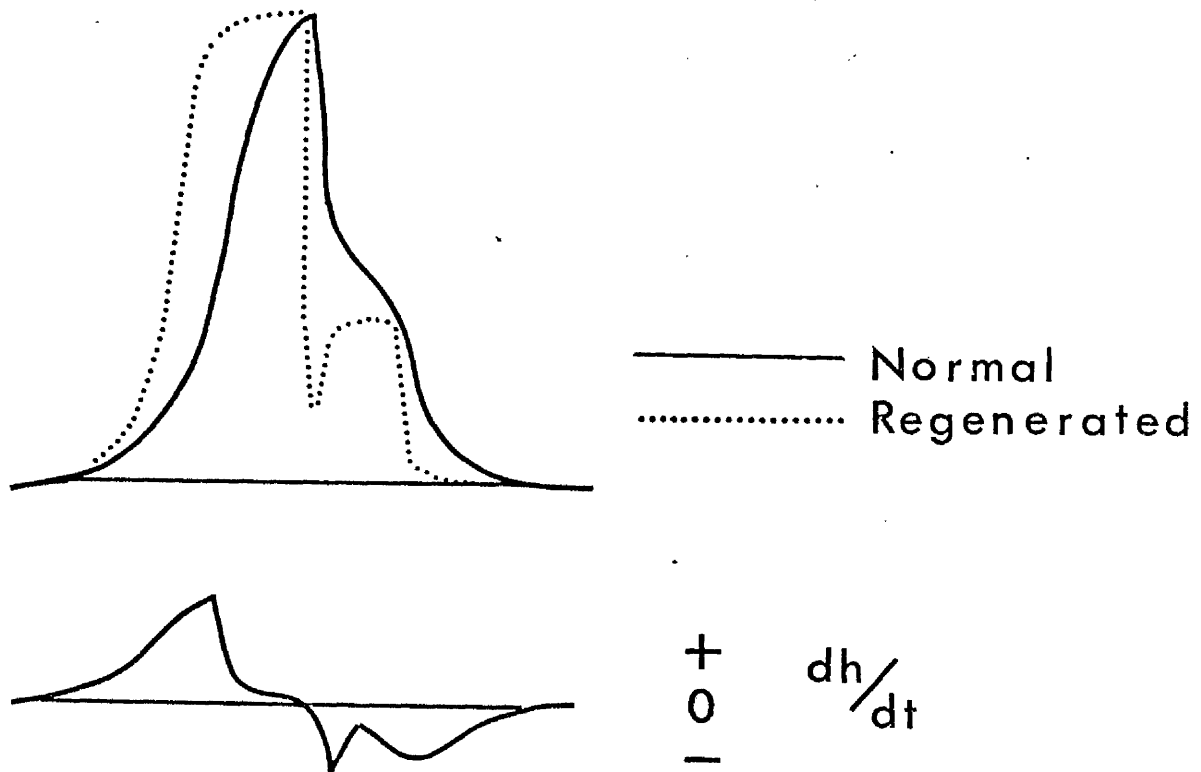


Figure 20

Resolution of merged peaks by the Curve Regeneration algorithm

2.4.1.7 120/h sampling rate for continuous-flow analysis

Investigation of the rate-limiting steps in continuous flow analysis in the author's laboratory led to the construction, during 1974/75 of a 120 samples/h analyser for the electrolyte profiling work of the department, (Plate VIII) since the workload and the constraints of specimen delivery (Section 1.1.4), had exceeded the 60/h analytical capacity of available commercial instrumentation at that time. A block diagram of the analyser is shown in Fig 21. Full evaluation details of the instrument have been presented elsewhere (McLelland and Torrance, 1976). The instrument incorporated some of the findings from previous sections.

a) Sampler (Section 2.4.1.1). The sampling device was a Hook and Tucker A40 sampler electronically modified to receive a timing signal from the quartz clock of the processor used for data acquisition (Section 2.5). Synchronisation of the sampler with the processor in this manner gave such a precise sampling cycle that the peaks from all five colorimetric channels reached an absorbance maximum within the same seven second time window.

b) Pumps (2.4.1.2) The Ismatec pumps chosen for the analyser were featured in the pump evaluation trial (Fleck et al 1972). They offered variable speed control and it was therefore possible to slow the pumping rate and use wider bore tubing to minimise both carryover and the possibility of blockages within the lines.

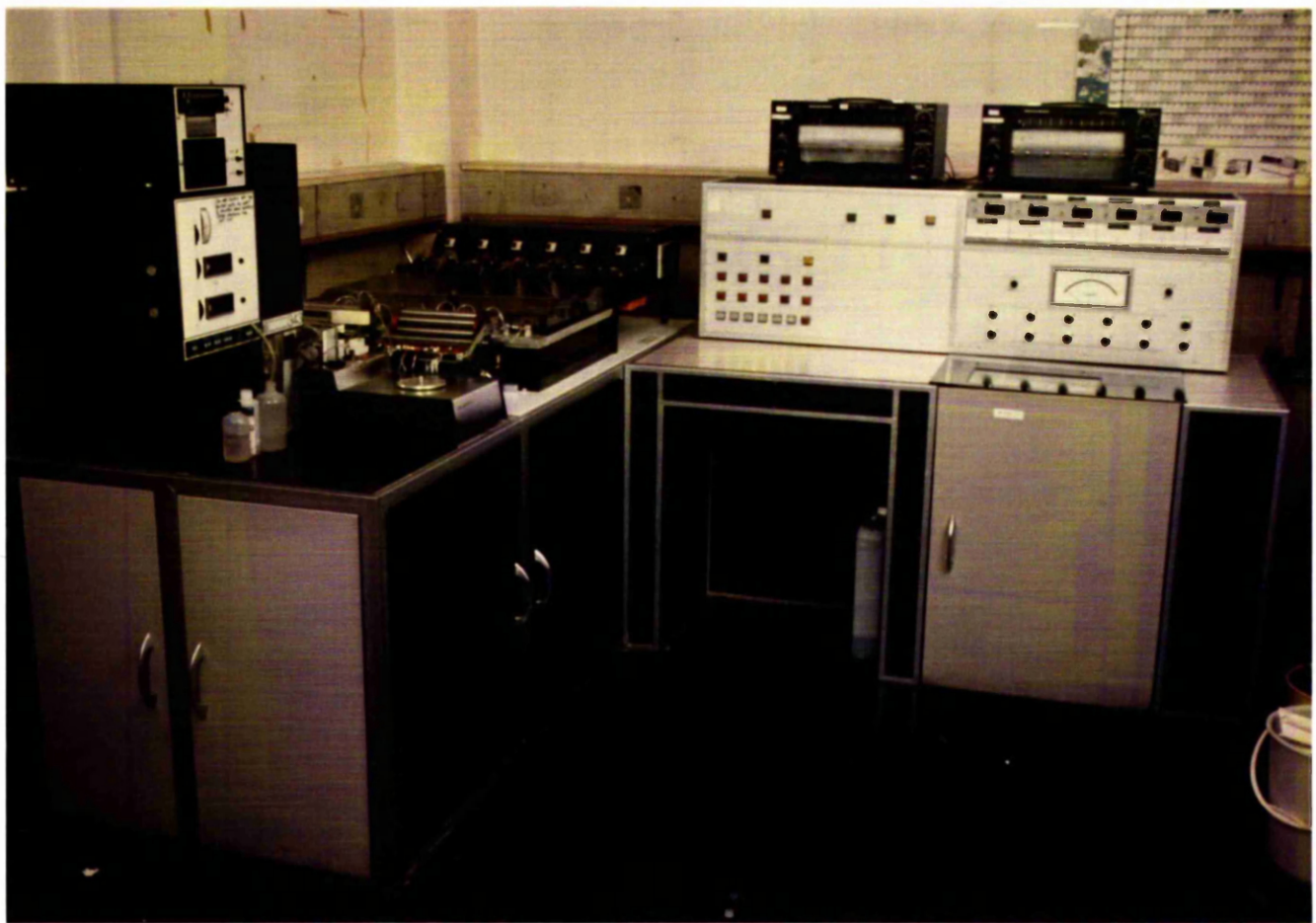
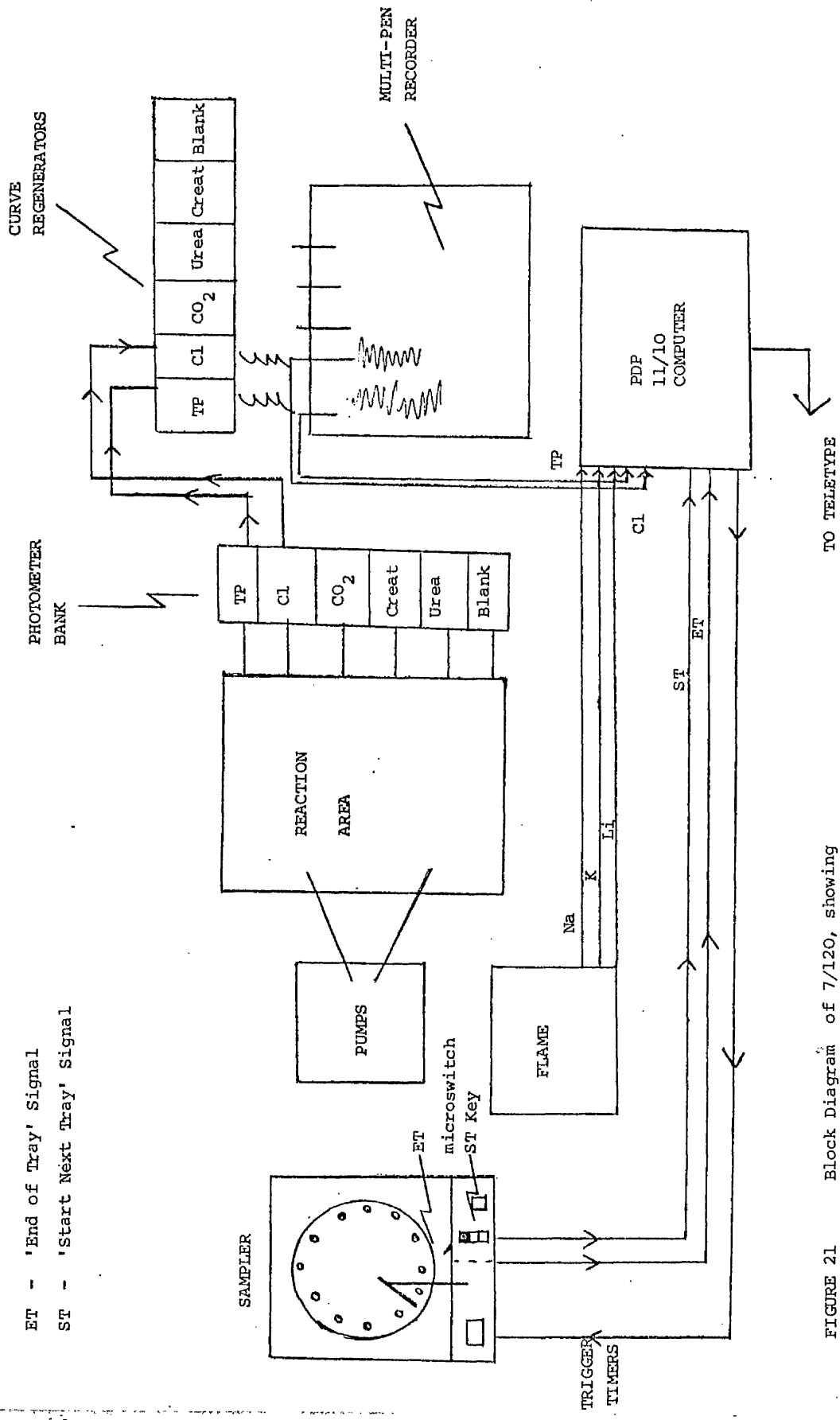


PLATE VIII 7/120 - a seven-method, 120 samples/h continuous flow analyser

- c) Dialyser. The analyser employed AutoAnalyser II components with small dialysers whenever possible in order to reduce the excessive carryover attributable to the dialysis process (Torrance, 1978).
- d) Flow cell/Photometry (2.4.1.4). Hellma Flowcells (Tweedie, 1973) with integral debubblers were used with a modification of a Fisons single channel colorimeter. The small dead space and high emptying rate (Tweedie, 1973; Habig et al, 1969; Torrance, 1978) contributed to the high sampling rate.
- e) Fluid Flow (Section 2.3.1.5) The total path length of each method was minimised as much as was practically possible (Fleck et al, 1971) and acidic conditions were used where practical (Fleck et al, 1971; Torrance, 1978).
- f) Curve Regeneration (Section 2.3.1.6). With the availability of proven, commercially available curve regeneration modules (Carlyle et al, 1973) it was decided to use them rather than construct a bubble-gating system similar to that developed by Neeley and coworkers (1974).
- g) Data Acquisition. Where an instrument is capable of generating 840 results per hour, and particularly where the data is being received in the main as continually varying analogue signals, some form of appropriate data acquisition is essential. This topic will be discussed further in Section 2.5.



ET - 'End of Tray' Signal
 ST - 'Start Next Tray' Signal

FIGURE 21 Block Diagram of 7/120, showing Electrical Connections

The major commercial high-capacity continuous-flow developments during the 1970s were the development by the Technicon corporation of a computer-controlled SMA system (SMAC) working at 150 samples/h and capable of analysing up to 20 parallel channels simultaneously; the development of a replacement data acquisition module which permitted 120/h operation for 60/h SMA systems by Vickers Ltd, and the introduction in the late 1970s of a 120/h commercial continuous flow analyser by Rank Hilger ltd (Chemispek). The pioneer work into the rate-limiting areas of continuous flow analysis had clearly been noted by manufacturers, as well as by clinical chemists. From the mid-seventies onwards total path lengths were being shortened, bubble gating circuitry was being employed on SMAC and Chemispek. A pecking probe was introduced on SMAC to air segment the initial sample stream (Torrance, 1978) and the sophisticated data acquisition system used on the Vickers modified the requirements for steady state working in a manner analogous to curve regeneration used by the Royal Infirmary's in-house development.

2.4.1.8 Limitations of Continuous Flow Analysis

The limitations of continuous flow analysis are related primarily to its design concepts. The use of a proportioning pump to push fluids through the system causes carryover which restricts the maximum achievable sampling rate to around 150/h at present. The continuous pumping also requires that the reaction mixtures pass a fixed detection point at a fixed time interval after sampling; the

system is therefore inappropriate for reaction rate methods - such as enzyme estimations. However, increasing investigation of the traditionally end-point methods such as creatinine and albumin are uncovering interferences (Cook 1971; Webster, 1974) which may be eliminated by application of rate methods. A bubble gating system such as SMAC does offer the option of reading absorbance from a number of detectors in sequence, since the integrity of each fluid segment has not been destroyed, but the limited amount of information provided in this way is inferior to the continuous reaction rate monitoring offered by a number of discrete analysers (Section 2.5.3).

Continuous flow analysers are not selective. The steady expansion from single channels to six, twelve, eighteen and finally twenty-three channels all fed from a single sampler is in many respects a logical and cost-effective one. Neill and Doggart (1969) however, suggested that where a profiling analyser was available, laboratory logistics made it unlikely that a single analysis from within the profile would be performed even if requested. While it has been shown that profiling has revealed unexpected, abnormal results which have been of value in the patient's treatment (Bryan et al ,1966; Vogelaar, 1978), fears have also been expressed that the multiplicity of results may cause the important numbers to be lost in the clutter (Williams and Dixon, 1979).

Given clinical disinclination to order single tests (Ormerod et al, 1976) and the minimal additional reagent costs of running further analyses on an existing multi-channel system, the author can see no reason for not performing an extended (>15 channel) profile, even if it is subsequently decided to report only that group of analyses originally requested supplemented by discussion of unrequested abnormals with clinical staff.

By this I refer not to the old statistical argument that in any 20-channel profile, one result will be outside the reference range for that method, but to unrequested results which are sufficiently abnormal to warrant a follow-up by telephone. The only critical limit which suggests itself, given that problems of calibration and selectivity of reporting can be solved, is the total capacity of the analyser.

Experience has shown that the haphazard selection of methods for a multi-channel analyser can result in overloading the instrument. This problem can be due to the inclusion within the profile of a test, or group of tests, which have little in common with the others. This creates a sub-set of the total number of specimens analysed which involves little or no cross-requesting with the major groupings of tests on the analyser. This largely independent sub-group becomes an obvious candidate for transfer to a separate instrument through time. The concepts of the cross-requesting of functional groups has been discussed previously in Section 2.2.2.

The advocates of selectivity in analysis do not yet appear to have made a convincing economic case, nor have the consequences of postponing or omitting a necessary test, been evaluated. Worse, it can be envisaged that an analysis which was not requested initially could be later deemed necessary, and that the laboratory might be unable to comply with such a retrospective request because of limitations of sample storage or insufficient sample.

2.4.1.9. Future Developments

Studies into the rate-limiting steps in the late 60s and early 70s have raised the sampling rate from a typical 60/h to over 100/h at present, mainly because of the removal of a major source of carryover by use of bubble-gating circuitry or of correction for signal distortion by curve regeneration. The future of continuous flow analysis is less easy to predict. It may be assumed that existing research will be incorporated into improving sampling rate (Northam, 1981), but there have been comparatively few papers which have led to increased knowledge of the theory of continuous flow analysis since the mid seventies (Walker and Andrew, 1974; Spencer 1976; Torrance, 1978; Snyder et al, 1976; Spencer et al, 1977a,b; Katzenell, 1978; Dixon, 1982; Simpson, 1977) and little of the present work seems likely to increase sampling rates dramatically, although new techniques like immobilised enzymes (Leon et al 1977; Zaborsky, 1978), and ion selective electrodes (Cowell 1978) have been incorporated into existing systems.

Perhaps the most promising area for continuous flow analysis is the throughput potential possible through removal of the air segmentation which itself contributes to the minimum possible analytical path length. This fundamental approach to analytical chemistry has been labelled "flow injection analysis" by its initiators, Ruzicka and Hansen. It has been under development since 1975 (Ruzicka and Hansen 1980), has been used primarily in industrial analytical chemistry but has much in common with the traditional continuous flow methods (eg the report in 1978 (Ruzicka and Hansen, 1978) that it was better to decrease carrier stream velocity than increase the total path length of the system (cf Section 2.4.1.2.2)).

It has attracted the interest of clinical chemists to some extent, (Renoe et al (1980)) and Ruzicka and Hansen have applied it to serum (Ruzicka et al 1977). It also has a potential throughput significantly better, at 240 samples/h than current air segmented continuous flow systems (Ruzicka and Hansen 1980).

2.4.1.10 Effects on the critical path network of improving sampling rate

The revised (1981) network of Figure 13 has already been introduced to assess the effect of improved data preparation techniques (Section 2.3.2.1) since the original network diagram was constructed in 1975 (Figures 8 and 9). It will be noted from comparison of Figures

9 and 13 that the analytical branch (nodes 2, 8, 9, 5) has become rate limiting despite reduction in the mean elapsed time by around 30 minutes, when compared with the 1975 data.

In practice, efficient data preparation, with data entry at a variable number of terminals should always make the analytical branch rate limiting, since the latter will be constrained by the sampling rate of the analyser. This implies that successive replacements of the analyser by faster instruments will continue to improve the throughput time for the network, and that data preparation can be disregarded until such time as the analytical sampling rate exceeds 240/h.

The other potential improvements in the 1981 network include the removal of the worksheet stage, to allow analysis to begin virtually immediately upon receipt of samples, and a direct connection between analyser and computer to obviate the necessity for tape transfer.

The former activity would require some form of positive sample identification as discussed in Section 2.3.1.

2.4.2 Discrete Analysis

The proposed definition of discrete analysis as "a method of analysis in which for the greater part the reactions involving different samples are carried out in separate containers or compartments", (Fleck et al, 1974), highlights the major difference between continuous flow and discrete analysis and explains the major potential advantage of the latter - if the reactions are carried out in separate containers there is less opportunity for them to interact one with another and hence, with less possibility of carryover, sampling rate ought to improve.

Skeggs (1957) had considered the construction of a robot capable of performing the steps required of a conventional manual colorimetric analysis, but rejected this concept as impractical given the state of technology in the late 1950s, even although it was the more obvious approach to automation of manual methods (Mitchell, 1969).

The advance of technology which permitted complex sequences of activities to operate automatically at fixed times relative to one another had produced, by the end of the 1960s, analytical equipment capable of running at considerably higher sampling rates than continuous flow analysers - the Aga Autochemist (135 samples/h); the Baird and Tatlock Analmatic (300 samples/h); the Linsen Autolab (240/h) and

the Vickers M300 (300/h) (Northam, 1969) and the place of discrete analysers seemed assured, at a time when most continuous flow analysers were restricted to sampling rates of 40-60/h.

In the early 1980s, however, the major instrument of the majority of Scottish Clinical Chemistry laboratories and of the UK as a whole was still some variant of Skegg's original continuous flow analyser (Table 20) running at sampling rates of between 60 and 150 samples/h, and so it seems that the higher sampling rates alone were not enough to commend discrete analysers to most laboratories.

The basis of discrete analysis has been described by Northam (1969), Mitchell, (1970) and Cook (1975), and the advantages and disadvantages of discrete analysis are summarised in Table 21.

2.4.2.1 Advantages and Disadvantages of Discrete Analysis

Some of the summary comments in Table 21 require some discussion at this stage.

Simplification of data acquisition implies holding the reaction mixture at the detector for a fixed length of time and will be discussed under section 2.5. This also renders discrete analysers eminently suitable for reaction rate methods of analysis.

A number of discrete analysers are capable of performing a variety of different methods using a single detector and a change of wavelength. The use of such analysers (Greiner GSA II and G 300, Dacos, Dupont ACA, Hitachi 702 etc) contrasts markedly with continuous flow where each method has a separate manifold and dedicated detector

TABLE 20

MAJOR ANALYTICAL EQUIPMENT IN SCOTTISH CLINICAL CHEMISTRY

DEPARTMENTS - 1980

Health Board	Lab	SMA (No. of Channels)	Other Continuous Flow Analysers	Discrete Reaction rate analysers	Centrifugal Analysers	Other discrete Analysers
Greater Glasgow	1	12	4	3	-	-
	2	6	6	2	1	-
	3	18	5	3	-	-
	4	7	14	4	2	5
	5	6	12	2	-	-
Lothian	1	14	7	3	1	2
	2	-	16	2	-	-
Highland	1	12	4	1	-	-
Grampian	1	-	14	1	-	4
Tayside	1	-	8	-	1	10
Fife	1	12	4	1	-	5
Argyll & Clyde	1	-	14	1	-	-
	2	6	7	2	-	-
Dumfries & Galloway	1	9	5	3	-	-
Forth Valley	1	6	3	2	-	-
Lanarkshire	1	6	-	2	-	-
		6	6	1	1	-

Note: Since these figures were compiled, a further 6 major (>£100,000) continuous flow analysers have been installed in Scottish Laboratories.

TABLE 21

ADVANTAGES AND DISADVANTAGES OF DISCRETE ANALYSIS

ADVANTAGES: Minimal carryover hence higher sampling rates

Simplified data acquisition

suitable for reaction rate analysis

potentially method-independent

selective reagent usage

fast response

ease of operation

wider range of methods

DISADVANTAGES: Transportation system

reagent addition by syringes/stepping motors

laundry systems or disposable cups/vials

multiple detectors increase transportation problems

protein removal

control systems triggers

system and different methods are performed on a single sample in parallel. The requirement to pass all reaction mixtures in front of a single detector severely limits the capacity of the discrete instrument in terms of analyses per hour, unless, like the Dacos, the detector itself is made to scan a group of reaction vessels. (Mitchell, 1979).

A few discrete analysers were constructed with multiple detectors and parallel specimen transportation systems similar in concept to a profiling SMA system, but faster. (eg Vickers M 300, Coulter Kem-O-Mat, Hycel Autochem). These were not conceived as discretionary analysers and anticipated continued demand for large scale profiling, since the transportation systems were not independent of one another.

The disadvantages of discrete analysers were primarily related to mechanical complexity. The need for an electro-mechanical control mechanism - either a clock linked to the various units in the sequence, or a more flexible, but failure prone system of microswitch relays to act as triggers which would index the transport mechanism, open and close reagent valves, activate stepping motors or syringe pistons, and record absorbance values militated against extensive use of such analysers until solid state electronics and integral mini- and micro computers could replace the original electro-mechanical linkages.

Over the ten years from 1970 - 1980 it has been noticeable that it was only where the unique features of discrete analysers provided an advantage which continuous flow analysers could not match

that they really became established in clinical laboratories. For example, it was ease of use, fast response and a repertoire which extended to over thirty methods, including some drugs, which encouraged the use of the Dupont ACA. Similarly, continuous flow analysis was unsuited to measurement of the osmolality of serum or urine, or of the group of ion-selective electrode methods which comprise the 'blood gas' profile.

An obvious example of the widespread use of discrete analysers is the reaction rate analyser used for enzyme analysis, or enzyme linked methods.

2.4.2.2 Applications of critical path analysis to discrete analysers

The author's department used LKB 8600 60 samples/h reaction rate analysers (Plate III) for enzyme analysis in the mid 1970's, replacing existing unsatisfactory continuous flow methods. The network analysis for the sequence necessary to generate a four-result cardiac enzyme profile has been depicted earlier in Figure 10 and discussed in Section 2.1.1.

It is clear from the timings in Figure 11 that the analytical processes of compiling a worksheet, loading racks and performing analyses took of the order of two and a half hours. There were a variety of reasons for this - the necessity to perform LDH and CK analyses in sequence on the same instrument for example, and the batching of samples for cardiac enzyme analyses so that the batch would be run only once per half day.

It serves as an example of both the advantages and limitations of discrete analysis. These analysers were often easier to use and undoubtedly more accurate than continuous flow instruments, but were method-specific, that is, their most efficient mode of operation was to process all samples for any one method, before changing the method and re-running the samples, and they were also labour-intensive since they could not readily be grouped to run in parallel from a single sampler, despite the laboratory objective of a four-method profile.

It is noteworthy also that only completed profiles were reported, and so it was only during the last half-hour or so of the network as the CK results were becoming available that any reports could be issued by the laboratory staff. This aspect will be raised again in Section 2.4.3. et seq.

A second application of discrete analysis involves the use of a glucose analyser in the diabetic clinic of the Royal Infirmary. The details of this development have been published (Morrison et al, 1972), and are similar to other attempts within the United Kingdom to provide a fast analytical service where a fast result could influence clinical decision-making. The network diagram of operations within the clinic is shown in Figure 22.

Two points should be made about the network - Figure 22 focusses attention on the analytical process (nodes 3-4). It must be rate-limiting on the network as a whole since it is the only procedure

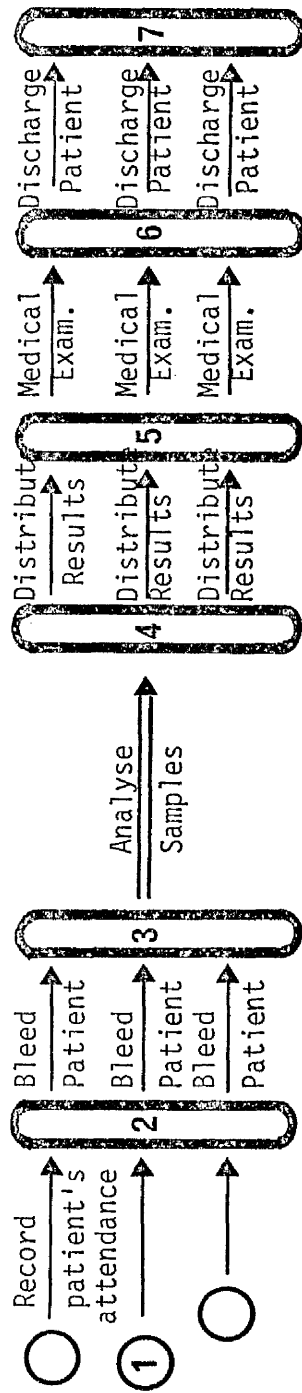


FIGURE 22 Network analysis of operations within a diabetic clinic

which is not performed in parallel. The throughput time for nodes 2 to 5 varied between 9 and 15 minutes (Morrison et al 1972) and it is doubtful whether a faster analyser would have brought about a significant improvement in the overall elapsed time for the network, which varied between twenty minutes and two hours.

The example illustrates again some of the specific advantages of discrete analysers. The glucose analyser used was simple to operate and could be transported to the clinic site and made operational within fifteen minutes. The fast response and digital results also made this discrete analyser more efficient than its continuous flow counterpart, despite the comparable sampling rates of the two analysers (50-60 samples/h).

The major advantage of this system however, was a reduction in transportation times and streamlining of reception and analytical processes, previously recognised as a major element of the cardiac enzyme network of Figure 11, and this was made possible primarily by restoring the close proximity of patient and analyst referred to in the introduction to this thesis.

One final example of the use of discrete analysers within the author's laboratory illustrates the way in which even the improved timings of high-speed discrete analyser can be nullified by laboratory logistics.

In 1973-76 the author's department performed an assessment of the Vickers D300 analyser for the Scottish Home and Health Department (McLelland and Fleck, 1977) and the instrument was in routine use for serum calcium analysis at a sampling rate of 300 samples/h from 1973 to 1976 replacing an atomic absorption device in use prior to 1973. Calcium formed part of a bone profile within the laboratory, the other analyses of the group being phosphate, total protein and albumin with alkaline phosphatase as a further requesting option, and these methods were run on continuous flow equipment at that time. The relevant network is shown in Figure 23, where the only obvious effect of the improvement in sampling rate was to shift the rate-limiting step to the analysis of protein and albumin.

Thus, in order to be fully effective, the D300 ideally should have performed all four methods, but apart from problems with the albumin and phosphate methods this involved the type of design constraints of method specificity outlined in the cardiac enzyme profile example, and it had also been recognised that the instrument required about 30 minutes to change over between methods (McLelland and Fleck, 1977; Brown et al, 1973).

2.4.2.3 Discussion

Discrete analysers, though capable of sampling rates superior to continuous flow equipment, failed to make substantial improvements in turnround time where they were introduced piecemeal into an existing laboratory logistic framework, except in special cases such as clinics

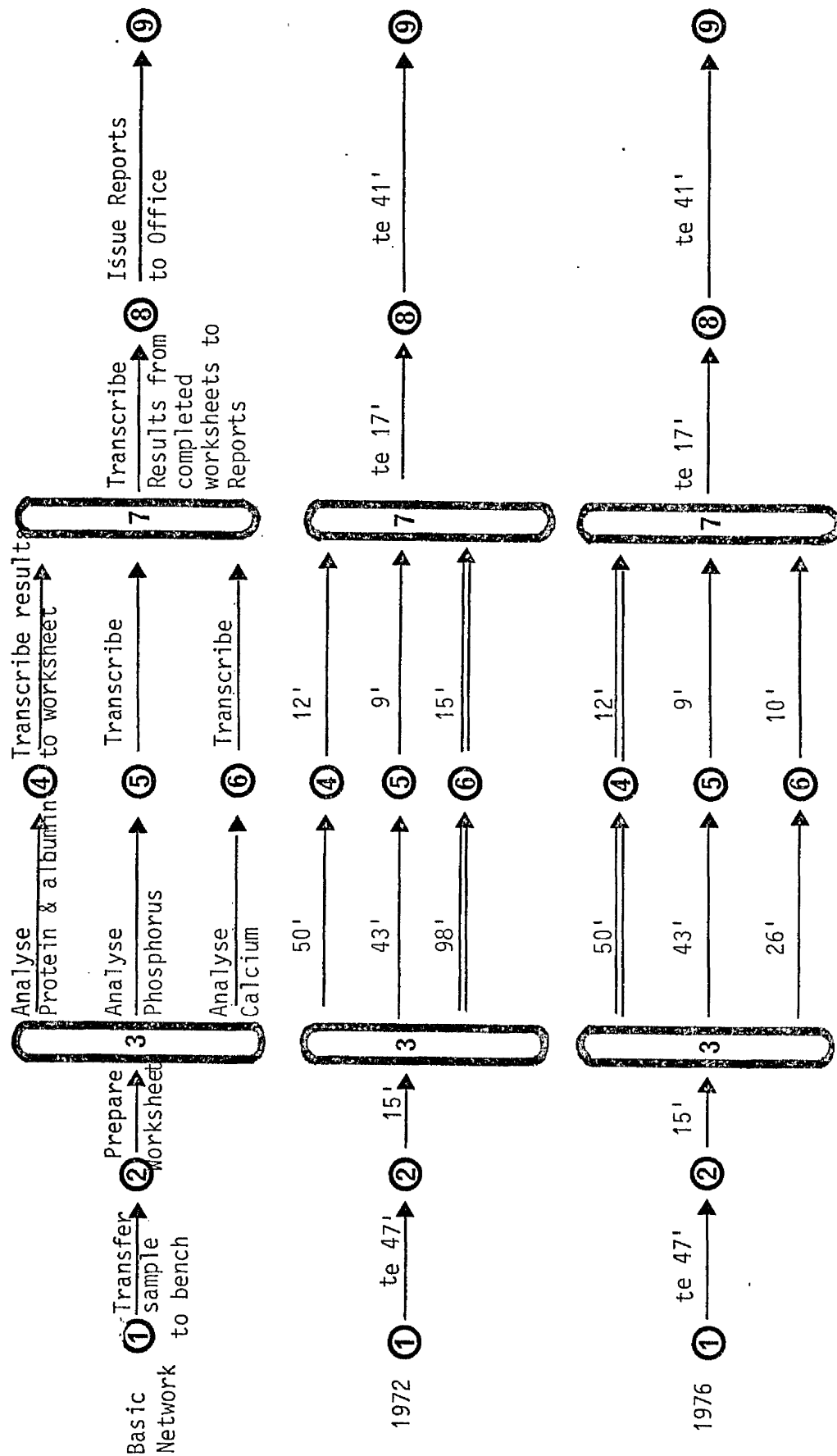


FIGURE 23 Generation of a 'Bone' Profile, GRI 1972-1976

where they could be demonstrated to be extremely effective. This latter case, however, was not so much a property of discrete analysers, as a radical change from the concept of a remote laboratory to which specimens were sent.

The versatility of some discrete analysers could be effective on a light workload where the analyser was the sole major instrument and would perform rapidly any desired combination of test; instruments in this category include the IL Clinicard, Dupont ACA and Greiner G300.

Finally, a complete changeover to a major, high-capacity discrete analyser such as the Vickers M300, Autochemist, or LKB Prisma could also be effective, although the mechanical complexity of such analysers has so far limited sales in comparison with multi-channel continuous flow analysers which have remained the workhorses of most laboratories in the early 1980s (Table 20). Also it must be said that the very diversity of manufacturers competing for a limited market has caused concern about the long term viability of the companies supporting such instruments, in comparison to continuous flow where a major single manufacturer has become established over the last twenty five years

2.4.3 Centrifugal Analysis

Centrifugal analysers may be considered a subclass of discrete analysers, because they satisfy the definition of Section 2.4.2. They were devised in part, to minimise the problems of trans-

port mechanism and mechanical complexity discussed in Section 2.4.2.1 in three ways - firstly by using centripetal force to expel the reactants from the transfer disc to the cuvettes; secondly by spinning the cuvette ring between a single stationary light source and detector, and thirdly by separating the mechanically complex sampler unit from the analyser, and using the machine operator to transfer the loaded disc between the two instruments (Anderson, 1970 and 1978; Tiffany, 1974 and 1981; Price and Spencer, 1980) - although the more reliable technology of the 1980s has permitted the two separate units to be merged in some current models.

The advantages and disadvantages of this type of analyser are summarised in Table 22, but it should be added that the limited batch size can also be an advantage, since although these instruments are method specific in operation, like the LKB 8600 and the Vickers D300 of Section 2.4.2.1, the method of operation and fast changeover between methods permit them to be used as medium-capacity profiling analysers.

2.4.3.1 Critical Path Analysis of the Centrifugal Analyser as a profiling instrument

The logistic problems of a number of method-oriented analysers have been discussed in Section 2.4.2.2. As the LKB 8600s in the author's laboratory aged, the possibility of replacing them with a single centrifugal analyser (Centrifichem-Baker Ltd Plate IX) was investigated during 1978. The operational specifications of such an

TABLE 22

ADVANTAGES AND DISADVANTAGES OF CENTRIFUGAL ANALYSERS

ADVANTAGES: Separation of mechanically complex pipettor from analyser
parallel analysis
fast changeover between methods
ability to perform both end-point & reaction rate analyses
adaptable to a variety of additional methods (eg
nephelometry, fluorescence, EMIT)

DISADVANTAGES: Limited batch size (16-40 place rotors)
limited number of reagent additions (normally 1 or 2)
temperature control
labour intensive



PLATE IX Centrifichem 400 Centrifugal Analyser

analyser are detailed in Table 23. While the capacity of the analyser was important, given a workload of 168,000 analyses per annum during 1977, the primary requirement was the second one on the list since the ability to perform a four-method profile was expected to improve the slow turnround of the cardiac enzyme group. A description of the instrument has been published (Henry and Saunders, 1976).

The network analyses involving bench activities before and after purchase of such an instrument for the Liver Function Test and Cardiac Enzyme profiling are depicted in Figures 24 and 25.

While it might appear, from these Figures, that the upper networks are more satisfactory, since analysis of individual serum constituents proceeds in parallel on the LKBs rather than sequentially, as on the Centrifichem, the superior analytical rate of the centrifugal analyser gives the improved timings of Figures 26 and 27.

Other less obvious inferences from Figures 26 and 27 are

- 1) the sequence of operations on the Centrifichem is very closely controlled from the point at which analysis of the four-method profile begins. This produces a small σ^2 term for the sequence from Node 14 to Node 19 in Figure 26 and from 12 to 17 in Figure 27. This reflects the extremely efficient use of the pipettor/analyser combination, since the transfer disc for the next analysis is being prepared while the contents of the previous disc are being spun and analysed in a six-minute cycle.

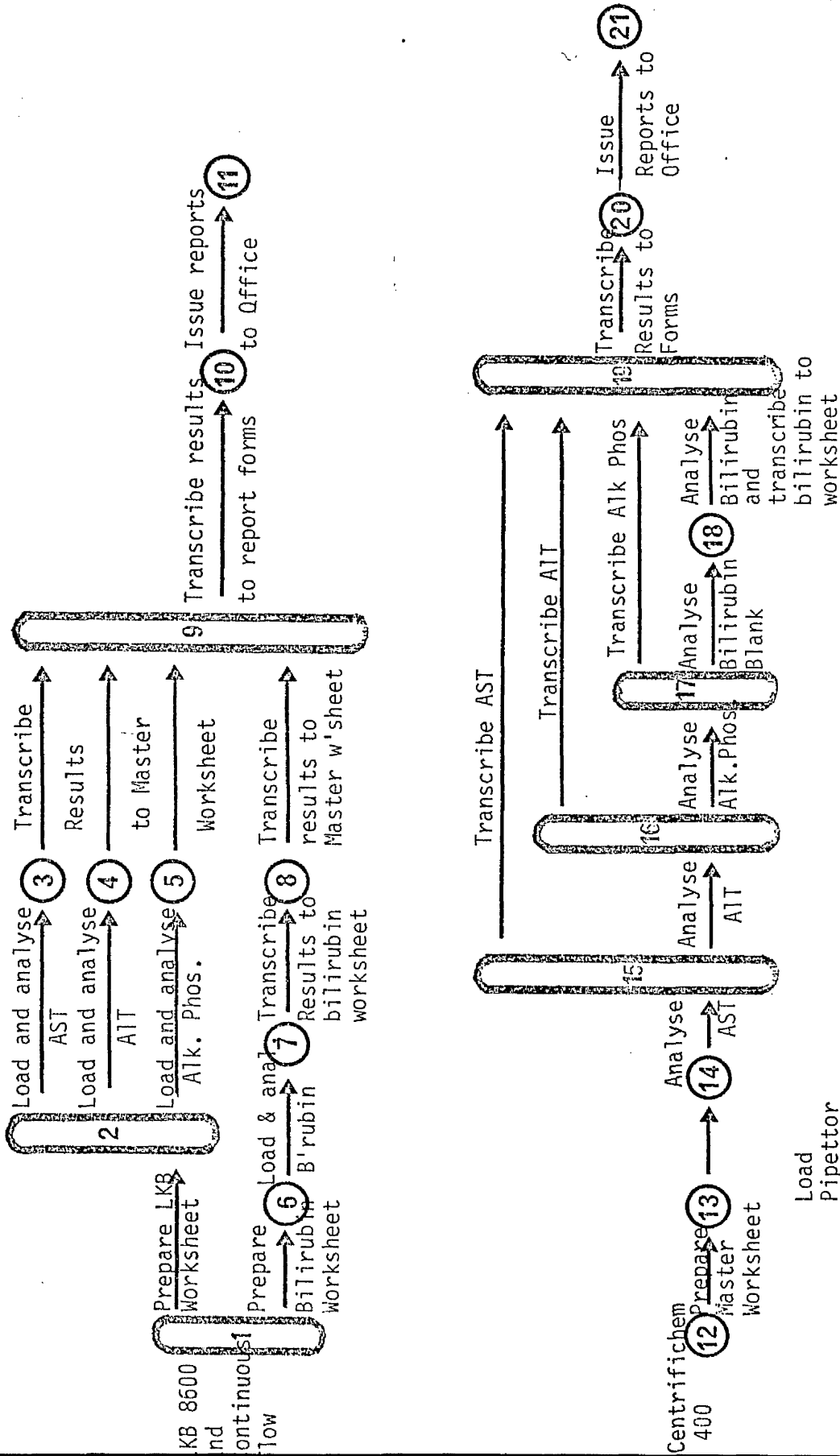


FIGURE 24 Network Diagram of operations required to generate a Liver Function Test Profile before and after implementation of a Centrifugal Analyser

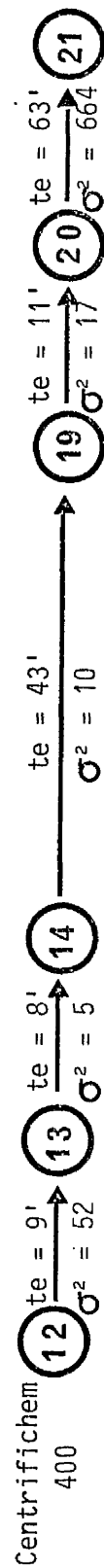
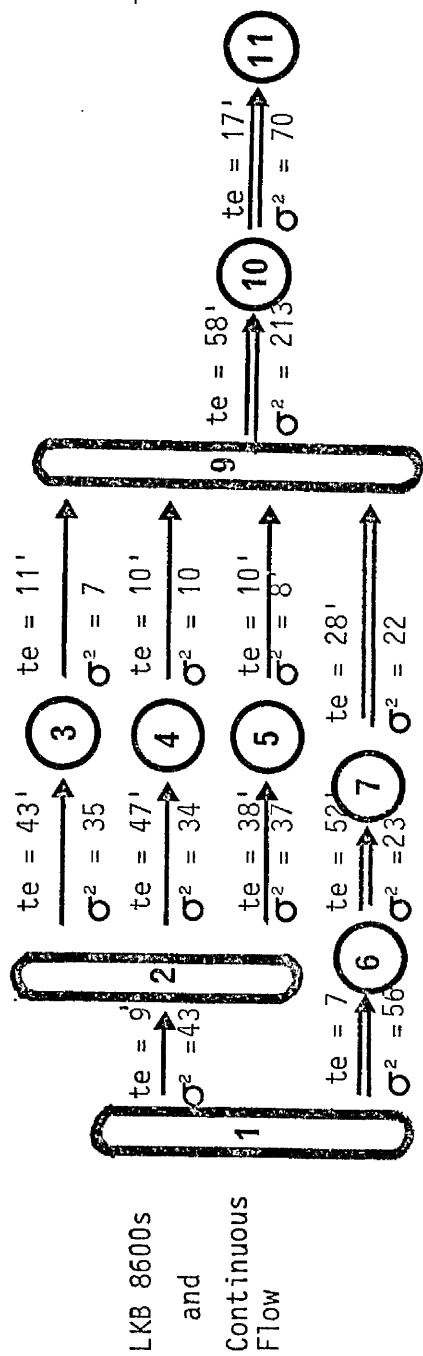


FIGURE 26 Critical Path Analysis of activities necessary to generate a Liver Function Tests Profile before and after implementation of a Centrifugal Analyser. Nodes numbered as in Figure 24.

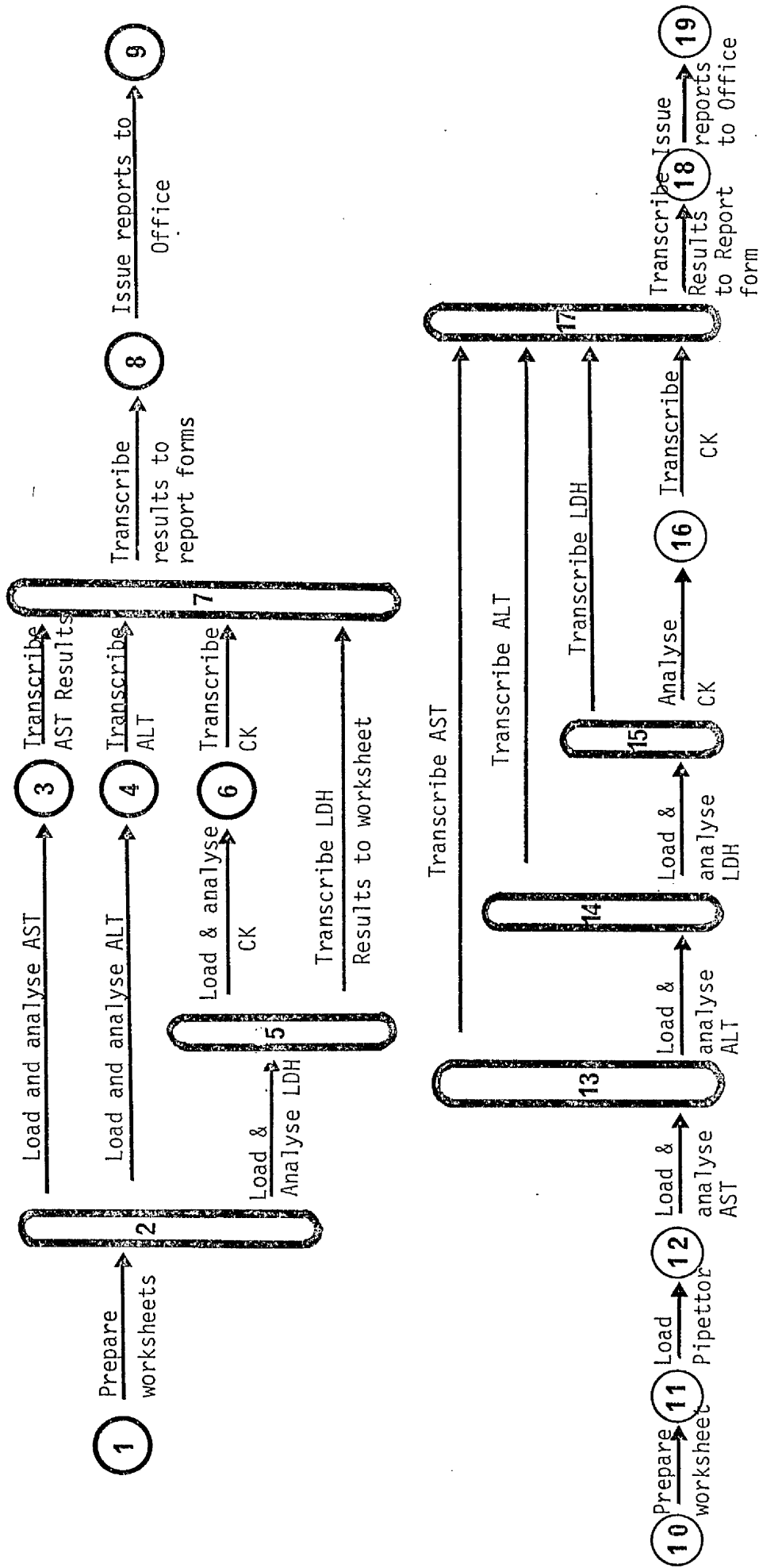


FIGURE 25 Network diagram of operations necessary to generate a cardiac enzyme profile before and after implementation of a Centrifugal Analyser

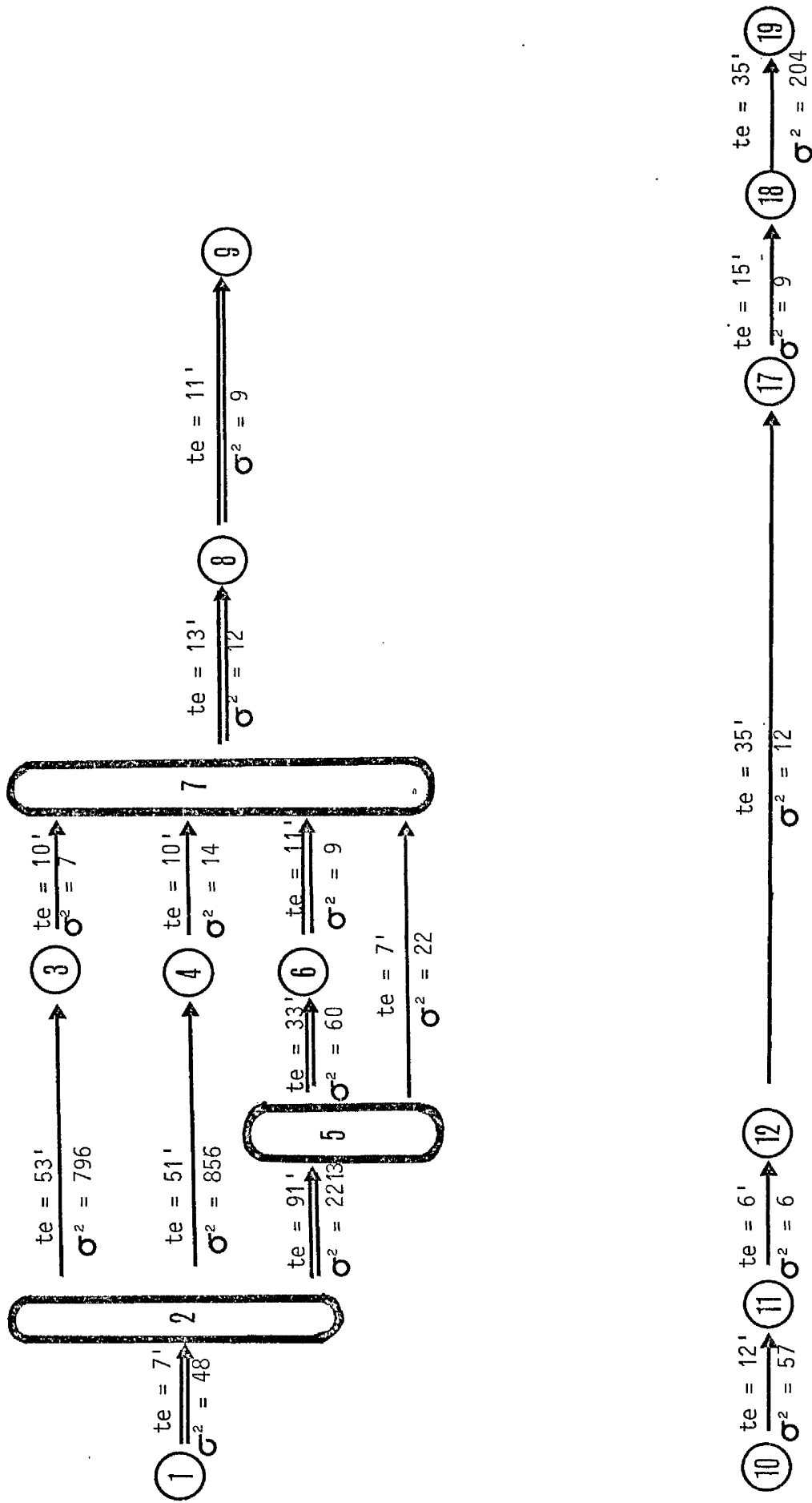


FIGURE 27 Critical Path Analysis of operations necessary to generate a cardiac enzyme profile before and after implementation of a Centrifugal Analyser (Nodes numbered as in Figure 25).

TABLE 23

OPERATIONAL REQUIREMENTS FOR A SINGLE REPLACEMENT

REACTION RATE ANALYSER

GLASGOW ROYAL INFIRMARY 1978

- 1) Proven record in UK Clinical Chemistry
- 2) Profiling rather than method-specific
- 3) Capable of both end-point and reaction rate analysis
- 4) No more than 60-70% utilisation at December 1977
- 5) Final output in machine readable form

2) Results are written to reports comparatively quickly when the Centrifichem is used, (Nodes 19 to 20 Figure 26; 17 to 18, Figure 27) since all the results for the full profile for each batch are to hand within 30-40 minutes of beginning the batch. This compares particularly favourably with the "method-specific" procedures of the LKB. Here individual results were written to the master worksheet by the technician responsible for each analysis, and the batch completion was dependent on both the speed of the slowest analysis, and on the senior analyst at the bench assuming responsibility for reporting the completed profiles. This took place at a fixed time of day - late morning or late afternoon - and gave rise to a lengthy and variable time period for the transcription step of the LFT networks (Nodes 9 to 10 in Figures 24 and 26). Indeed, the final common path of nodes 9-11 in Figure 26 often took as long as the total analytical procedures preceding them.

It should be noted in passing that a similar type of time delay occurred when using the Centrifichem (Nodes 19-21, Figure 26). This was a reflection of the geographic separation of bench and reporting office on two separate floors of the laboratory, and contributed to the periodic overloading of the manual reporting system which will be further discussed in Section 3.1.

3) The delay referred to above is much less marked for the Enzyme Profiles of Figures 25 and 27, because of the priority accorded the processing of these results, and because the enzymes were normally batched and analysed late in the morning or afternoon when the bench were reporting profiles in any event.

4) The analytical procedures for LFTs on the Centrifichem (fig 24) initially involved 5 analytical cycles since a blank value was required for the total bilirubin analysis.

It was subsequently shown (Kelly et al, 1979) that bichromatic bilirubin analyses could remove the need for a bilirubin blank run, and the time for a profile was reduced by a further six minutes to the figures shown in Fig 26.

2.4.3.2 Effects of Centrifugal Analyser on Quality of result.

The analyser has been shown to be an effective routine instrument of satisfactory precision (Fleetwood et al, 1977).

An improvement in precision was also demonstrated with this instrument when compared with the LKB analysers previously in use, particularly for the enzyme analyses (Table 24). Since the bilirubin method showed no perceptible change on transfer it is concluded that it was the removal of the inter-instrument component of variance, as enzyme analysis was transferred from four separate instruments to a single one, which caused the improvement in quality of result, particularly since no single LKB 8600 had been previously reserved for analysis of any particular enzyme.

TABLE 24

PRECISION OF ANALYSES EXPRESSED AS ONE STANDARD
DEVIATION, BEFORE AND AFTER IMPLEMENTATION OF
A CENTRIFICHEM 400

<u>Method</u>	<u>Unit</u>	<u>Mean Value</u>	<u>Standard Deviation</u>	
			<u>Pre-Centrifichem</u>	<u>Post Centrifichem</u>
Bilirubin (total)	$\mu\text{mol/l}$	34 77	1.4 3.7	1.8 4.2
AsT (total)	U/l	53 151	3.3 10.0	3.1 6.3
ALT (total)	U/l	49 175	4.0 7.6	3.3 9.2
Alk Phos (total)	U/l	322 734	33.2 67.0	13.6 27.3
CK	U/l	331	33.8	20.0

2.4.3.3 Discussion

The ability of centrifugal analysers to perform both end-point and kinetic reactions has been shown to permit a high workload of liver function test and cardiac enzyme profiles to be analysed rapidly. Advantages of such an instrument include the availability within 30 minutes of a 4-method profile for 25 patient samples (corresponding to around 240 total analyses/h).

Speed of analysis has been shown to compensate for the sequential manner of performing each method. The installation of this type of analyser to replace an equivalent configuration of single instruments with about the same overall analytical capacity has been shown to reduce analysis times and to improve analytical precision.

2.5 Data Acquisition

Data acquisition has been defined simply as the "transfer of information into the computer from outside" (Abson et al, 1977). While the analytical problems of increasing workload have indeed been met by the development of a range of instruments, the next step in the sequence, that is, the capture of the data from these analysers and the onward transmission of this data to a reporting computer has often been left to the individual laboratory. The difficulties associated with this process have recently been reviewed (Pangritz, 1981). One such application will be discussed in detail below, after a consideration of the different methods available for data acquisition.

2.5.1. Methods of data acquisition

Despite the variety of both biochemical analysers and associated data acquisition devices, there are only a limited number of methods for data acquisition (McLelland, 1979; Challand et al, 1979). In order of increasing sophistication these are (1) Direct data entry (2) chart reading (3) data logging (4) on-line hard wired calculators (5) programmable calculators and computers. The advantages and disadvantages of each class are summarised in Table 25.

Direct data entry involves typing data either into the computer through, for example, a visual display unit, or on to a storage medium such as paper tape magnetic tape, or disc. This method is commonly used for patient ID entry and for entry of small batches of results.

TABLE 25

ADVANTAGES AND DISADVANTAGES OF THE MAJOR METHODS OF DATA ACQUISITION

Method	Advantages	Disadvantages
Direct Data Entry	Flexible; visual confirmation of patient	Transcription errors; no reduction in number of transcription steps from analysis to report
Chart Readers	Flexible - copes with both reaction rate and end-point analyses Inexpensive - £3-4,000 per unit	No positive patient identification. Results can be missed Tedious to align charts on reader Batching of samples delays results Potential bottleneck
Data Loggers	Most appropriate for 'steady state' or stopped flow equipment, when triggered by clock or valve mechanism Capable of acquiring data from more than one analyser	No positive patient identification Data on storage medium must be re-processed before results are made available. No results until slowest analyser has stopped.
Hard wired calculators	Interim results available	Inflexible electronic calculation logic. Instruments normally analyser-specific High cost per channel
Programmable mini and micro-computers	Flexible. Can be re-programmed if required. Potentially independent of analytical hardware	Cost - typically £1-2,000 per channel

Chart reading has historically found a major use in association with the analogue output from continuous flow analysers (Flynn 1969; Mitchell, 1970b; McLelland et al, 1974; Smith et al, 1978). Two problems are apparent: these are the location of the top of the peak, which defines the relationship between the unknown sample and the standard curve, and the shape of the peak, which determines in part the validity of the result. Using a chart reader, the first problem is solved by visual assessment, as the operator places a cursor on the apex of the peak and transmits the X,Y, coordinates to a computer file or storage medium, while peak validation is performed visually. The alternative, manual chart reading, takes two staff around three minutes per channel for a standard 40-cup batch and has been shown to be a significant source of error (Tilstone and Fleck, 1970), whereas Flynn (1969) reported conversion of 1000 peaks/h to machine-readable form by chart reader.

Data loggers store data from detectors at fixed time intervals. This approach applied to a typical continuous-flow analyser output will require storage of large amounts of unnecessary data. However, a continuous flow analyser generating "steady-state" conditions, or a discrete analyser where a valve system holds the flow cell contents static for a short time, can use this method to advantage since only a single voltage will be necessary for each sample.

Hard-wired calculators combine data logging with real-time calculation to give interim results quickly. Many of these are of the "black box" type where a rigid logic sequence is performed automatically. Some instruments in this class (eg the Kemtronix amino acid peak integrator (Plate X)), offer switch-selectable options, but here again the logic within the options is inflexible. Manufacturer supplied integral microprocessors can also be considered as part of this class, since modification of the logic, while possible relatively cheaply is not normally within the abilities of laboratory personnel.

Programmable calculators and computers can be re-programmed to cope with deficiencies in the original logic. While the larger analysers (Technicon SMAC, Vickers M300, IL Multistat I and III, and IL 508, and Aminco Rotochem for example) now contain integral mini-processors which combine process control and data acquisition functions, it is in this area that laboratory staff have also acquired some experience.

2.5.2 Applications of mini-computers to data acquisition

Several laboratories have been constrained to develop their own data acquisition devices (Blaivas 1966; Flynn et al, 1966; Blaivas and Mencz, 1967, 1968; Whitby and Simpson 1969; Griffiths and Carter 1969; Gray and Owen, 1969; Carter and Griffiths, 1971; Undrill and Gibson, 1978) primarily for acquisition of data from continuous flow



PLATE X Kemtronix Data Acquisition Unit

analysers since (a) these instruments are widespread (Table 20) and (b) this type of continually-varying analogue output with transient peaks is in many ways the most difficult to analyse

In 1974, the author's laboratory was faced with the problem of acquiring data from the 120 sample/h continuous flow system which was being developed for electrolyte analysis (Plate VIII). The reporting processor in use at that time was a batch-oriented IBM 1130 with a configuration designed for report production rather than data capture. Programs were therefore developed on a PDP 11/10 processor to acquire data and report results from the analyser in machine-readable form for transfer to the IBM 1130. A modification of the program was applied to a second, four-channel Autoanalyser II system.

2.5.2.1 Materials and Methods

The equipment used was a DEC PDP 11/10 processor, (Digital Equipment Co, Maynard, Mass) using the BASLPS operating system and programmed in BASIC. A full description of the design specification, and systems analysis for two such projects will be found in Appendix II. Once software development had been completed for the electrolyte analyser the complete instrument was assessed against the instrument in routine use, a Technicon SMA 6/60, using the methods of Broughton et al (1974). For the 4-channel version the computer produced data were compared with the manually read results by means of linear regression analysis and pair-difference t test. The time taken to read the AutoAnalyser charts manually was also noted.

2.5.2.2 Results

The results of the electrolyte analyser evaluation have been presented elsewhere (McLelland and Torrance, 1976) and are summarised in Table 26. The main findings were that within-batch precision was satisfactory (Table 26b) when compared with Target Values incorporated into the Technicon Instruments Preventative Maintenance Scheme (Schedule D) and that correlation between the new analyser and existing methods was appropriate, but that there were accuracy changes in four out of the seven methods (Table 26a). Of the four methods, the difference in CO₂ content is attributable to re-sampling from non-gas tight containers and that in creatinine to differences in method to permit the higher sampling rate. The chloride and protein results gave a closer approximation than the routine analyser to the UK national consensus as expressed by the value assigned to the quality control sera which had also been included in the study to provide clarification where such differences were encountered(26c).

Correlation and pair-difference analysis in 250 samples randomly drawn from the calcium group data is shown in Table 27. Results show no significant difference between the automatic data acquisition method and the manual chart reader.

However, during the course of parallel running, 14 discrepant results, outwith rounding error, were obtained out of a total of over 2,000 comparisons. Of these, thirteen were due to manual reading or transcription errors, eight of which were protein results 10g/l

TABLE 26

SUMMARY OF EVALUATION RESULTS - 7/120 vs TECHNICON SMA 6/60

a) Correlation/Regression

Channel	No. of Points	Correlation Coefficient	Line Equation x = 6/60, y = 7/120	Mean	Pair Difference Students t	t- test probability
Sodium (mmol/l)	200	0.94	$y = 0.95x + 7.0$	-0.16	1.18	NS
Potassium (mmol/l)	200	0.99	$y = 0.99x - 0.23$	0.07	0.22	NS
Chloride (mmol/l)	200	0.95	$y = 0.95x - 1.6$	-0.54	4.02	$p < 0.001$
CO ₂ (mmol/l)	200	0.94	$y = 0.95x + 3.6$	-1.10	10.30	$p < 0.001$
Urea (mmol/l)	200	0.99	$y = 1.00x - 0.03$	-0.01	0.16	NS
Creatinine (μmol/l)	200	0.99	$y = 0.98x + 7.5$	-4.22	4.11	$p < 0.001$
Total protein (g/l)	200	0.98	$y = 1.10x - 6.2$	-0.9	5.93	$p < 0.001$

TABLE 26

SUMMARY OF EVALUATION RESULTS - 7/120 vs TECHNICON SMA 6/60

b) Precision Studies - within batch & overall

Channel	No. of Points	Mean Value	Within Batch Standard Deviation (SD)	Target* Value	Overall SD 1976	Overall SD Jan, 1982
Sodium (mmol/l)	20	140.9	0.64	1.0	0.85	0.99
Potassium (mmol/l)	20	4.80	0	0.07	0.03	0.05
Chloride (mmol/l)	20	96.1	1.21	1.3	1.08	1.06
CO ₂ (mmol/l)	20	16.7	0.57	1.0	0.83	1.03
Urea (mmol/l)	20	9.1	0.15	0.20	0.16	0.28
Creatinine (μmol/l)	20	170	4.2	5.1	3.9	8.4
Total Protein (g/l)	20	78.8	0.95	1.5	2.0	-

* Technicon Instruments Preventative Maintenance Scheme (Schedule D)

TABLE 26

c) USE OF WELLCOME NATIONAL QUALITY ASSESSMENT SERA TO EVALUATE

ANALYSER ACCURACY OVER 20 BATCHES

SERUM		Sodium	Potassium	Chloride	CO ₂	Urea	Creatinine	Total Protein
K0841	Observed		6.13	103.3		28.6	770	85.4
	target		6.25	104.5		29.1	725	84.5
K7075	Observed	144.7	4.95	100.6	18.8	9.1	84	75.1
	target	143.6	4.98	100.8	18.7	8.9	90	74.6
K9797	Observed	154.8	4.06	105.4	24.4	8.3	222	75.5
	target	153.8	4.13	104.7	23.8	8.2	220	75.3

TABLE 27

COMPARISON OF MANUALLY-READ RESULTS FROM FOUR-CHANNEL AUTOANALYSER SYSTEM
WITH THOSE OBTAINED FROM THE AUTOMATIC DATA ACQUISITION UNIT OF APPENDIX II

Channel	No. of points	Correlation	Line equation (computer = y, manual = x)	Pair-difference Mean	t	Probability
Calcium (mmol/l)	250	0.9928	$y = 0.98 x + 0.067$	-0.0054	1.44	NS
Phosphate (mmol/l)	250	0.9940	$y = 0.99 x + 0.014$	-0.001	0.23	NS
Total Protein (g/l)	250	0.9944	$y = 1.01 x - 0.22$	-0.12	1.83	NS
Albumin (g/l)	250	0.9949	$y = 1.02 x - 0.80$	-0.11	1.67	NS

different from the true result (eg 62 instead of 52). One result, of total protein 5 g/l different from the manual reading ~~5.7~~ remains unexplained.

Mean elapsed time to read a single batch of 40 peaks manually amounted to 4.6 minutes excluding drift correction (which accounted for a further 1-2 minutes per channel) (Section 3.2.4) for each of two staff over 32 timings on different days and using different staff members.

On this basis, the two 11/10 processors at one time saved around 846 minutes of staff time per day, given an average of 10 batches of electrolytes (6-method profile) and 8 batches of bone profiles (4-channel profile), or alternatively, they are worth around one and a half members of staff.

2.5.2.3 Discussion

Since data acquisition is such a necessary part of high-capacity analysers it is rarely considered separately from the analyser. It should not be forgotten, however, that the impressive reduction in time taken for electrolyte analysis between 1975 and 1981 (Nodes 2 to 8 - Figures 9 and 13) is due as much to improved data acquisition as to the incorporation of improved design features in the construction of the high speed continuous flow analyser. The original network analysis of Figure 9 makes it clear that the critical path was clerical rather than analytical in 1975, and in practice, the superior

sampling rates of the re-designed electrolyte analyser made little impact on the laboratory turnaround of electrolyte reports until the advent of the new computer in 1977.

2.5.3 Result calculation

The final step in data acquisition from an analyser is the calculation of the result for each sample. Paradoxically, continuous flow colorimetry while causing a number of difficulties in data capture, involves one of the simplest computation steps since most common methods can be made linear over the range of results which interest one, and calculation is done by simple proportion against a single standard value, or by linear interpolation from a multi-point standard curve. At worst, the points on the standard curve may be fitted to a polynomial and the sample value calculated from the resulting equation (Bennett et al 1970; Abernethy et al 1970). Radio-immunoassays present the opposite problem, where the data capture is very simply performed by reading the number of accumulated single counts over a given time period, but the computation of results from the basic data of counts vs time is still the subject of considerable discussion (Challand, 1978).

An intermediate situation is that of reaction-rate analysis and in particular first order enzyme kinetics. In theory the data acquisition is simple since the output from an analyser should give a line of fixed gradient which can be multiplied by a factor incorporating the temperature of the reaction, the ratio of sample volume to total reaction mixture, and the molar absorptivity of the absorbing species, to give the activity of the enzyme.

However, a number of analytical interferences are possible, some of which are depicted in Figure 28. Some form of result validation is normally necessary, and involves digitising and recording the analyser output at intervals, rather than simply using two absorbance values at either end of a fixed interval to determine the enzyme activity. In addition to these methodological difficulties, equipment design can cause problems by limiting the number and timing of possible data points; electronic noise can cause spurious values to be recorded, and the computational technique may fail to identify correctly a linear section of output.

A publication reviewing a number of enzyme analysers (Saunders and Burns 1977) prompted the author to look at the options available for calculation of initial reaction rate, and to attempt to identify the most satisfactory method.

2.5.3.1 Materials and Methods - Collection and Simulation of Algorithms

Algorithms for the calculation of reaction rate were collected in three ways - available literature was scanned for specific examples, manufacturers were approached and asked to submit their methods for scrutiny, and a small number of fundamental theoretical approaches were developed, primarily on the basis of common statistical techniques. A total of seven calculation routines were simulated in BASIC on the PDP 11/34 in the author's laboratory, and a list of those used is given in Appendix III. They could be classified into two

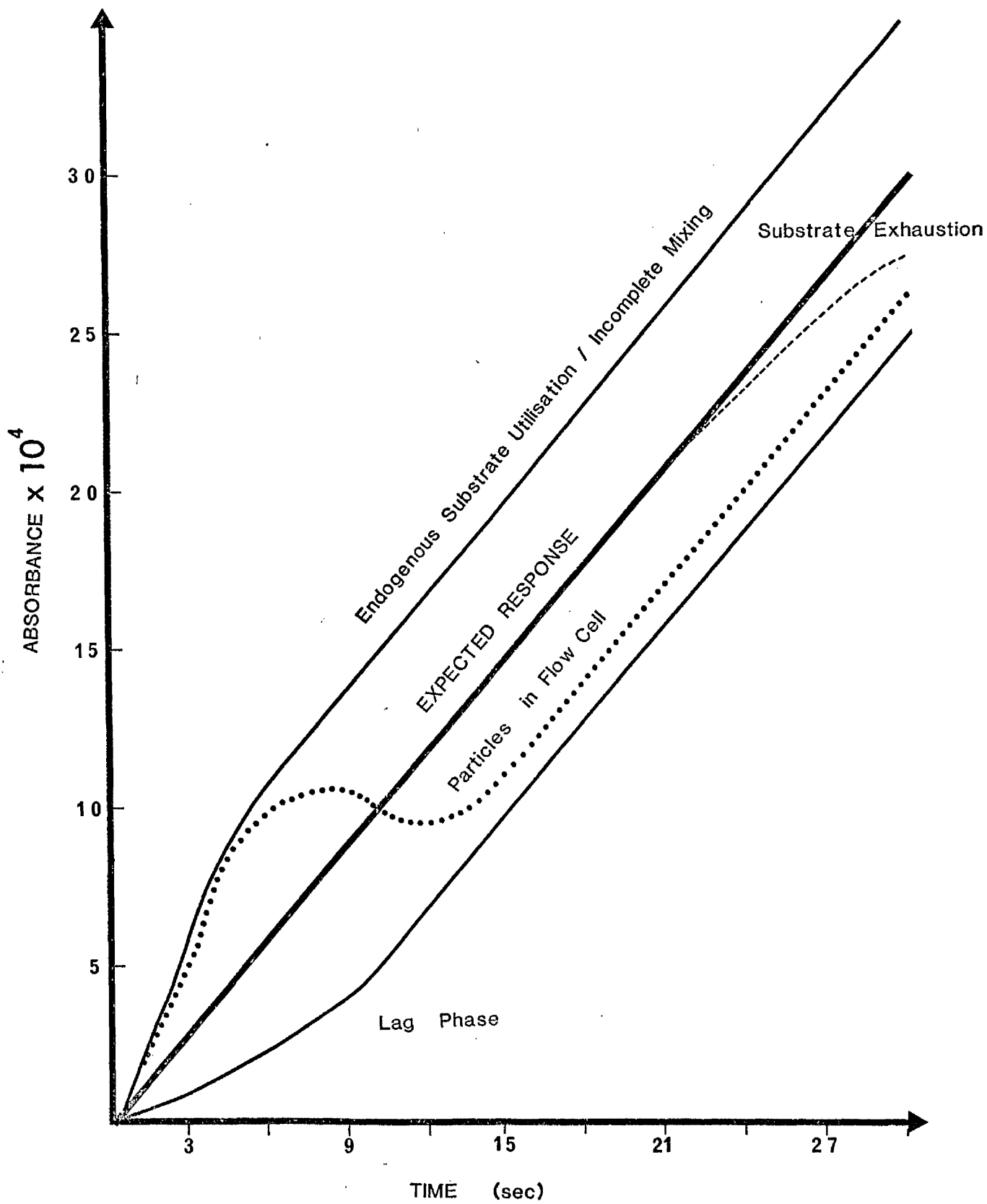


Figure 28

PROBLEMS OF ENZYME MEASUREMENT

Potential distortions of the linear response

groups - either 'validation only' algorithms, which simply printed a supplementary figure with the calculated result to indicate whether or not the quality of analysis had been satisfactory, or "line-seeking" algorithms, which attempted to identify a segment of the data where the reaction had truly followed first order kinetics, and to use that satisfactory segment to calculate the rate of change of absorbance. Each algorithm was in turn applied to a total of 200 data sets, representing both experimentally determined analytical output from the recorder charts of LKB 8600 analysers and hypothetical data based on the type of distortions which have occasionally been noted in practice and which are indicated in Figure 28. Each 'validation only' algorithm was examined on its ability to distinguish between good and bad peaks and to report accordingly, and each line seeking algorithm on its ability to recognise the 'true' slope of the line and, more importantly, its capacity to be misled.

2.5.3.2 Results of Simulations

Sample output from one of the simulation programs, together with a section of the data file to which the algorithm was applied is shown in Tables 28a and b and the results from each of the simulations are summarised in Table 29. While any algorithm correctly reported around 98% of the experimental analytical data, it was possible to identify conditions under which the line-seeking algorithms were at risk of reporting an incorrect result without an error indication, particularly among those algorithms which were designed to be used in

TABLE 28(B)
SPECIMEN OUTPUT FROM CALCULATION PROGRAM

COL	CURVEFIT 2 - LINEAR REGRESSION ACTIVITY	STD ERROR	TO(SEC)	COMMENT
1	300.0	0.0	0	LINEAR
2	300.0	0.0	0	LINEAR
3	300.0	0.0	10	LINEAR
4	300.0	0.0	10	LINEAR
5	300.0	0.0	7	LINEAR
6	300.0	0.0	14	LINEAR
7	301.4	1.2	17	LINEAR
8	300.0	0.0	16	LINEAR
9	TOO FEW POINTS!			
10	300.0	0.2	20	LINEAR
11	300.0	0.0	10	LINEAR
12	300.0	0.2	20	LINEAR
13	300.0	0.0	10	LINEAR
14	300.0	0.0	10	LINEAR
15	300.0	0.0	10	LINEAR
16	300.0	0.2	18	LINEAR
17	300.0	0.0	7	LINEAR
18	300.0	0.2	18	LINEAR
19	305.7	5.4	5	UNSATISFACTORY
20	297.3	2.3	20	LINEAR
21	300.0	0.0	9	LINEAR
22	297.8	1.7	20	LINEAR
23	300.0	0.2	18	LINEAR
24	304.1	1.6	5	LINEAR
25	300.0	0.0	9	LINEAR
26	297.8	1.8	20	LINEAR
27	300.0	0.0	14	LINEAR
28	278.5	5.2	14	UNSATISFACTORY
29	300.0	0.0	18	LINEAR
30	126.4	67.8	2	UNSATISFACTORY

LEGEND:

- COL - COLUMN NUMBER FROM WHICH DATA IS DERIVED
 ACTIVITY - ENZYME ACTIVITY CALCULATED FROM RAW DATA
 STD ERROR - MEASURE OF THE SPREAD OF DATA AROUND THE
 BEST-FIT STRAIGHT LINE FROM WHICH THE
 ENZYME ACTIVITY WAS CALCULATED
 TO (SEC) - THE STARTING POINT OF THE MOST LINEAR
 ONE-THIRD OF THE DATA POINTS
 COMMENT - INTERPRETIVE ASSESSMENT OF STD ERROR OF
 GRADIENT

TABLE 29

SUMMARY OF RESULTS OF SIMULATING REACTION-RATE CALCULATION
ALGORITHMS ON A DEC PDP 11/34 COMPUTER (SEE APPENDIX III FOR
DETAILS)

Algorithm Number	Description	Line-seeking?	Comment
1	3-segment check with absolute limit	No	Fails at low activity
2	Sliding least-squares linear regression	Yes	Satisfactory
3	Sequential gradient analysis	Yes	Fails with short-lived high activity responses early in the analysis
4	12-segment check in pairs	No	Satisfactory
5	3-segment check with % limit	No	Satisfactory
6	Sequential area comparisons	Yes	Fails with early short-lived linear response.
7	7-segment check	Yes	Fails if there is a problem in the mid-section of the response curve

real-time and where undue emphasis was placed on the initial points with the aim of restarting the analytical cycle as soon as a satisfactory result had been obtained for the previous analysis.

2.5.3.3 Discussion

Clearly some compromise is necessary between this approach and the 'validation only' algorithms which consistently rejected assays, requiring them to be rescheduled with consequent potentially substantial time delays (see Section 3.2.3). The common practice of allowing the operator to designate a 'percentage tolerance' within which results will not be flagged is unsatisfactory, particular where the operator may not be aware of the significance of the tolerance limit. Likewise, the reporting of a percentage as an error indicator is unsatisfactory since it is clear from the survey that the method of calculation of a percentage error varies from instrument to instrument and it is the author's experience that not all operators understand the significance or basis of calculation of a percentage error, even where only a single analyser is used.

2.5.3.4. Recommendations for Reaction Rate Algorithms

The main recommendations arising from the study are as follows: a) satisfactory algorithms should actively seek a linear portion of the curve; b) they should report deviations from a straight line in units of enzyme activity so that a 95% confidence interval could be constructed around the result; c) they should require linearity over at least one-third, but less than one-half of the data

points (which should be evenly spaced across the line) d) they should be adaptable to real-time applications, (with the proviso that it is advisable to consider further points before exiting from the routine on the assumption that a comparatively short, early straight-line segment represents the true slope of the curve) and e) should, where possible, take the mean of a number of voltages at each data point to exclude spurious values from the instrument.

The most satisfactory of the four line seeking algorithms was a program which performed calculation of line gradient and standard error of gradient using common statistical techniques on all possible line segments which contained one-third of the data points.

Results from this calculation are printed in Table 28 with the time at which the best linear portion commenced. The only identified method of obtaining an incorrect result from this algorithm was where two separate straight line segments both persisted for at least one third of the data points. In batch mode, it was a simple procedure to cause the program to seek a second line and report an error, but this involved scanning the data points over the entire time period. Inclusion of this option in a real-time system whose main objective was to maximise the throughput of samples would not be feasible.

CHAPTER 3 - DATA PROCESSING

Gaddie predicted, in 1967, that with sustained improvements in analytical automation, the rate limiting factors on turnaround of analyses would be the handling and reporting of results.

Methods of applying automation and work simplification to the analytical and reception processes leading to the production of a result from the patient's specimen were described in Chapter 2. In this chapter some aspects of the refining of the basic result, and the production of a final report, particularly in association with a laboratory 'clerical duties' computer will be considered.

3.1. Manual reporting system

Raymond (1974) in a survey of laboratory computers reported that most were "on-line, real time data acquisition systems, programmed on the naive assumption that arithmetic is the most critical problem facing the laboratory".

That arithmetic is manifestly not the problem can be seen by presenting the lower half of Figure 7 in the form of a network diagram detailing the steps involved in generating and issuing a manual report from the author's laboratory in 1976 (Figure 29). The network takes as a starting point the existence of a hand-written report which has been delivered into the reporting office by the bench staff.

If the network is then considered as the latter half of the cardiac enzyme analysis network of Figures 10 and 11, it can be seen that the major components of the total turnaround time required to

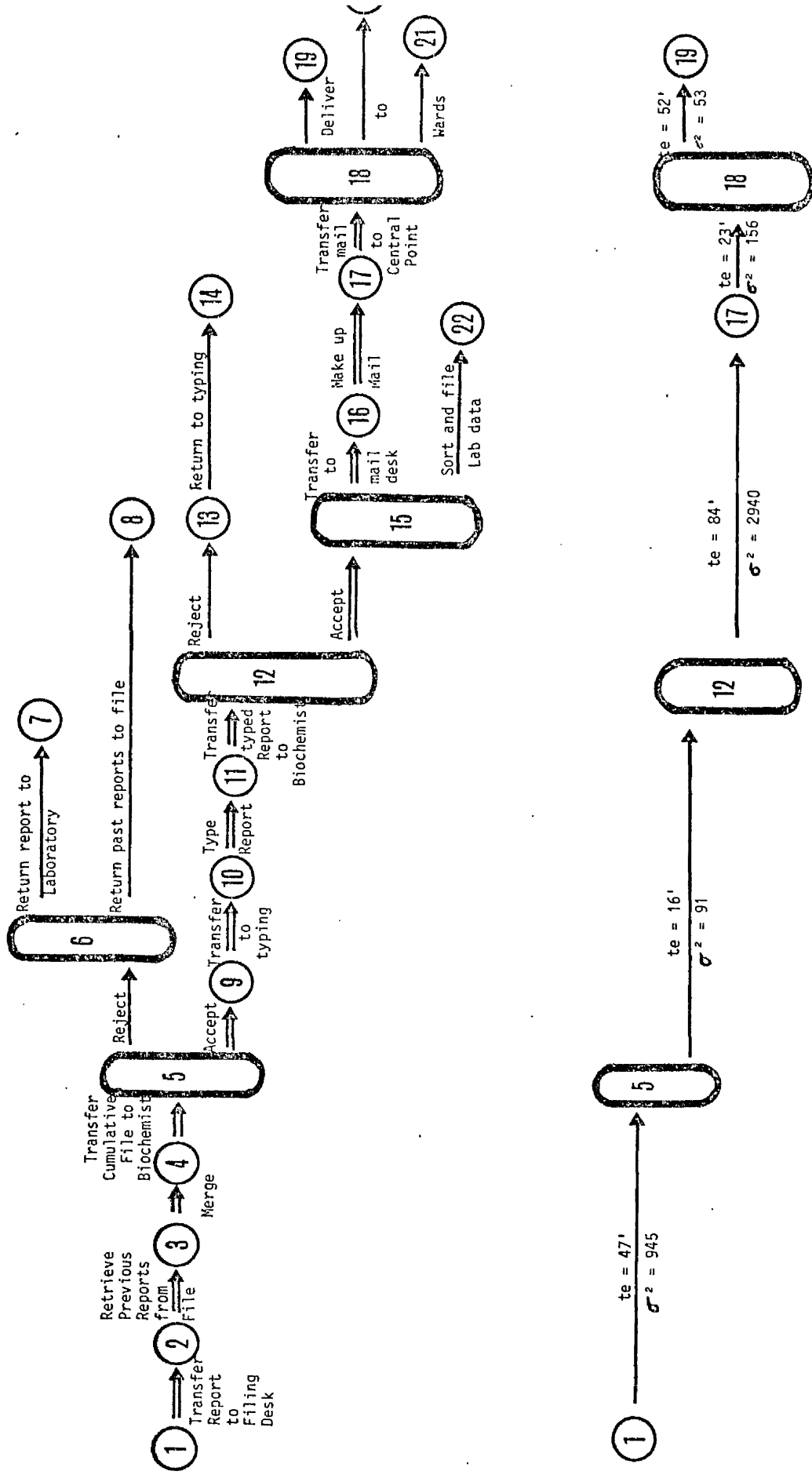


FIGURE 29 Office procedures 1976 - Report production and delivery

analyse and report a set of cardiac enzymes in 1976 were : specimen transportation, one and a half hours , reception/analysis - two and a half hours, report production and checking one hour, report delivery two and a half hours

The major time delays within the reporting office were attributable in part to the daily sequence of filing, responding to telephone enquiries and mail delivery deadlines. This could result in delays of over one hour before incoming laboratory reports were first merged with previous files, and is reflected in the large and varied time for the first activity in the network of Figure 29.

It is noteworthy, too, that the cumulative filing procedure on initial receipt of a request necessarily assumed the existence of previous reports and thus time was lost where this proved not to be the case. Although the data in Table 14, which shows that around 20% of forms related to patients who had no subsequent request, refers to electrolytes, it is reasonable to infer that a substantial minority of incoming 'B' group requests would also not require cumulation.

Finally, in this sub-section it should be noted that Figure 10 and Figure 29 need not quite fit together. The gap between analysis and the report appearing in the office arises for a number of reasons including batching of requests at the bench, and the necessity to transfer the form to some other analytical area, a topic which will be discussed further in Section 3.4.1.

Intermittent delivery of batches of forms to the reporting office had the twin consequences of lengthening turnround, while overloading the clerical resources in a manner akin to the effect on reception of the distribution pattern of specimen arrival in Figure 5.

It should be noted also that these figures relate to the delivery times of reports by the Royal Infirmary's internal messenger service - no allowance is made in Figure 29 for the transit times of the van service which provides transportation facilities for the other hospitals within the Health District (Table 9).

A possible solution to the requirement for fast production of reports, and a possible method of circumventing the lengthy time delays of manual data-handling is the use of a computer system concerned mainly with automation of the clerical activities involved in report production and maintenance of a data base for fast response to enquiries, cumulation of results, and research activities. A number of United Kingdom systems have been described (Flynn, 1969; Whitby and Simpson, 1973; Peters, 1976; Abson et al 1977a, b, c; Undrill and Gibson, 1978; Hirst, et al, 1979; Naylor et al, 1979; Scottish Health Service Planning Council, 1979). The functions and potential of such systems will be discussed below.

3.2 Computer Reporting - Drift Correction

The initial steps in production of a report are those which refine the raw data of the data capture system to a final form, and the first of these is the process known as drift correction. Webster's dictionary defines drift as a "gradual change . . . in a quantitative characteristic of a piece of equipment" (Grove, 1966). That continuous-flow analysers, in particular, are subject to drift is well recognised (Whitby and Simpson, 1969; Bennett et al, 1970). The drift may be a consequence of various factors - temperature effects (Horn et al, 1974) deterioration of pump tubing, or electronic drift in detectors. Irrespective of the cause of the systematic alterations in the signal, the objectives of drift correction are to remove the distortion in the analytical results.

3.2.1 Methods of drift correction

Three methods of drift correction were considered - two derived theoretically, and one from common analytical practice. Suitable programs were constructed on a desk top calculator (Wang 600) and the drift correction simulations applied to the 143 channels of raw data obtained from the fifteen laboratories with SMA continuous flow systems which participated in a United Kingdom survey of performance of multi-channel analysers (McLelland, Fleck and Burns, 1978).

The simulation of a commercially available drift correction routine involved recalibration of the analyser every time a standard was encountered in the course of the run - in practice, every ten cups.

The second approach - constrained regression - was based on the concept that drift was linear with time over the period of the test. If this were indeed the case then the observed fluctuations in the drift standards throughout the batch could be fitted to a regression line, constrained to pass through the calibration point of each analytical channel, and the test results corrected as a proportion of the adjusted reference value at each sample position. The third algorithm involved two stages. Horn et al (1974) had indicated that drift had two components -baseline drift, which affected the intercept of the calibration line, and sensitivity drift, which affected its slope. This batch method which could be described as a geometric correction, because of its derivation from consideration of the geometry of a batch of results, required that all results be first corrected proportionally for baseline drift, which was assumed to be linear across the batch, and then corrected for sensitivity drift in small batches of ten, bounded by drift standards at each end.

3.2.2. Aims of Drift Correction

Appropriate drift correction should aim, firstly, to improve the accuracy of analyses and secondly, to reduce the spread of replicates. In addition, the data from the DHSS survey (McLelland et al , 1978) was designed to permit the use of the pair-difference t-test to measure discrepancies between the first and second trays. Clearly a satisfactory drift correction method should decrease the significance of such a measure. Further, if drift contributed substantially to

inter-laboratory variation, drift correction should reduce the spread of all replicate results from all laboratories for any one test serum and method.

3.2.3 Results of drift correction

After determining, by application of the pair-difference t-test that over two-thirds of the 143 channels of raw data showed evidence of significant drift, the raw data was corrected by all three methods and the resulting data re-evaluated for improvements in accuracy, within-batch precision, and reduction in spread of results between laboratories. This work, which has been published elsewhere (McLelland and Fleck, 1978), indicated that the geometrically derived correction was the most satisfactory of the three, although the method, unlike the prospective recalibration method, did incur significant overheads including the measurement of baseline at the beginning and end of each batch. Some subsequent work using 80 consecutive replicates of the same material on the SMA 18/60 configuration at Gartnavel General Hospital showed the effect of the different types of drift correction even more graphically than the data from the DHSS study, although providing many less channels of data for analysis. The creatinine channel from the Gartnavel trial is presented in Figure 30 to illustrate both the need for drift correction, the effects of the 3 algorithms, and the considerable improvement in precision which can be achieved where the best available drift correction procedures are employed.

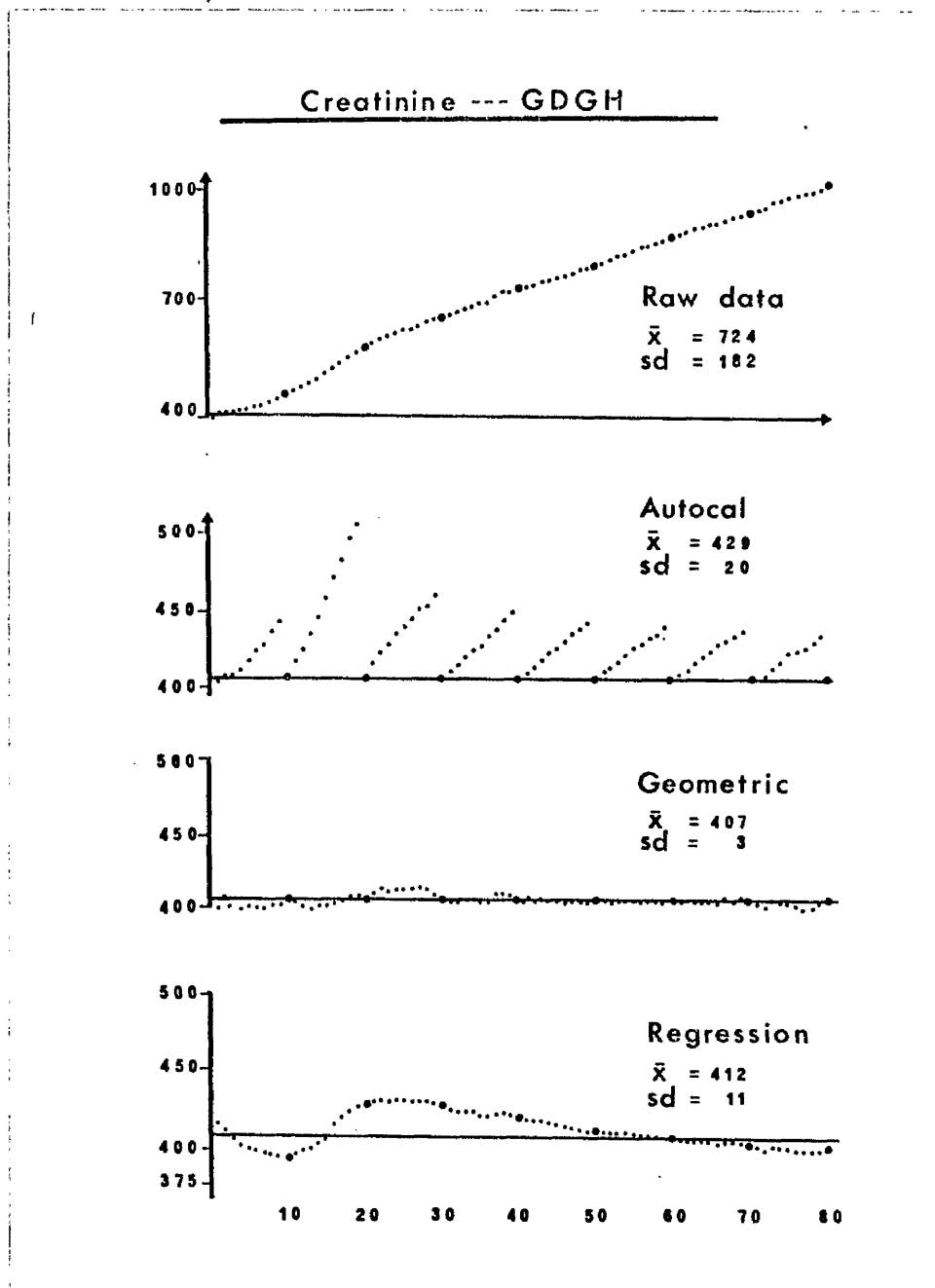


FIGURE 30 The effects of various forms of drift correction on eighty replicate sera run on a SMA 18/60 multi-channel continuous-flow analyser. 'Autocal' and 'SMA' are trademarks of Technicon Ltd., Basingstoke, UK.

While discrete analysers seem in general, to be less susceptible to drift, it was noticeable that over a full tray of 60 calcium samples for analysis on a Vickers D 300 analyser, there was often a significant and substantial change in the value of the calibration standards throughout the batch, reaching up to 0.2 mmol/l by the end of the batch. Since the development of the drift correction algorithms is independent of analytical method, the geometric correction was also applied successfully to the output from this instrument. Nisbet and Owen (1979) also reported correctable drift in discrete analysers.

Where no calculation facility is provided, drift correction of a batch of forty results from continuous flow analysers has been timed at around one to two minutes per channel and is performed less well and more slowly where the analytical results differ substantially from the value assigned to the calibration material, since the correction is proportional rather than absolute.

3.3. Performance Monitoring and Batch Authorisation

Drift correction is the last automatic step in the production of a result from a patient's specimen and it generates a batch of results which must then undergo some form of authorisation procedure. From Figures 8 and 9 (Nodes 5 to 6) it is clear that this authorisation can be a slow process, and this section will look at some of the aspects of performance monitoring, and how they may be expedited. The basis of any authorisation is the consideration of the quality of a batch of results, as reflected by Quality Control materials within the batch and any other pointers to the accuracy of the patient data.

Patients' data can be used to indicate the analytical accuracy of results, and a number of papers have looked at the use of the batch mean of the patient samples as an indicator for the need for further refinement of the results (Whitehead and Morris, 1969, Dixon and Northam, 1970, White, 1978) on the basis that the random mix of samples within any one batch will reflect the expected distribution of the hospital population, given the absence of undue interferences like a high proportion of outpatient samples for an assay such as protein or sodium where clear differences between embedded and ambulant subjects have been noted (Lewis and Dixon, 1973). The corollary to this is that the batch data should present the same mean and median as the total hospital population, and that where this is not the case, and where abnormal sample distributions can be eliminated, an accuracy change in

the data has taken place. This should also be reflected in the results for quality control sera and requires that further action be taken to refine the batch of results.

3.3.1 Calibration and Imprecision

While it was at one time standard practice to process a "standard curve" with each batch of patient samples, the overheads of such procedures and the need for a single serum standard for multi-channel analyses ensured that current practice commonly employs secondary or tertiary standards on the linear response portion of the analytical range and interpolates the patient values by proportion between a single high standard reading and a low standard or baseline. A number of analysers now routinely feature this type of calibration (eg Technicon SMAC, IL508). However, the detector response to that initial high standard will vary from batch to batch, in accordance with the variance of the components of the system, both electronic, mechanical and hydraulic. In accordance with the Central Limit Theorem, the pattern of detector response to the repeated samplings of the standard will form a Gaussian distribution. The appropriate SD will be approximately the observed within batch method SD at the level indicated. Thus, if a sodium method has an SD of 1.0 mmol/l at a level of 160 mmol/l, then the detector response to the standard will produce a voltage corresponding to a sample within the range 158-162 mmol/l on 95% of batches. Conversely, once every twenty batches, the stated value of the standard will be assigned to a detector signal appropriate

to a material where sodium concentration is outside the range and that batch of serum sodium results will be calibrated at an inappropriate level. This finding was demonstrated during the evaluation of SMAC at Edinburgh Royal Infirmary, where re-calibration markedly altered the accuracy of each batch (Dr I Percy-Robb - personal communication). The exercise was repeated in the author's laboratory, giving the results of Figure 31, where it is clear that recalibration after each group of eight replicates alters the accuracy of the batch.

3.3.2 Result Editing

From the preceding section, there is scope for a further refining of the batch data on the basis both of the batch mean and median, and the quality controls within the batch, and this responsibility is usually given to the person authorising the batch results. It is uncommon to have indices like batch mean, daily mean and cumulative mean over a longer time period available where result reporting is not automated, but they are easily computed and serve as a further instance of the ways in which application of automation can improve the quality of the final results

3.3.3 Rescheduling of Analyses

Requests for a repeat analysis of a patient's sample (Figure 6) can arise either through initial unsatisfactory analysis, through the occurrence of particularly abnormal results, through incompatibility between current results and the clinical information on the request, or through unexpected rates of change between current and

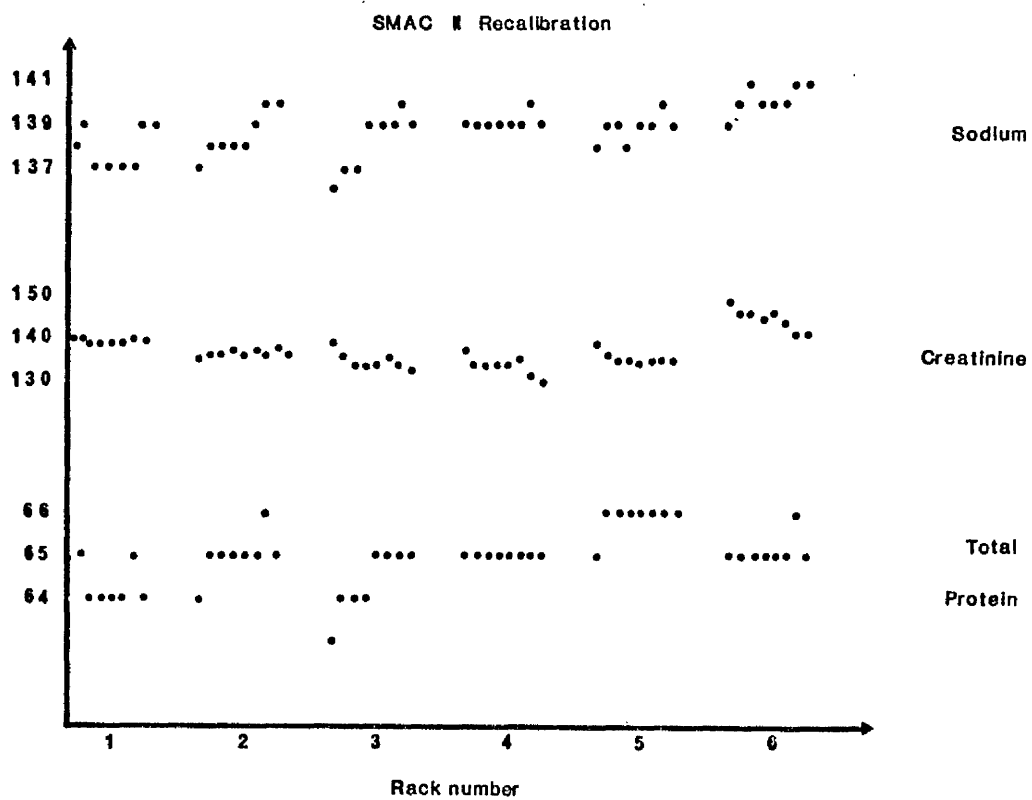


FIGURE 31 The figure shows the differences in the mean level of 6 groups of eight replicate samples following recalibration

previous results. All of these considerations affect the batch authorisation procedures and may lead to one or more samples from the batch being referred for further action. It was noticeable, during timing studies in the author's laboratory, that the rescheduling of analyses in a larger laboratory could add days to the overall turnaround of time, either because the laboratory performed the assay infrequently; because of the time consuming process of locating the sample and performing the repeat analysis; because of the number of samples which had accumulated in the interim, or because of the general lack of a suitable mechanism for dealing with such repeat samples, and of assigning appropriate priority to them.

While automating the reporting sequence of the electrolyte group of tests by use of a computer, provision was made for such a mechanism in the production of a further requisition for analysis which is automatically generated when the full report is not authorised for printing. This requisition is delivered by the computer operations staff to the analytical area in question, thus informing them positively, within minutes of the decision, of the need for re-analysis. Although no particular priority is normally allocated to the requisition, it is noticeable that the repeat analysis is available within a further 1 to 2 hours and that the ease of operation of this procedure may well encourage its use, since requests for re-analysis of computer-based tests are far in excess of those for other sections of the laboratory. For example, during the month of April, 1981, no fewer

than 426 requests for repeat analyses of individual tests from the electrolyte group were made by the reporting team, contrasting with a typical figure of around 80-100 for the whole of the remaining repertoire.

3.4 Report Production

Following authorisation, some form of printed report is necessary. Recommendations for the format and contents of a report form have been made (Bold, 1976) and suggest that, where a computer is used, additional simple arithmetic, in this case indication of the degree of abnormality of a result when referred to the most appropriate reference range, can significantly assist interpretation. Before looking closely at the advantages of computer-based reporting however, it is useful to consider the operations involved in the generation of a final report by the two systems (manual and automated), presently in use in the author's laboratory.

3.4.1 Network Analysis - Manually reported multiple requests

All previous calculations concerning turnaround time have considered primarily requests for a single analysis or functional group such as liver function tests or electrolytes. It will have been noted from Table 12 however, that comparatively few test groups are requested in isolation.

Figure 32 (a) shows the network required to process a combined request for LFTs, proteins and immunoglobulins in 1980, prior to the computerised reporting of the 'B' group analyses, and Figure 32(b) shows a similar combined request for LFT, proteins and magnesium.

While the analyses proceed in parallel, a major element of the critical path clearly relates to the need to pass the request form around 3 separate work areas so that the results can be added to it.

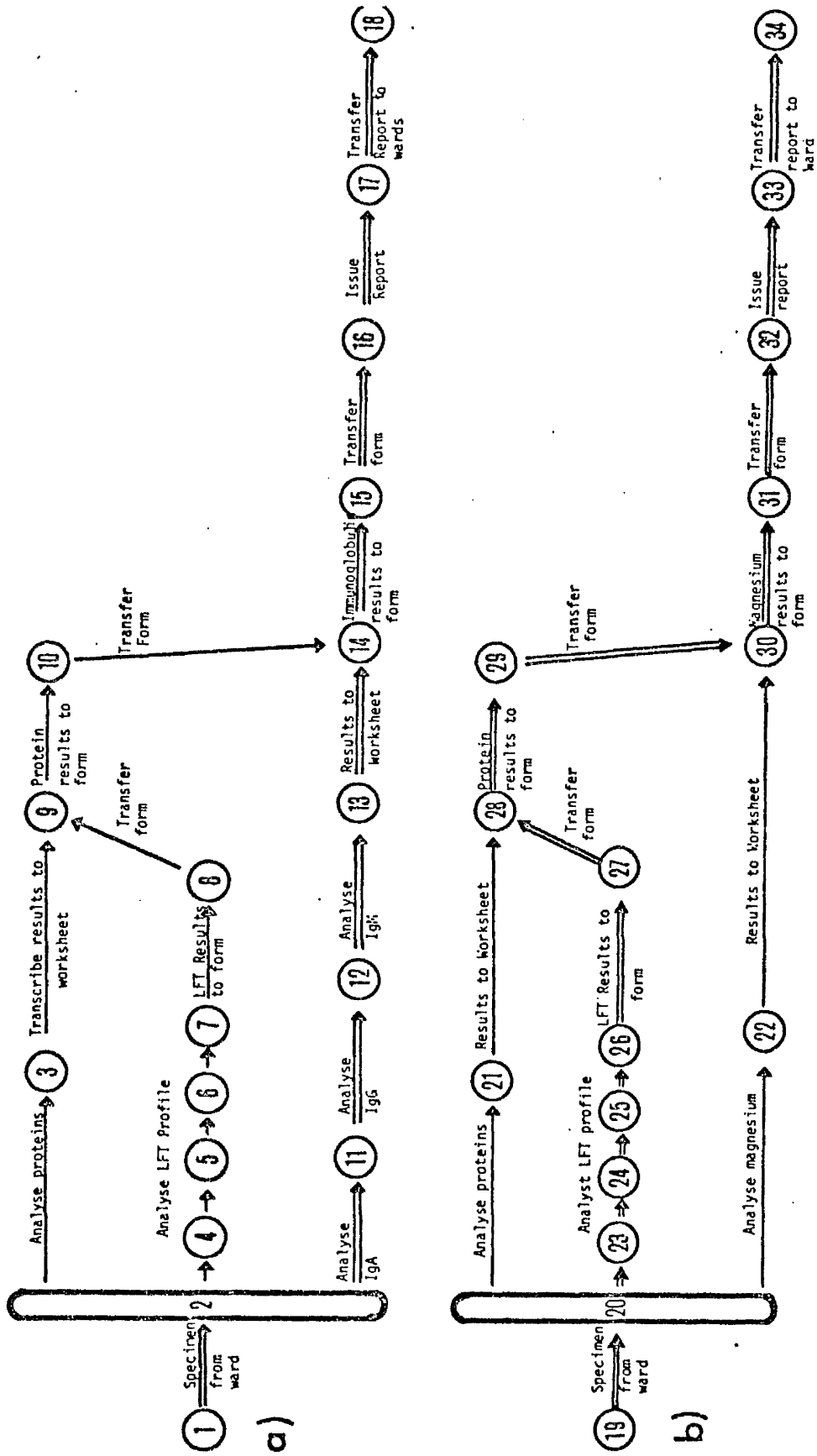


FIGURE 32 Network Analysis for manual reporting of a) combined LFT, protein and immunoglobulin request, b) combined LFT, protein and magnesium request, showing the critical path in each case.

The major difference between Figures 32(a) and (b) relate to the twice weekly performance of immunoglobulin analysis. This was almost always rate-limiting on the production of a complete report which normally took a number of working days. In contrast, serum magnesium (Figure 32(b)) was analysed daily, normally within a few hours of receipt of the sample hence the other tests in the group, and the need to pass the request form from bench to bench, became the rate limiting factor, and combined to delay report production at least until the next working day after receipt of the request.

3.4.2 Network Analysis - computer produced reports

In contrast, the network analysis for the same requesting patterns in 1981, when all analyses from each network were being reported by computer, is shown in Figure 33 (a) and (b).

The major difference between the Figures 32 and 33 is that the parallel nature of the analysis has been continued into the reporting procedures with separate means, at bench level, for data entry into the processor. This has removed the time delays of transferring the single request forms in the manual system from bench to bench. A further distinction between the two networks is that time delays in the reporting office are reduced, as many of the filing and typing functions of Figure 29 which could not be performed until after the arrival of the results in the reporting area have been transferred to data preparation and can be performed much earlier in the sequence. This provides a more even pattern of clerical activity across the

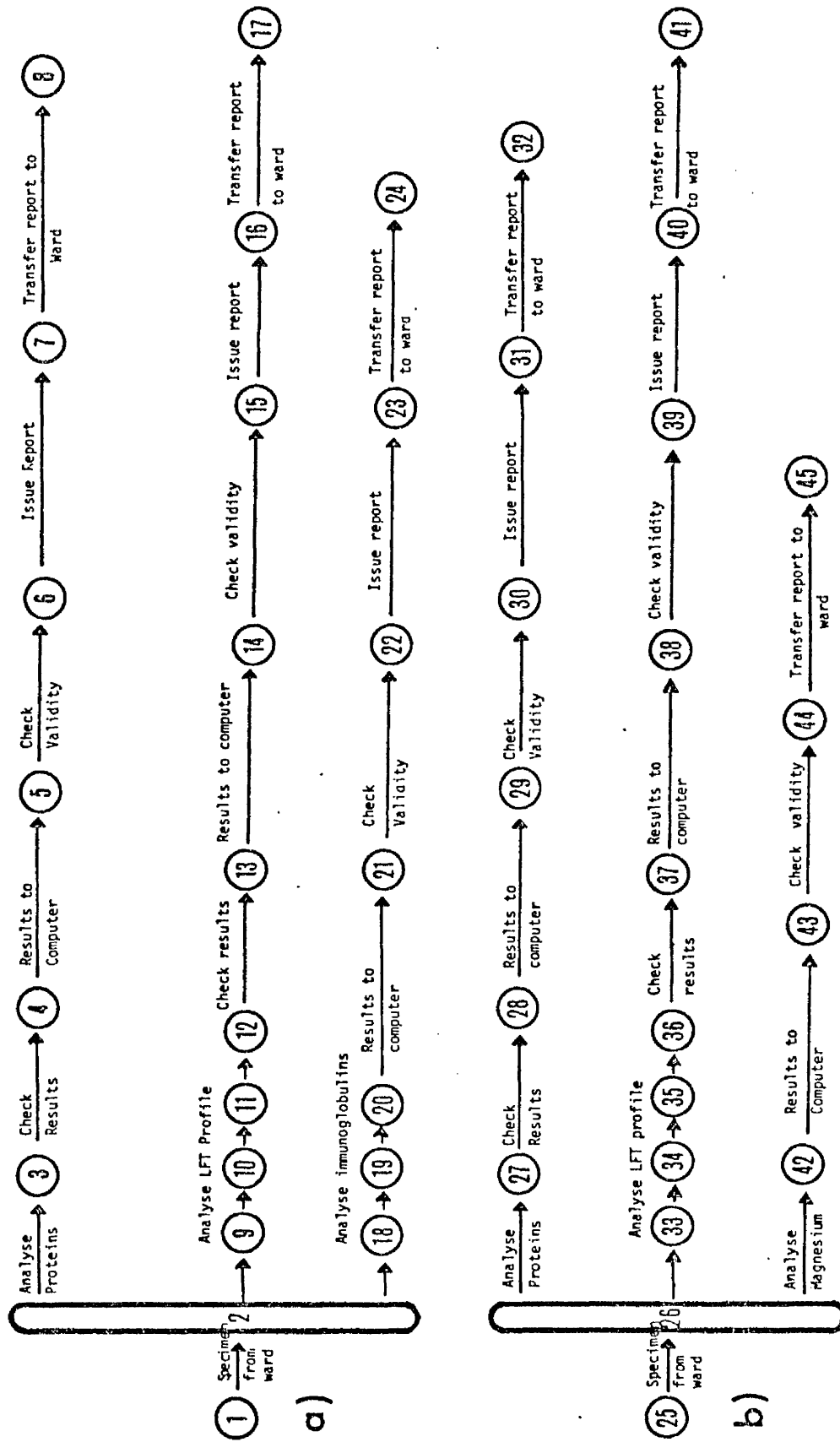


FIGURE 33 Network Analysis for computer-based reporting of a) combined LFT, protein and immunoglobulin request, b) combined LFT, protein and magnesium request; showing that each group now has an independent reporting sequence, GRI November 1981.

working day, and avoids the overload effect of a large batch of hand-written results arriving late in the day. The effects of Figure 33 on report delivery are discussed in more detail in Section 3.4.4.

3.4.3 Cumulative Reporting

Both Bold (1976) and Ormerod et al (1976) reported little interest among clinical staff when cumulative biochemistry reports were offered to them as an option (in the Western Infirmary study 58% of physicians and 42% of surgeons stated that they did not want daily cumulative reports). It has been the author's experience that, where clinical units manually cumulate results, they do so over the range of laboratory disciplines and so the sub-set of clinical chemistry results, however much of the laboratory repertoire is reported by computer, is of limited value.

The justification for cumulative reporting has therefore been questioned because of the associated need for large, fast access, relatively expensive hard disc systems (£10,000 for 28 Mb exchangeable disc drive and controller at 1980 prices) which are required so that total time to print a cumulative report can be kept to around 15 secs maximum.

The cumulative report can be regarded simply as the end product of a cumulative filing system, since a cumulative patient record is a pre-requisite for the production of such a report, and the more fundamental questions then relate to the need for cumulative patient files on the processor.

Within the laboratory, the patient data base serves three major identifiable functions: quality control, result retrieval and consultation.

3.4.3.1 Quality Control and Cumulation

Quality control using patients' data has been dealt with under Section 3.3.3 where it was indicated that unacceptable rates of change between current and previous results would lead to re-scheduling of requests. Moreover, subjective impressions are that it is the gross analytical errors - the misplaced decimal point, for example, which are picked up by this checking procedure and the release to the clinician of this type of order of magnitude error will, at minimum, seriously effect the credibility of all laboratory results for a period. Computers have been used to flag results exceeding the maximum permissible rate of change since the last analysis, and indeed, systems have been devised to stream-split a batch of reports into those which satisfy reference range and rate of change criteria for routine issue, and those which do not, and are held back for biochemists scrutiny (Clark et al, 1980).

3.4.3.2 Enquiry facilities and cumulation

Retrieval of current and previous results in response to enquiries is a necessary function of an efficient laboratory and, without a well-structured data base and patient record management system, response to enquiries will be excessively prolonged.

3.4.3.3 Consultation and cumulation

Arguably the most important function which laboratory staff fulfil is that of consultation with clinical colleagues who are not specialists in laboratory medicine. While limited information may be derived from current results alone, constructive comment will often depend on rate of change information.

These three arguments form the basis of the justification for the cumulative disc files, and cumulative report production by the laboratory can then be justified on the grounds of efficiency, and of selection of relevant tests.

3.4.3.4 Efficiency of cumulative reports

While there is no reason not to issue single reports, it is demonstrably more efficient to print relevant previous results on the same piece of paper, than to create the need for a separate enquiry for past results at a VDU screen for the quality control check described above. Logistic difficulties also tend to invalidate this option, since there will be few laboratories who can afford to reserve both the manpower and the VDUs necessary to validate a substantial batch of reports. The requirement for an additional activity to call up previous results will understandably extend the time taken to check a batch of reports, even where terminals and adequate computer core memory are available. For example, the typical retrieval times of 5-15

secs to scan all available previous results mean that a batch of 200 report forms will take around half an hour to check since the enquiry would have to be made even where the patient had no previous reports.

The generation of cumulative reports implies that the end user, in this case the clinician, obtains not only the current results, but also the context in which these results must be considered, since all recent relevant previous results will also be on the report. Finally, as Bold also remarks, given that some clinicians do wish the option of cumulative data at some stage, whether these are produced routinely or only on demand has little influence on the size of hardware configuration required (Bold 1976).

3.4.4 Interim reports

Many laboratories which use manual reporting procedures make little or no attempt to provide anything other than the return of each patient's report to the clinician, either as a single report or as a cumulative sheet. Since this involves the kind of time constraints mentioned in Section 3.4.1. especially where fast and slow turnaround requests are grouped together on the same request form, a partial solution, that of photocopying the master results cumulative card each time a sub-group of analyses is available, is commonly used, the major alternative being the segregation of urgent and less urgent request groups on different forms as previously practised in the authors

laboratory (See Section 2.2.2), together with continual reminders to the requesting clinicians that multiple requesting on any one form is likely to delay the return of a results (Section 3.4.1).

Both methods remain dependent on the messenger system, yet a major benefit of a reporting computer is its ability to issue partially-completed reports. Any analytical groups or single results, if available, can be fully reported and issued, even where the other elements of the multiple request have not yet been analysed. In this way, the activities involved in processing each single analysis or functional group can be considered independent of the other requests on the form from the point at which reception have issued a sample to each bench no matter how many groups of tests are requested, or what their individual turnround times are (Fig. 33). Indeed, without this capability, the combined 'X' request form of Plate IV could not have been contemplated.

3.4.5 Enquiry facilities - local and distributed

The use of a variety of access keys can allow retrieval of the patient data by hospital and ward, laboratory accession number, and hospital case reference number in addition to what has come to be regarded as the standard method of search by patient surname.

Fast retrieval of data using these keys offers the first significant advantage over a manual system in that it is relatively easy to list all current results for any given ward or clinic in response to a telephone enquiry. In a manual system, the tedious

process of retrieval of results for each named patient has to be undertaken on an individual basis, from the variety of manually maintained files and locations shown in Figure 29.

Timing studies indicated a median of 2-3 minutes search time for each record in the manual system, but this depended on the experience of the biochemist or clerkess conducting the search, and required careful interrogation of the enquirer to determine the most likely starting point within the manual system. For example, on the manual files of 1978 a request for cholinesterase phenotyping, received two days prior to enquiry, was most likely to be still pending, while a request for a two-day old liver function test profile had over a 95% probability of being stored in the completed results file, but only if it had been requested on a separate form, rather than as part of a combined request.

Also, from Figure 29, it is clear that the patients' results would be transferred from location to location within the reporting office during the checking process, and a number of these locations did not hold the results in alphabetical order. Retrieval time could therefore be prolonged, depending on the time of day at which the enquirer telephoned. For example, between 4 and 5 pm the number of records in the temporary files increased considerably and were not actively cleared, since clerical activity around this time was geared

to presenting the maximum number of records to the biochemist for checking, and to sorting and issuing reports in the final delivery of the day.

In consequence, a telephone enquiry late in the afternoon might require a search through over a hundred records in these non-indexed temporary files with a consequent delay in response.

A considerable advantage of a computer system is the ability of a single enquiry program to indicate the progression in status of any request as it is processed by the laboratory, irrespective of the number of locations to which results will ultimately be written. Again this contrasts markedly with the manual system where the change in status of a request from 'pending' through 'result available but not yet checked' to 'result fully validated and report issued' is marked by a change in the physical location of the request within the confines of the reporting office.

Since enquiry facilities are an essential component to any laboratory computer, and since modern processors will support a number of simultaneously operating terminals, the provision of peripherals in Ward areas is an obvious extension of the intra-laboratory terminal network.

Ward terminals have 2 major advantages to the clinician -they can be made available outside normal laboratory working hours and they can help to reduce turnaround times. This latter objective can be achieved either by automatic printout of interim reports using a

program initiated by the real-time clock inside the computer, or by enquiry facilities enabling clinicians to retrieve results as soon as they become available, with no delay through messenger delivery of reports (See Section 3.4.7).

Enquiry programs for ward areas use subsets of the full facilities accorded to the laboratory user, and reinforce the requirement for a status marker, since only those results which have been fully validated by the laboratory are normally made available at such terminals. The provision of terminals at distant sites also brings the problems of confidentiality to the fore since these terminals are no longer under the close supervision of the laboratory staff.

3.4.6 Confidentiality and remote terminals

Requests for laboratory analyses are requests for a consultation between the requesting clinician and the department concerned (Marks, 1972). Consultation requires the release of clinical information to the laboratory and this information will be stored, with the results, in any clerical system, whether it be manual or computer based. It is therefore clearly necessary that laboratories safeguard this information entrusted to their keeping, and that, in particular, laboratory computer systems be designed to prevent unauthorised third parties from obtaining access to sensitive medical data, which may be classified as information which would be potentially damaging or embarrassing to the patient were it to fall into the hands of ill-intentioned persons.

A number of publications have attempted to establish guidelines on who shall have access to personal data on NHS and other computers (NHS Circular 1978 (GEN)23; MRC, (1973); HMSO Cmnd 7341, (1978); Griesser, et al 1980) but these documents base their recommendations round the concept of a medical record in the sense of patient data stored by a medical records office, the patient's case notes and subsets of that information such as patient Master Index files on hospital computers.

Only recently, and only in the Scottish Health Service, has a code of conduct considered the particular requirements of laboratory computers, in view of the increasing use of modern multi-terminal processors in clinical laboratories (Challand et al 1979; SHSPC, 1979; DHSS, 1975; Siemaszko, 1978).

Discussions leading to the publication of NHS Circular 1982(GEN)19 identified at least three identifiable areas of concern where sensitive data is stored on a computer. These are:

- a) uncontrolled access by means of clinical information fields and laboratory results, since these keys can group together patients by diagnosis or by diagnostic result. Raised Carcinoembryonic antigen levels could identify a group of suspected cancer subjects, for example. These keys are not available within the alphabetically ordered manual files of Figure 29 (Nodes 3 and 22).

- b) lack of control by the laboratory over access to remote terminals, particularly where the computer is left running, unattended, overnight to provide a patient results enquiry service in the evenings.
- c) Disposal of interim reports.

Appropriate counter measures to each potential risk include limiting the number and type of programs available at such terminals; the specific exclusion of programs which use clinical or result data as part of the key; installation of terminals at secure sites such as nursing stations or medical staff rooms to attempt to prevent unauthorised access; exclusive use of keys, such as hospital case reference number, which demand knowledge of the user which is normally restricted to hospital personnel; and stringent limitations on the amount of text information associated with reports printed at ward sites. For example the content of a printed interim report or enquiry program printout should not include clinical information or interpretive comment and patient identification must be restricted to patient name, ward and hospital number as the minimum required to ensure proper matching of patient and result.

All of these confidentiality requirements considerably limit the use of Ward Terminals to the extent that one might question the advisability of the laboratory installing them at all. The main drive behind the installation of Ward Terminals, however, is the considerable impact which they can have on turnaround times.

3.4.7 Effect of Ward Terminals on Turnround time

Conscious of the advantages to be gained from Ward Terminals, the Biochemistry Department in Glasgow Royal Infirmary installed the first two 30 cps printing terminals at selected sites within the medical and surgical blocks of the hospital in September, 1978, offering 24 h availability of data and a suite of enquiry programs supplying information within the constraints of Section 3.4.5 and 3.4.6, and also offering general information on request procedures (Section 2.2.3).

Additional terminals have since been installed or specified at the Renal Unit, Outpatient Department, and the surgical floors of Phase 1 of the new Royal Infirmary.

To evaluate the usage of these terminals, which in 1978 were capable only of reporting electrolyte profiles and associated 'A' group tests, each access at a terminal was logged. The data on usage over the first 5 months is shown in Table 30. Data in Table 30 excludes multiple enquiries made in quick succession, and data from the first two weeks of operation, to eliminate the effect of the novelty value of the terminals.

TABLE 30

WARD TERMINAL ACCESSES

a) Oct '78 to Feb '79

Terminal	Program	In Hours	Out of Hours
Medical Block	Current Results	273	220
	Past Reports	84	68
Surgical Block	Current Results	212	40
	Past Reports	41	25

b) Oct '81 to Feb '82

Terminal	Program	In Hours	Out of Hours
Medical	Current	511	11
	Previous	58	5
Surgical	Current	265	25
	Previous	74	8
Renal	Current	132	15
	Previous	15	2

The data indicates a significant rate of usage, particularly out of hours, encouraging the belief that at least some of the effects of the overnight close-down of the laboratory are being minimised. The different pattern of out-of-hours accesses at the two sites was expected and is attributable to the decision to provide interim lists of all current results in Ward order at 1730 hrs at the Surgical Terminal and not at the Medical block printer.

Subjective comment on the terminals at the time was also favourable, and it is now the regular duty of the resident assistants on at least one surgical ward group to interrogate the files at lunchtime to obtain current results for his patients. This practice contrasts with the delivery of full reports which are uplifted from the laboratory at 1.45 pm and are still subject to around one and a half hours time delay before reaching the Ward (Figure 29).

Since late 1981, computer-reporting of the 'B' group analyses have increased the utility of these remote terminals. The monitoring process of logging accesses has been continued, and data for October 1981-February 1982 is also shown in Table 30.

There are now three active terminals in the system. All three carry interim printouts of electrolytes during the day, and a full listing of all computer-reported results processed up until 1730 hrs on the late afternoon printout, and this has succeeded in minimising out-of-hours requests. The number of accesses has increased considerably, however, and a histogram of access times (Figure 34)

Frequency of usage of ward terminals.

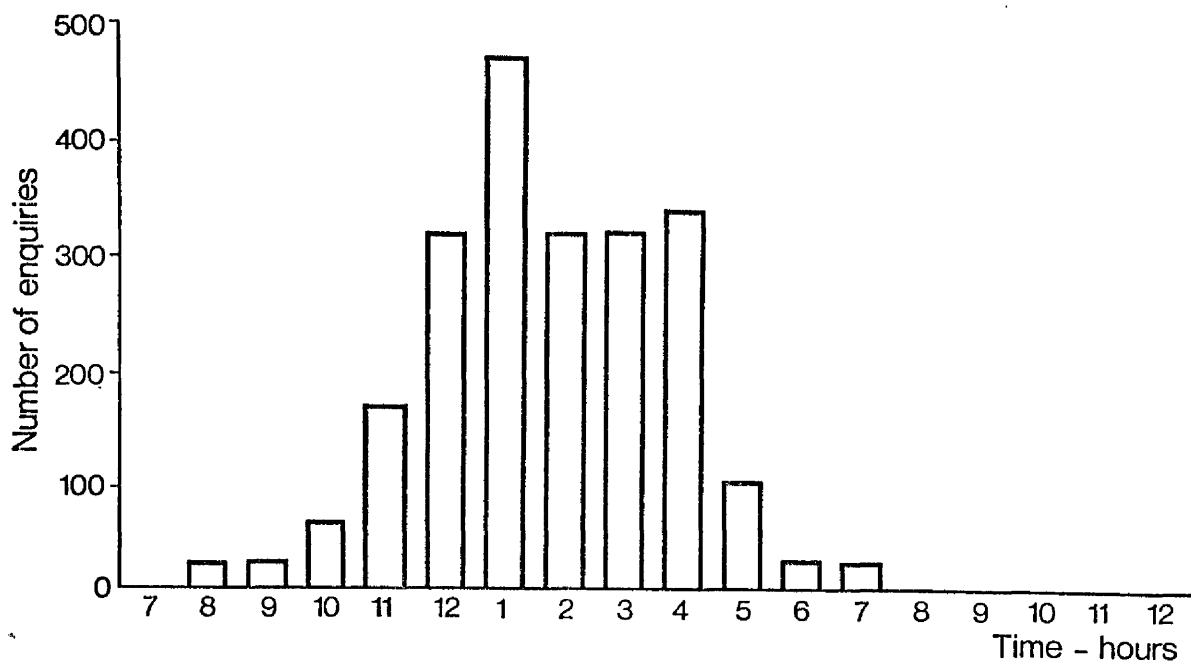


FIGURE 34 Histogram of 2300 access times of Enquiry programs at Ward-based terminals in Glasgow Royal Infirmary

shows that peak activity is indeed taking place around lunchtime, and a high level of enquiry is sustained throughout the afternoon, by which time the majority of results for all specimens reaching the laboratory in the morning might be expected to be available.

CHAPTER 4 - SUMMARY OF EFFECTS OF AUTOMATION ON TURNROUND TIME 1972-82

Some of the effects of applying automation to analysis and reporting systems within the authors laboratory over the last decade are shown in summary in Figure 35, which represents the total turnround time of a combined request from a Medical Block Ward for Electrolytes, LFTs and bone analysis on a fasting specimen - the most popular test grouping from Table 12 - at various times throughout the decade.

1972 Electrolytes were requested separately from 'B' group tests. The main time delays related to the slow analysis of calcium, and phosphate, and to the necessity to transfer the request form between the LFT and calcium benches, hence a combined 'B' request would not be reported and issued until the evening (See Section 3.4.1).

1976 Electrolytes were analysed on a fast, 120/h continuous-flow analyser designed and built in the laboratory (Section 2.4.1.7.) Calcium analysis was performed by Vickers D300 (Section 2.4.2.2.). The computer-based electrolyte reporting system was time-consuming, but allowed interim reports to be sent to a teletype in the Medical Block twice per day, so that results could be made available on-site in advance of the manual delivery of reports.

1978 Liver function tests were analysed by Centrifichem 400 (Section 2.4.3.1) and the calcium groups by a four channel Auto analyser II (See Appendix II). Electrolytes were available at Ward

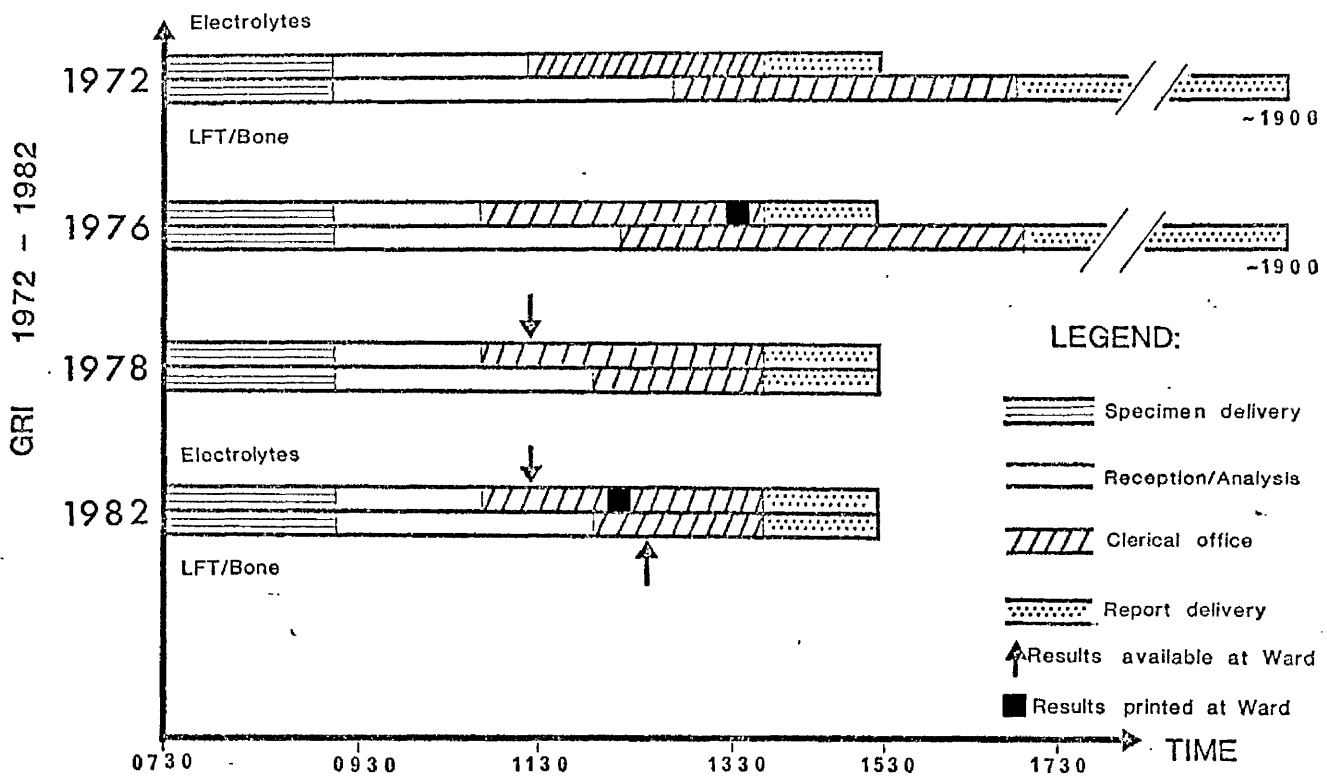


Figure 35

Turnround time of early-morning Electrolyte LFT & Bone Profiles

Enquiry terminals within 30 minutes of completion of each batch of samples (Section 3.4.5) and all results would typically be issued by lunchtime, reaching the wards in the late afternoon.

1982 In addition to availability through enquiry programs, interim electrolyte results were, and are currently published in Ward order three times per day at each Ward terminal. 'B' group tests are available on enquiry as each batch of profiles is authorised by the reporting team, and can be obtained by the Wards in printed form by lunchtime (Section 3.4.7).

The request pattern chosen for this section is not one which illustrates remarkable reductions in turnaround, but rather the sort of sustained reductions seen in the turnaround time of the high workload sector of the laboratory (Table 3) as automation is employed in the critical, rate limiting activities in a sequence.

This is not to say that remarkable reductions have not been achieved, principally by implementation of computer reporting permitting small functional groups of results to be reported independently of other requests on the same form (Section 3.4.2), and LFTs which previously were delayed for 24-48 hrs because they were combined with for example, acid phosphatase or immunoglobulin requests are now typically available within the same working day on enquiry terminals in Ward Areas.

However, as analytical and reporting times are reduced, attention is focussed on the fixed overhead of 1 to 2 hours minimum before the laboratory obtains the specimen from the local hospital. It will be noted from Figure 35, that, despite more rapid analysis and computer reporting, the specimen delivery time has remained virtually constant over the last ten years.

Thus some limitation to the progressive reduction in turn-round time seems inevitable, with the present sequence of operations.

CHAPTER 5 - DISCUSSION

Automation has been and still is, an essential feature of clinical chemistry laboratories in the United Kingdom. DHSS figures have indicated that the costs of all laboratory services account for around 3% of the total NHS budget. If staff numbers in clinical chemistry had risen pro rata with the increase in workload, the specialty would by now be the largest of the four main laboratory disciplines in terms of space requirements and manpower.

Use of automation has helped contain costs, and currently allows the larger laboratories to cope with workloads of over one thousand requests, and over five-thousand analyses, each working day of the year. Clinicians are able to request any of up to two to three hundred different biochemical analyses, some of which, by the nature of the analytical methods used may take up to several weeks to be completed. However, the majority of clinical requests relate to a small group of around fifteen to twenty of the available analyses, and it is with these few methods, which together account for somewhere between 60 and 90% of the total workload of any United Kingdom biochemistry laboratory, and the means by which they may be expedited, that this thesis is concerned.

As the workload rose it was generally considered that the problem was primarily an analytical one, relating to insufficient analytical capacity within the laboratory, lack of trained staff, or

lack of equipment. Automated equipment, purchased to overcome this early bottleneck in the request-result-report cycle, was initially of the single channel continuous flow type. By the end of the 1960s, alternative technology in the form of discrete analysers was available, but as the original automation was replaced it was a more subtle difference in philosophy between laboratories which largely determined their approach to the processing of the bulk workload, and two main types of laboratories emerged - the first equipped with a single, large, parallel, high-capacity instrument of the SMA 18/60 or Vickers M300 type, the second with a number of smaller instruments, each capable of analysing a group of tests which together comprised a small profile related to the function of a particular organ or structure - heart, kidneys, bone etc.

The first approach has, in its favour, organisational simplicity, in that up to 90% of the blood samples arriving in the laboratory are passed to a single analyser, and so there are minimal complications of request form transfer within the laboratory. Conversely, these instruments have tended to be non-selective, and there is some evidence that presentation of large profiles can swamp important results. Large analysers can be difficult to back up in the event of unplanned down-time; they do not always use optimum methods of analysis, and, even at sampling rates of 100/hour and over, there is a finite limit to the number of specimens which can be accommodated within the working day.

The second approach allows analysis to proceed in parallel at different work stations; it allows for more flexibility in selecting appropriate methods; it reduces the dependency of the laboratory's catchment area on a single machine, and it presents the clinician with a smaller number of results, which ought to be more directly relevant to his patient's condition than a large multi-channel non-selective profile. However this proliferation of semi-independent work stations tends to obscure the relationships between the various activities which comprise the overall turnaround time of a group of analyses. This in turn makes it difficult to determine which activities are rate-limiting, or what impact on turnaround will be made by new analysers, which might be advocated for quite different reasons such as ease of use or lower running costs.

In such a laboratory, a critical path network can be an extremely useful management tool. It provides a useful visual impression of the ways in which activities inter-relate, and it highlights the critical path and focusses attention on the individual activities which directly affect the total turnaround time of a request. Further, it allows one first to predict, then finally to measure, the effect of changing an activity, on replacing one analyser by another, for example.

Critical Path Analysis is effective in a number of situations. It has been used to examine activities both in a laboratory and in a clinic, and to assess the amount of turnaround time attributable to both analytical and clerical activities.

It showed, as expected, that one of the main time delays at each work station was the throughput rate of the analyser, and this department, among others, was active during the mid 1970s in exploring the maximum sampling rate to which continuous flow analysis could be increased. Critical Path Analysis has indicated the improvements which were made in analysis, but confirmed that faster analysis alone was not sufficient to speed up the return of the final report. One of the main findings from the application of Critical Path Analysis in this way is that, where groups of tests are requested on a single form, and analysed in a variety of locations, clerical handling of requests can cause major time delays, amounting in some cases to days.

Thus, while I have devoted some time to the differences between continuous flow analysis and the various types of discrete analyser; have considered methods of data acquisition from biochemical analysers, and have shown that there are time savings to be made in many of the "analytical" activities within a laboratory, their impact on turnaround time could not be fully realised until the clerical activities within the laboratory were transferred to a computer based reporting system.

Automation in this area has been more difficult - in general, until the advent of the Dundee computer system, the group of "Phoenix" program suites arising from the DHSS 3-Lab project, and the Technicon LDM system, laboratories have had little option but to develop their own software, and laboratory computing seemed often to be given lower priority than replacing or enhancing analytical hardware until it became clear that the bottleneck in the requesting cycle had shifted from analysis to reporting.

I have used Critical Path Analysis to show how effective transfer of reporting from a manual to computer-base can remove the constraint of the single request/report form and can convert integrated and lengthy chains of activities into a number of parallel sequences (Figs 32 and 33). This has the effect of setting up independent activity sequences for each group of the individual and profile requests on a single form, implying that each sub-set of a combined request form is treated as if it had been requested alone on an independent form from the time at which the combined request is entered into the computer. Thus the concept of analytical activity proceeding in parallel on a number of sites is extended through the associated clerical activities to the production of a report, and even to the delivery of the result to the Ward via a local interactive terminal. Only at this stage does the work expended on improving the analytical capabilities of the laboratory really begin to pay off in terms of reduced overall turnaround times as shown in Figure 35.

However, in estimating the effects of automation in the laboratory, Critical Path Analysis is not the complete answer. There are aspects of automation such as costs, improved performance, and effects on staff which it is not designed to assess, and, even in defining relationships between activities, it suffers from five identifiable disadvantages.

Firstly, laboratories, unlike major development projects, have no fixed starting point. Patient specimens are sent to this laboratory throughout the working day (Fig. 5), and are processed continually, and this creates problems within a strict "cause and effect" network.

Secondly, and associated with the above, fixed-time events are not easily assimilated into such a network. The laboratory may postpone analysis until a reasonable batch size has been reached, but the report delivery to the Wards will take place at a specific time whether all reports are available or not, so the sequence of events which states, in effect, that activity B cannot start until activity A has been completed does not adjust well to events which occur at fixed times of day, unrelated to the completion of previous activities.

Thirdly, a critical path network is not designed to permit loops in the structure. Thus, where a decision is taken to repeat an estimation (Fig. 6) there is no provision within the framework of Critical Path Analysis to have an activity loop back to an earlier, analytical segment of the network.

Fourthly, the method is designed around activities and events. Underlying requirements common to more than one branch of a network are not immediately visible. For example, the parallel reporting streams of Figure 33 all depend ultimately on availability of the reporting computer, but Critical Path Analysis implies independence of each stream.

Finally, Critical Path Analysis seeks to identify the relationship of one event to another. Clearly, for there to be a Critical Path, at some stage different activities must converge on the same event node. The corollary to this is that, where the final common path has been modified (as in the attempt to remove rate-limiting effects of transferring forms from bench to bench) to provide a method whereby activity sequences may take place in parallel without affecting one another, the critical path concept may apply equally to all the elements of several, parallel, non-branching sequences. While such information is not without value, the need for Critical Path Analysis at that point becomes questionable.

The effects of the introduction of automation on quality of result have been no less important than the improvements in sampling rate over the years. Some comparatively limited-speed analysers are capable of impressive precision, but, to me, the most significant aspect is that current high-throughput analysers are able to run at sampling rates of over 100 samples per hour and still return precision figures as good as or better than those achieved ten to fifteen years

ago, despite more than doubling the sampling rate. The ACB analytical methods working party (1979) showed that automated multichannel equipment performed much more reliably than manual methods, but the fact that precision of automated analysers has not improved markedly over the last decade argues that biochemists have, perhaps, been more aware of the need for faster, rather than more precise, analyses.

Perhaps now that the rate of increase in the workload does seem to be falling, improved precision, particularly for radio-immunoassays and assays of enzyme activity, will be a goal of the profession during the 1980s.

Nor has accuracy been a prime goal of clinical chemists over the past ten years. Northam (1981) points out that a surprising number of UK laboratories entered the 1980s with methods known to be inaccurate. This almost certainly reflects a disadvantage of automation in that methods which are simple to automate may well be chosen because of the analytical capacity which they provide, rather than because they have been shown to be the most precise or most accurate methods.

Measurement of the costs associated with clinical laboratories and automated equipment have been made elsewhere (DHSS, Krieg et al, 1978; Rollason, 1978; Worth, 1980; Stillwell, 1981; Broughton and Hogan, 1981). I have made no attempt to cost activities or equipment within this thesis, but the data in Figure 2 of the rise in workload compared with the rise in technician numbers shows, I believe, that automation is cost effective.

There is one further effect of automation which must be discussed - its direct effect on the staff of clinical chemistry laboratories. Rising workload and automated analysers have meant that laboratory staff run the twin risks of losing touch with individual patients, and not fully comprehending the processes within automated equipment. Manufacturers have a vested interest in suppressing information about their products which may be of advantage to rival companies (during the reaction rate algorithm work, at least one company categorically refused to divulge details of the mathematical model within their software) but this can often leave the instrument operators feeling that they are not in control of the equipment which is in their charge. In my view, this is an intolerable situation which, if not reversed, will reduce skilled analysts to the status of mere machine-minders, responsible, through the Head of Department for the provision of an analytical service to their clinical colleagues, but wholly unable to influence the manufacturers to correct observable errors within their equipment. Laboratory staff, at the time of purchase of an instrument, have the opportunity to require a full disclosure from a manufacturer of the software routines within the process control computers. This option must be exercised, and users kept informed throughout the lifetime of the equipment. In this respect, biochemists who take a deeper interest in the functioning of laboratory equipment perform a service to the profession, and ultimately to the practice of medicine.

The future of automation in clinical chemistry laboratories is less easy to define. If laboratories retain their present form, then Critical Path Analysis, despite its deficiencies provides one method of keeping control over an extremely complex situation. One way of improving its effectiveness might be to make it run as a set of programs on a real-time computer.

I have shown in this thesis that it is possible to create a network analysis model of some of the activities within a laboratory. If such a model could be installed on a laboratory computer, input programs like data preparation and result entry, and output programs for report generation could be used to update the model so that the processor could give advance warning of excessive time delays in the various analytical and reporting areas which would cause the current workload to extend beyond the time limits allowed to meet existing schedules for uplifting of reports, engineers' preventative maintenance visits and the like.

But there is a further aspect to the work presented in this thesis which has only had the briefest of mentions up until this point, that of on site analysis.

In the Introduction I outlined the gradual retreat by the analyst away from the patient and into fixed-site laboratories and Chapter 4 concluded on the pessimistic note that there remained a

problem with specimen delivery, and that, as elapsed timings for the other activities were reduced, this rate-limiting factor would account for an increasingly large percentage of total turnaround time.

Conversely, there is an example in Chapter 2 of the use of a discrete analyser in a diabetic clinic, where the close proximity of patient and analyst markedly reduces the turnaround time. This argument extends to 3 minute turnaround of blood gas results, in, or near to, operating theatres, twelve minute turnaround of electrolyte profiles in casualty units, and clinics held in laboratories to ensure fast analytical response.

The concept of performing analyses closer to the patient, and of reverting to the situation of Figure 1, albeit with the aid of rather more modern technology, has been discussed in a number of papers in recent years (Astrup 1979; Mitchell, 1979a,b; Weiner, 1980; Watson, 1980; Anderson et al, 1981).

The drawbacks are many and include labour costs, limited repertoire quality control problems with Ward based instruments, loss of data affecting the laboratory's interpretive function, a potential loss of impetus for laboratory research and development and Health and Safety considerations. Despite this, analyses by the patients bedside minimise or remove so many problems of patient identification; of specimens collected in inappropriate containers; of uncertainties in interpretation (fasting samples, recumbency, use of tourniquets etc); of time delays in requesting fresh specimens and of availability of

clinical staff to act promptly on abnormal results, that there are considerable benefits to be obtained from bringing analytical activities full circle, back out of the central laboratories to which circumstances have so far confined them throughout the 1900s.

Given that the technology now exists to permit many of the common analyses of Table 3 to be performed in a Ward side-room, I foresee considerable benefits to patient care from reorganisation of laboratory services to reduce to an absolute minimum the major remaining time delay of figure 35, and expect that, as more laboratories become conscious of the rate-limiting areas in their turnaround of results, the reversion to "bedside biochemistry" will be a major aspect of biochemistry services during the 1980s.

APPENDIX I

THIS PROGRAM ANALYSES THE REQUESTING PATTERNS OF THE HIGH-VOLUME FUNCTIONAL GROUPS OFFERED ON THE 'X' REQUEST FORM

```

100 DIM T(40),D(50,10),A(60),B(60),S$(50)
105 DIM #2,X$(10000)=12 \ OPEN 'DF1:ALABND1' AS FILE #2
106 DIM #3,B$(10000)=18 \ OPEN 'DF1:ELABND1' AS FILE #3
107 FOR K9=2 TO 2
110 GOSUB 1572 \ GOSUB 1570 \ GOSUB 1580
115 FOR I=1 TO 5 \ PRINT \ NEXT I
120 PRINT " ** 'B' REQUESTING PATTERNS **"
130 PRINT "LAST AMENDED 14-MAY-83"
135 PRINT "NOTE: RECORD PRINTING S/R AT LINE 460"
136 PRINT "ONE WEEKS DATA ONLY!! (NORMALLY 1ST-7TH OF THE MONTH)"
137 PRINT "THERE IS ROOM ONLY FOR UP TO 10,000 LAB NOS OF EACH FORM TYPE."
140 IF K9=2 THEN D3$="JUNARCX" \ D6$="01/06/83" \ D7$="07/06/83"
150 IF K9=1 THEN D3$="JULARCX" \ D6$="01/07/83" \ D7$="07/07/83"
151 IF K9=3 THEN D3$="MARARCX" \ D6$="01/03/83" \ D7$="07/03/83"
152 IF K9=4 THEN D3$="APRARCX" \ D6$="01/04/83" \ D7$="07/04/83"
154 IF K9=5 THEN D3$="MAYARCX" \ D6$="01/05/83" \ D7$="07/05/83"
180 D1$="IRO:L200,210J"+D3$+".DAT" \ PRINT "DATA FILE = ";D1$
240 OPEN D1$ FOR INPUT AS FILE #1
250 PRINT "FILE CONNECTED AT ";CLK$
260 D$=D6$ \ PRINT "START DATE = ";D$ \ GOSUB 1410
270 IF F<>0 THEN PRINT "ERROR IN DATE - TRY AGAIN" \ GO TO 260
280 L1$=D$ \ D1=M
290 D$=D7$ \ PRINT "STOP DATE = ";D$ \ GOSUB 1410
300 IF F<>0 THEN PRINT "ERROR IN LAST DATE -TRY AGAIN" \ GO TO 290
310 L2$=D$ \ D2=M
320 IF D2-D1>48 THEN PRINT "DATE RANGE OVER 48 DAYS - TOO BIG" \ GO TO 260
325 P1=0 \ P2=0
330 INPUT #1:A$
340 T=T+1 \ IF T/100=INT(T/100) THEN PRINT "TIME: ";CLK$;T;"READ"
350 IF END #1 THEN PRINT "OUT OF DATA AT LINE 350" \ GOSUB 460 \ GO TO 530
360 IF SEG$(A$,1,1)<>"1" THEN PRINT "1ST CARD ERROR, RECORD#";T;" - ";A$ \ E1=E1+1 \ GO TO 330
370 IF SEG$(A$,8,8)="A" THEN L=4 \ GO TO 400
380 IF SEG$(A$,8,8)="B" THEN L=5 \ GO TO 400
390 PRINT "WRONG FORM TYPE, RECORD#";T;"- ";A$ \ E1=E1+1 \ GO TO 330
400 A$(1)=A$
410 FOR I=2 TO L
420 INPUT #1:A$ \ A$(I)=A$
430 IF END #1 THEN PRINT "OUT OF DATA AT LINE 430" \ GOSUB 460 \ GO TO 530
440 NEXT I
450 GO TO 490
460 FOR I=1 TO L \ PRINT A$(I) \ NEXT I
470 PRINT \ RETURN

```

```

490 GOSUB 750
510 IF L3<=D2+5 THEN IF L3<=D2+6 THEN PRINT "HIGH DATE STOPPED PROGRAM" \ GOSUB 460 \ GO TO 530
515 IF X3=0 THEN IF A(0)<>P1 THEN PRINT " 'A' COUNT MISMATCH";P1;"/";A(0);"AT RECORD";T1 \ GOSUB 460 \ X3=1
517 IF X4=0 THEN IF B(0)<>P2 THEN PRINT " 'B' COUNT MISMATCH";P2;"/";B(0);"AT RECORD";T1 \ GOSUB 460 \ X4=1
520 GO TO 330
530 REM PRINT TOTALS \ CLOSE #1
540 PRINT \ FOR J=1 TO 10 \ D(50,J)=0 \ NEXT J
550 PRINT "ARCHIVE ANALYSIS - ";L1$; " TO ";L2$
560 PRINT T;"FORMS READ"; "E1;"ERRORS"
570 PRINT "NO OF ROUTINE A FORMS ON FILE=";A(0)
590 PRINT \ PRINT "ANALYSIS ROUTINE EMERGENCY"
600 I=41 \ GOSUB 1020
610 RESTORE \ FOR I=1 TO 31 \ READ X \ NEXT I
620 GOSUB 1570
630 FOR I=1 TO 16 \ READ S$(I)
640 PRINT USING "LLLLLLLLLLLLLLLLL" ##### "S$(I),A(I)
650 NEXT I
660 PRINT \ PRINT "B FORMS ON FILE ";L1$; " TO ";L2$; " =";B(0)
670 PRINT "ANALYSIS NUMBER"
680 I=22 \ GOSUB 1020 \ GOSUB 1570
690 FOR I=1 TO 21 \ READ S$(I) \ IF I=10 THEN 710
700 PRINT USING "LLLLLLLLLLLLLLLLL" #####,S$(I),B(I)
710 NEXT I
720 PRINT \ GOSUB 1260 \ GOSUB 1900
725 NEXT K9
730 PRINT "OUT OF DATA. TO REPRINT STATS, TYPE 'GO TO 530 <CR>'"
740 A=SYS(4)
750 REM SPLIT ARCHIVE RECORD
760 D$=SEG$(A$(1),10,11)+"/"+SEG$(A$(1),12,13)+"/"+SEG$(A$(1),14,15)
770 GOSUB 1410 \ L3=M \ IF L3=D1 THEN IF L3<=D2 THEN 790
780 GO TO 1010
790 RESTORE
800 H$=SEG$(A$(1),44,46) \ N$=SEG$(A$(1),16,35) \ W$=SEG$(A$(1),48,53)
805 L$=SEG$(A$(1),62,67)+STR$(M)
810 IF L=5 THEN 920
820 E$=SEG$(A$(4),47,47) \ IF E$="E" THEN 1010
830 L1=45 \ IF SEG$(A$(3),48,48)<>" THEN P1=P1+1 \ X$(P1)=L$ \ GO TO 840
835 GO TO 1010

```

```

840 FOR I=1 TO 7
850 READ L2 \ S$(I)=TRM$(SEG$(A$(3),L1+1,L2)) \ L1=L2
860 NEXT I
870 S$(8)=TRM$(SEG$(A$(4),16,18)) \ S$(9)=TRM$(SEG$(A$(4),19,22))
880 S$(10)=TRM$(SEG$(A$(2),62,66)) \ S$(11)=TRM$(SEG$(A$(2),67,71))
890 L1=47
900 FOR I=12 TO 16 \ READ L2 \ S$(I)=TRM$(SEG$(A$(4),L1+1,L2)) \ L1=L2 \ NEXT I
910 GO TO 1009
920 REM B FORM SPLIT
930 FOR I=1 TO 12 \ READ X \ NEXT I \ L1=45
940 FOR I=1 TO 6 \ READ L2 \ S$(I)=TRM$(SEG$(A$(3),L1+1,L2)) \ L1=L2 \ NEXT I
950 L1=15
960 FOR I=7 TO 19 \ READ L2 \ S$(I)=TRM$(SEG$(A$(4),L1+1,L2)) \ L1=L2 \ NEXT I
970 S$(20)=TRM$(SEG$(A$(2),62,66)) \ S$(21)=TRM$(SEG$(A$(2),67,71)) \ L1=47
975 F2=P2+1 \ GOSUB 1800 \ B$(P2)=L$
980 GO TO 1009
990 FOR I=1 TO 15 \ PRINT S$(I) \ NEXT I \ RETURN
1000 PRINT H$,N$,W$,D$,E$
1009 GOSUB 1030
1010 RETURN
1020 FOR J=1 TO I \ PRINT '-'; \ NEXT J \ PRINT \ RETURN
1030 REM COUNT S/R
1040 IF L3>=D1 THEN IF L3<=D2 THEN 1060
1050 GO TO 1250
1060 Q=L3-D1+1
1070 IF L=4 THEN A(0)=A(0)+1 \ D(Q,1)=D(Q,1)+1
1080 IF L=5 THEN B(0)=B(0)+1 \ D(Q,2)=D(Q,2)+1
1090 IF L=4 THEN IF E$='E' THEN A(60)=A(60)+1 \ D(Q,3)=D(Q,3)+1
1100 FOR I=1 TO 25
1110 IF S$(I) <> '' THEN IF S$(I) <> ' ' THEN IF S$(I) <> ' ' THEN IF S$(I) <> ' ' THEN 1130
1120 S$(I) = '' \ GO TO 1170
1130 IF S$(I) = ' ' THEN S$(I) = '' \ GO TO 1170
1140 IF L=4 THEN IF E$ <> 'E' THEN A(I)=A(I)+1 \ GO TO 1170
1150 IF L=4 THEN IF E$ = 'E' THEN A(I+30)=A(I+30)+1 \ GO TO 1170
1160 IF L=5 THEN B(I)=B(I)+1
1170 NEXT I \ IF L=4 THEN 1250

```



```

1410 REM CONVERT DATE TO DAY #
1420 IF POS(SEG$(A$(1),10,15),"/",1) <> 0 THEN M=0 \ GO TO 1440
1430 IF LEN(D$)=8 THEN IF SEG$(D$,3,3)=SEG$(D$,6,6) THEN IF VAL(SEG$(D$,1,2)) < 32 THEN IF VAL(SEG$(D$,4,5)) < 13 THEN 1450
1440 PRINT "ERROR IN DATE, RECORD#"; T; ", "; D$ \ GOSUB 1400 \ P=1 \ E1=E1+1 \ GO TO 1560
1450 M=0 \ K=VAL(SEG$(D$,4,5)) \ Y=VAL(SEG$(D$,7,8))-79
1460 FOR I=1 TO K-1
1470 IF I <> 4 THEN IF I <> 6 THEN IF I <> 9 THEN IF I <> 11 THEN IF I <> 2 THEN M=M+31 \ GO TO 1510
1480 IF I <> 2 THEN M=M+30 \ GO TO 1510
1490 IF Y=1 THEN M=M+29 \ GO TO 1510
1500 M=M+28
1510 NEXT I
1520 IF Y=1 THEN M=M+365
1530 IF Y=2 THEN M=M+731
1540 IF Y=3 THEN M=M+1096
1545 IF Y=4 THEN M=M+1461
1550 M=M+VAL(SEG$(D$,1,2))
1560 RETURN
1570 FOR I=1 TO 50 \ S$(I)=" \ NEXT I \ RETURN
1572 T=0 \ FOR I=0 TO 40 \ T(I)=0 \ NEXT I \ RETURN
1580 FOR I=0 TO 60 \ A(I)=0 \ B(I)=0 \ NEXT I
1590 FOR I=0 TO 50 \ FOR J=1 TO 10 \ D(I,J)=0 \ NEXT J \ NEXT I \ RETURN
1600 REM 12 A FORM LIMITS
1610 REM 19 B FORM LIMITS
1620 DATA "SODIUM", "POTASSIUM", "CHLORIDE", "CO2", "UREA", "CREATININE", "TOTAL PROTEIN", "SERUM OSMO.", "URINE OSMO."
1630 DATA "GLUCOSE", "AMYLASE", "PH", "PCO2", "BASE EXCESS", "PO2", "PCV"
1640 DATA "AST", "ALT", "BILIRUBIN", "ALK PHOS", "CALCIUM", "PHOSPHATE", "GLOBULINS"
1650 DATA "TOTAL PROTEIN", "ALBUMIN", "CHOL", "GAMMA GT", "URATE", "LITHIUM", "DIRECT BILI"
1660 DATA "ACID PHOS", "IGA", "IGG", "IGH", "MAGNESIUM", "LDH", "CK"
1662 DATA "LFT, CAP, ENZ", "LFT, PP, ENZ", "LFT, ENZ", "LFT, CAP, ENZ"
1664 DATA "LFT, PP, ENZ, PP", "LFT ONLY", "CAP ONLY", "ENZYMES ONLY"
1666 DATA "PROTEINS ONLY", "TOTALS"
1670 STOP
1800 IF S$(3) <> "" THEN L$=L$+"L"
1810 IF S$(5) <> "" THEN L$=L$+"C"
1820 IF S$(20) <> "" THEN L$=L$+"E"
1830 IF S$(8) <> "" THEN IF S$(5)="" THEN L$=L$+"P"
1899 RETURN

```

```

1900 PRINT \ PRINT "ANALYSIS OF REQUESTING PATTERNS:"
1901 PRINT "ANALYSIS BEGINS AT ";CLK$
1910 FOR I=1 TO P2
1920 FOR J=1 TO P1
1925 IF X$(J)=SEG$(B$(I),1,LEN(X$(J))) THEN P3=2 \ GO TO 1950
1930 NEXT J
1940 P3=1 \ T(1)=T(1)+1
1950 F=POS(B$(I),"LCE",1) \ IF P<>0 THEN L=2 \ GOSUB 2100 \ GO TO 2025
1952 F=POS(B$(I),"LEP",1) \ IF P<>0 THEN L=3 \ GOSUB 2100 \ GO TO 2025
1960 F=POS(B$(I),"LE",1) \ IF P<>0 THEN L=4 \ GOSUB 2100 \ GO TO 2025
1970 F=POS(B$(I),"LC",1) \ IF P<>0 THEN L=5 \ GOSUB 2100 \ GO TO 2025
1980 F=POS(B$(I),"CE",1) \ IF P<>0 THEN L=6 \ GOSUB 2100 \ GO TO 2025
1990 F=POS(B$(I),"LP",1) \ IF P<>0 THEN L=7 \ GOSUB 2100 \ GO TO 2025
2000 F=POS(B$(I),"EP",1) \ IF P<>0 THEN L=8 \ GOSUB 2100 \ GO TO 2025
2002 F=POS(B$(I),"L",1) \ IF P<>0 THEN L=9 \ GOSUB 2100 \ GO TO 2025
2004 F=POS(B$(I),"C",1) \ IF P<>0 THEN L=10 \ GOSUB 2100 \ GO TO 2025
2006 F=POS(B$(I),"E",1) \ IF P<>0 THEN L=11 \ GOSUB 2100 \ GO TO 2025
2010 F=POS(B$(I),"P",1) \ IF P<>0 THEN L=12 \ GOSUB 2100 \ GO TO 2025
2025 IF INT(I/100)=I/100 THEN PRINT "I";"B' FORMS CHECKED AT ";CLK$
2026 NEXT I \ PRINT "ANALYSIS COMPLETE AT ";CLK$ \ PRINT
2030 PRINT "NO OF 'B' RECORDS ON FILE WITH ACCOMPANYING 'A' REQUEST =";P2-T(1)
2031 PRINT "THIS REPRESENTS";(P2-T(1))*100/P2;"% OF ALL 'B' RECORDS."
2035 PRINT "AND";(P2-T(1))*100/P1;"% OF ALL ROUTINE USE REQUESTS."
2039 PRINT "NO OF ROUTINE USE RECORDS ON FILE =";F1;" NO OF 'B' RECORDS =";P2
2040 PRINT \ PRINT " TEST TYPE TOTAL TOTAL AS % 'B' WITH 'A' AS %"
2042 FOR I=2 TO 12 \ T(13)=T(13)+T(I) \ T(33)=T(33)+T(20+I) \ NEXT I
2050 FOR I=2 TO 13 \ READ A$ \ X=T(I)+T(20+I) \ Y=X*100/P2
2051 PRINT USING "LLLLLLLLLLLLLLLLLLLL" ###.###,A$,X,Y;
2052 PRINT USING "###.###,(T(I))/(T(I)+T(20+I))*100"
2060 NEXT I
2070 PRINT \ RETURN
2100 IF P3=2 THEN T(L)+1 \ GO TO 2120
2110 IF P3=1 THEN T(20+L)=T(20+L)+1
2120 RETURN

```

APPENDIX II

DEVELOPMENT OF DATA ACQUISITION PROGRAMS

FOR 7-CHANNEL AND 4-CHANNEL CONTINUOUS FLOW ANALYSERS

1) Hardware, language and operating system

The processor in each case was a PDP 11/10 (Digital Equipment Co. Ltd., Maynard Mass) and the hardware specification is listed in Table 31. Since this was an experimental project for an in-house development the laboratory decided to use a high-level language, in this instance BASIC, so that the inevitable turnover in staff would not compromise the department's ability to modify the program on a continuing basis, and in response to changes in analytical methods. It was also felt that the processors might well outlast the analytical hardware and that a high-level language would be an advantage if the application changed. Digital's BASLPS (BASIC Lab Peripheral System) software was purchased, since it embodied calls in BASIC to low-level routines involved in real-time multiplexed sampling, sampler triggering, and clock operation. The connections to the seven-channel analyser are shown in Figure 21, and an identical computer configuration was used for the four-channel version.

2 System specification

The specification for the seven-channel electrolyte analyser involved triggering the sampler every 30 seconds; data capture from seven analytical channels (2 flame emission photometry and 5 continuous-flow colorimetry) identification of peak maxima for the colorimetric channels, and calculation of results with printout at the bench, both on hard copy and in machine-readable form for further processing by the

TABLE 31

PDP 11/10 DATA ACQUISITION PROCESSOR

HARDWARE CONFIGURATION

- 1) DEC PDP 11/10 Processor with 16K core memory
- 2) AR-11 Analogue real-time module with:
 - 16 channel multiplexer
 - A/D converter
 - Programmable Clock
 - Scope Display control
- 3) DL-11E 20 mA Single Asynchronous serial line interface
- 4) KE-11A extended arithmetic unit
- 5) TA-11 Dual Magnetic tape cassette unit
- 6) TE 308 Olivetti 10 cps teletype

SOFTWARE

CAPS-11 Cassette-based operating system

BASLPS Basic Language with support for laboratory peripheral system

reporting computer. Each channel was to be treated independently so that no phasing of the fluid system would be necessary. The specification for the four-channel calcium analyser, though broadly similar, covered a smaller number of channels, all using end-point reactions and continuous flow colorimetry at 60/h, but with the additional complication that the system should distinguish between test trays and "linearity" trays designed to test, on a regular basis, the linear range of the four methods and the assignment of the tertiary standard values when compared with material of known composition. Further, the analyser had to be capable of running either in a four-channel or two-channel mode, with data acquisition from the calcium and phosphate channels disabled so that those two channels could be given over to running analyses of urine and other fluids independently, and outside computer control.

To maintain a throughput of 120/h, on the electrolyte analyser, it became evident that a method would have to be found of informing the program of the presence of a second batch for analysis thus initiating sampling of Batch 2 concurrently with data acquisition and result reporting from the first batch. Since the console teletype was designed primarily for output of results, a low-level interrupt, analogous to the end of tray signal, was included in the systems analysis for both data acquisition systems. The sampler 'start' key was modified so that depression of the key while the sampler was on-line to the computer would generate a voltage indicating the presence of a further batch.

An additional analogue signal, the Lithium voltage used to correct sodium and potassium results for fluctuations in flame intensity, was thought necessary originally, but was discarded in favour of performing digital to analogue re-conversion of the lithium-ratioed sodium and potassium voltages. Commercial circuitry was purchased from Instrumentation Laboratories, the manufacturers of the flame unit.

On the calcium analyser, a simple switching device was constructed to switch out the signals from the calcium and phosphate channels and leave the protein and albumin signals on line, but otherwise the electrical connections were similar to those shown in Figure 21.

Flynn (1969) advised that "the visual vetting of peaks is worth a lot of computing time and programming effort" and it was decided that this philosophy should obtain in the Glasgow system, and that the instrument operators would vet the peak shape by visual inspection of the analogue output displayed on chart recorders for all channels (other than the flame emission pair where the data was taken from the 'steady-state' plateau (see below)), and the prime function of the processor should be identification and storage of the peak maxima.

3 Systems Analysis

The BASLPS system permits foreground/background operations within a PDP/11 series processor by allowing the user to set up a real-time data logging procedure. This is triggered by interrupts from the real-time clock which then stores data in a designated buffer until halted. The system was designed to operate with two buffers, each holding ninety readings from each of the data channels on the multiplexer, and corresponding to one complete sampling cycle.

While a buffer was being filled, the contents of the previous buffer would be analysed and appropriate action taken (print results, stop sampler triggering, start new tray etc).

The sodium and potassium signals were treated separately. Since the flame unit reached the 'steady state' plateau at about 18 seconds after sampling, the voltage at 22 seconds was stored directly for each sample, together with an initial baseline reading for each of the two channels.

All timings for colorimetric channels were based on the initial signal which triggered sampling of the first cup from each batch, with a baseline reading taken after a pre-determined delay time of 1 min 47 sec on the electrolyte analyser and 3 min 30 sec on the slower calcium four channel.

Thereafter each channel was monitored for a signal exceeding the baseline by a specified amount and this recognition of the priming peak for each channel incremented a counter which, when it reached maximum value, caused the program to divert to the printing subroutine on each subsequent iteration through the data interpretation steps. Where the calcium and phosphate signals were switched out, a decision based on elapsed time since triggering the first sampling cycle incremented the counter, and the computer reported zero values for those two channels.

After recognition of the first standard for any colorimetric channel, the next buffer full of data had gates applied within which the maximum voltage was sought and stored in the master array of forty-four cups by seven, (or four) channels and the results were

calculated from the observed voltages and known concentrations of the standard at cup 2 and printed as soon as it was recognised that all results for any sample were available.

The 'end of tray' signal was also monitored and sampler triggering suspended either if the voltage on this channel exceeded 2.5 volts or if the maximum batch size of forty cups had been achieved. Data acquisition on all channels continued for a further three cycles beyond the last sample peak to record a representative baseline voltage for drift correction (see section 3.2).

While data capture continued, the 'start tray' voltage was monitored and further trays, if present, were sampled after a computed time delay sufficient for the signals for all channels to reach baseline so that the previous baseline reading could be updated for the new batch.

Lack of external data storage also required that the data arrays were frequently overlaid, with signals from a second tray filling one end of the master array while results from the first tray were still being computed and printed from the other end of the array.

4. Program testing - calcium four channel - early development

Initially the interface with the 2-channel/4-channel switch contained circuitry to restrict the incoming data signals to a range of 0 to 2.5 volts since the normal operating mode of the analogue-digital converter was from -2.5 to +2.5 v bipolar.

Initial problems with mains spikes led to a change of specifications in components in the sampler circuitry which responded to the +5 v pulse from the processor and initiated the 1 min sampling cycle. The inception of the cycle was precisely timed in this way, although

the differentiation between the sample and wash periods within the overall timing used the independent mains-voltage timers within the sampler. Fluctuations when these triggered caused some under-powered components of the computer-associated circuitry to malfunction. A similar problem caused large, transient voltages on the two wires leading from the sampler carrying 'end of tray' and 'start tray' signals. The program was therefore modified to sample only the 90th reading from the 'end of tray' data, since the spikes attributable to the sampler timers occurred around the 60th and 84th readings. The start of tray signal was artificially prolonged, and the software modified (a) to look for a non-zero signal only after an 'end of tray' voltage had been detected, and (b) to reject a transient spike and act only on a series of sustained high values.

Parallel running was initially encouraging, with apparently satisfactory results for calcium, phosphate, and albumin, but a problem with total protein was apparent. This seemed to be related to calibration, since the replicate standards at cup positions 1 and 2 were satisfactory, but thereafter the results seemed to run with a mean value of around 80 g/l compared with an expected hospital population mean of <70 g/l. Since the program looked at a window of about 30% of the data points in the buffer, it was anticipated that the window might be taking in the trough between two peaks, rather than the peak maximum, and so the total protein data was isolated and a separate set of criteria used to alter the position and length of the window within the ninety readings to try to determine the cause of the problem. That some form of window is necessary is self-evident, especially where extensive peak validation is not performed. Since the processor

accepts the maximum voltage within the window, an extended or misplaced window may incorporate part of the fall curve of the previous peak, or of the rise curve of the next peak in succession, and thus give a false reading. The use of such windows has been previously reported (Whitby and Simpson, 1969; Gray and Owen, 1969).

Further detailed analysis of results from all four channels revealed a number of consistent errors, however. While the calcium channel results were satisfactory, the phosphate group showed distinctly poorer correlation between manual and computer produced readings, and the albumin results consistently dropped by around 4 g/l on the final three samples of any tray. They also did not correlate with manual readings as well as expected from the calcium data.

5. Troubleshooting

Mains voltage fluctuations were suspected, and a short program was written which constantly monitored and printed the voltage from any given channel at half-second intervals.

By coincidence, this program was printing continuous baseline results for the total protein channel while the twin channel calcium and phosphate analyser was being used independently, but while the selector switch was set to monitor all four channels.

Fifteen minutes of continuous monitoring had shown no fluctuations when the protein signal began to change showing sustained rises and falls with a one minute periodicity. It became obvious that these coincided with the peaks and troughs of the calcium and phosphate data being run on the independent twin channel and the relationship

between the data signals was re-evaluated. Each channel was isolated and continuously monitored while the signals from the others were altered.

The following relationships were noted - the calcium signal was unaffected by any other channel; the phosphorus signal by calcium alone; the total protein signal by phosphorus alone, and the albumin signal by total protein. These were in accordance with the full test results. Calcium interference could explain small discrepancies in the phosphate results. The widely fluctuating phosphate results would only begin to affect the protein signal at about the third result, since the time lag between sampler and photo-detectors differed by about two minutes, with protein being the faster. Since albumin had the longest time lag of the four, the protein interference present for the bulk of the tray would have terminated around three samples from the end, and so the albumin signal would decrease, as observed.

Interference was traced to the time constant of the external circuitry used to attenuate the data signals to a maximum of 2.5 v. The multiplexer within the Analogue/digital converter was sampling the channels in the order Calcium, Phosphate, Total Protein, Albumin, End of Tray, Start of Tray, and was not reaching zero between channels. This generated a type of electronic carryover between channels on all ninety readings in the data buffer. All incoming data channels were moved to different but still consecutive lines on the 16-channel multiplexer, but when no improvement was found a modification was made to the A/D converter to use a unipolar 0-5 v signal and the attenuating circuitry was scrapped. Results since that time have been satisfactory (see Section 2.5.2.2).

Only one further problem of note has since occurred on the calcium analyser. A preventative maintenance involving the replacement of the connection tubing on the calcium/phosphate twin channel increased the time delay on the phosphate channel to the extent that no priming peak was detected before the fixed time allowed for the channel counter to reach maximum had elapsed. The logic then concluded that the results from these two channels should be set to zero, and no results were printed. This minor embarrassment was quickly diagnosed and rectified by extending the time allowed for recognition of the priming peaks before the decision to suppress the calcium and phosphate results.

On the electrolyte analyser, a problem arose with the flame unit, in that the re-analoguing circuits, which had operated satisfactorily for about eighteen months, gave problems when the flame unit itself began to perform less well. The solution eventually arrived at was to take the analogue signal from all three detectors, sodium, potassium, and lithium, to the multiplexer and calculate the ratios within the program. This involved the loss of one half day of analyser operation, vindicating, at least in part, the decision to use a high level language to simplify fault-finding and re-programming where necessary.

APPENDIX III

ENZYME REACTION RATE CALCULATION

LIST OF SIMULATED CURVE-FITS

Line Fit Simulation 1

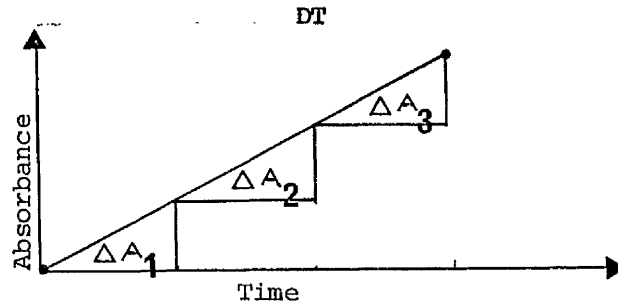
DESCRIPTION: 3-segment check with absolute limit

LINE-SEEKING: No

SOURCE: Commercial

INPUT 30 Data points (x = time, y = absorbance) equally spaced over the time course of the reaction.

ALGORITHM: Calculate reaction rate by

$$\text{Activity} = \frac{A_0 - A_{29}}{DT} \times F$$


Where A_0 = Absorbance at time zero

A_{29} = Absorbance at time 29

DT = Total measuring time (min)

F = Conversion factor from $\Delta A/\text{min}$ to U/l

VALIDATION: Divide line into three equal segments and calculate $\Delta A/\text{min}$ for each segment.

Line is valid where both

$$\Delta A_1 - \Delta A_2 < 0.0032$$

and

$$\Delta A_1 - \Delta A_3 < 0.0032$$

COMMENT:

Accepts unsatisfactory lines at low activities.

Line Fit Simulation 2

DESCRIPTION: Sliding least-squares linear regression analysis.

LINE SEEKING: Yes

SOURCE: Statistical theory

INPUT: 30 data points (x = time, y = absorbance) equally spaced over the time course of the reaction.

ALGORITHM: Linear regression analysis with calculation of standard error of gradient from the formula

$$S_m = \frac{\sigma_x}{\sigma_y} \sqrt{\frac{1-r^2}{n-2}}$$

(Ref - Sokal & Rohlf, Biometry, P 420 et seq)

Where S_m = Standard error of gradient

σ_y = Standard deviation of absorbance data

σ_x = Standard Deviation of time data

r = correlation coefficient

n = number of points

OPERATION: The program calculates the linear regression statistics for a minimum of one-third of the points on the line. If $S_m = 0$ the line is acceptable and the calculation passes to the next analysis.

If $S_m \neq 0$ the next point is accepted and the first discarded. The lesser of the two standard errors is stored, with gradient, and so on until either a 10-point section gives an S_m of zero, or all points have been assessed.

The program then prints enzyme activity from line with minimum Standard Error.

VALIDATION:

Print minimum S_m + comment on acceptability of this degree of error.

COMMENT:

Satisfactory line-seeking routine.

Line-Fit Simulation 3

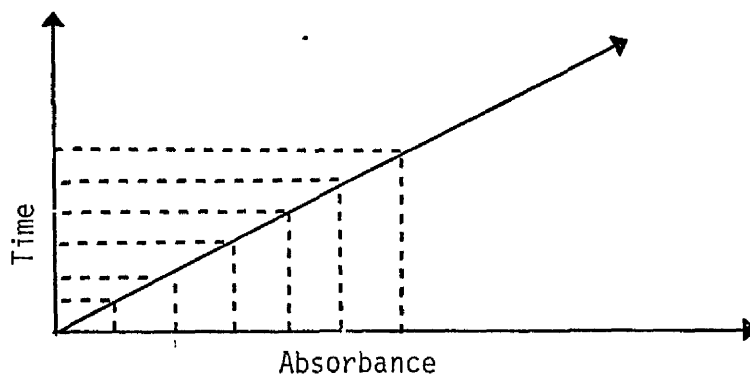
DESCRIPTION: Sequential gradient comparisons

LINE SEEKING: Yes

SOURCE: Commercial

INPUT: Variable number of time points at specific absorbance levels
 ie Times corresponding to absorbances from zero to 0.04A in steps of 0.002A, plus times corresponding to absorbances from 0.04A upwards in steps of 0.008A.

ALGORITHM: $R_i = \Delta A_i / \Delta t_i$ $R_m = (R_1 + R_2 + R_3) / 3$



- OPERATION:
- 1) Calculate reaction rate ($\Delta A / \text{min}$) for each of the first three pairs of points (R_1, R_2, R_3)
 - 2) Calculate the average Reaction Rate across the time period (R_m).
 - 3) Calculate the deviation of each R_i from the average and express the sum of these as a percentage of $R_m(D)$.
 - 4) If $D = 0$, Stop calculation

- 5) If $D \neq 0$, delete first point, accept next point, repeat calculation until either $D = 0$, or Data ends.
- 6) Print R_m for minimum D .

VALIDATION:

Print minimum percentage deviation with activity

COMMENT:

Gave bad results with initial, short-lived high activity responses.

Line Fit Simulation 4

DESCRIPTION: 12 segment check in pairs

LINE-SEEKING: No

SOURCE: Commercial

INPUT: Twelve mean absorbance values. (A_1 to A_{12})

ALGORITHM: Six ΔA s are calculated, of the form $A_{12}-A_6$ etc, each representing the absorbance change over one half of the line. The mean ΔA is calculated from the six values.

VALIDATION: If all six ΔA s are not within + 12.5% of the mean of the six then the result is flagged.

COMMENT: No line-seeking, otherwise satisfactory.

Line Fit Simulation 5

DESCRIPTION: 3 segment check with percentage limit

LINE SEEKING: No

SOURCE: Commercial

INPUT: 22 Data points, one second apart, in the assumed linear portion of the curve.

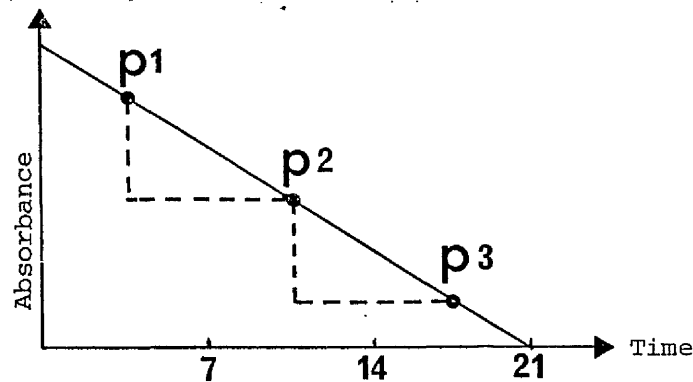
OPERATION: Split line into 3 sections of 7 seconds each

Calculate mean absorbance in each section (p1, p2, p3)

Calculate $\Delta A/\text{min}$ from $\frac{p1 - p3 \times 60}{14}$

since p1 and p3 are 14 seconds apart

VALIDATION:



Area of triangles within 10% of one another unless activity < 5 U/l.

Substrate depletion: initial absorbance outside limits.

COMMENT: No line-seeking. Requires careful calculation of T_0 .

Line Fit Simulation 6

DESCRIPTION: Sequential Area comparisons

LINE SEEKING: Yes

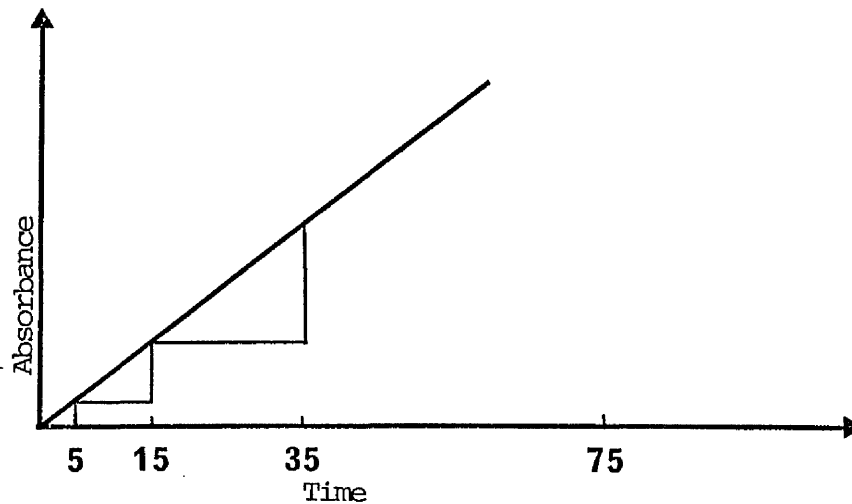
SOURCE: Commercial

INPUT: Sequential areas, beginning with a 5-sec timebase and doubling the time interval for each successive area to a total measuring time of 155 sec.

ALGORITHM: Calculate result from the larger area which satisfies the linearity criteria.

VALIDATION: Flag result if no large area can be found within the range $4 \times (\text{previous smaller area}) + X\%$ where X is an operator defined linearity tolerance.

COMMENT: Initial, short lived linear response can give a valid line over no more than 15 sec measuring time.



Line-Fit Simulation 7

DESCRIPTION: Sliding Data Sets

LINE SEEKING: Yes

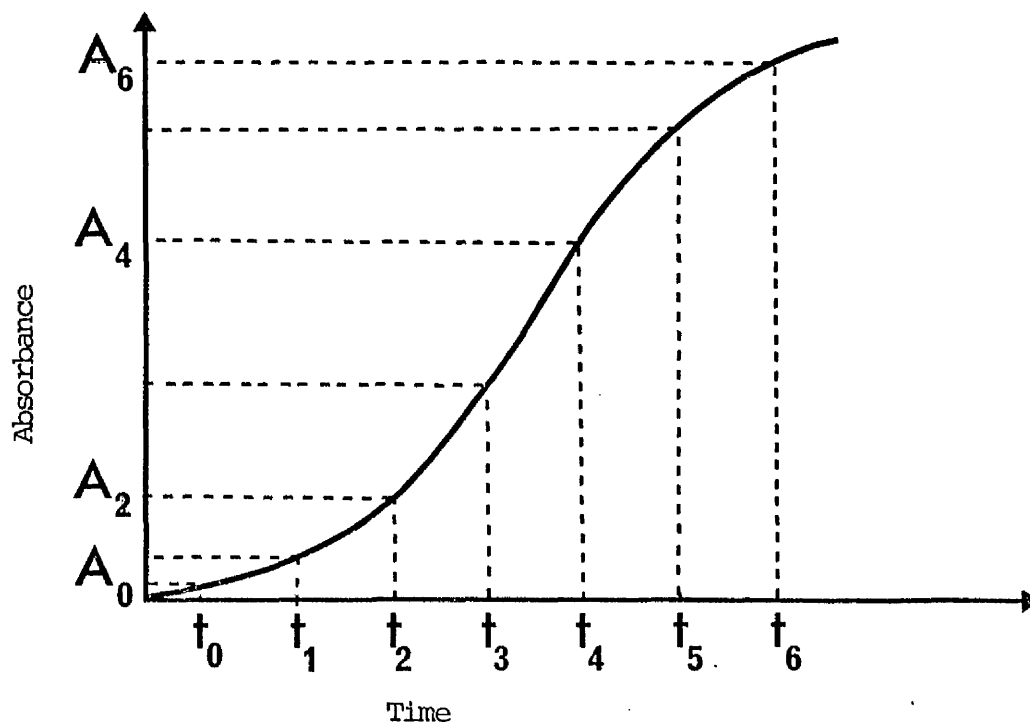
SOURCE: Commercial

INPUT: Seven equally spaced data readings, grouped into three sets as A_0-A_4 , A_1-A_5 , A_2-A_6 .

ALGORITHM: Calculate the average $\Delta A/\text{min}$ over the five points in any group which satisfies the linearity criteria.

VALIDATION: The absolute value of the slope of the line of the three second order differences from the four $\Delta A/\text{min}$ shall be less than an empirical "slope limit".

COMMENT: This algorithm has not been exhaustively tested, but will clearly fail if there is a spurious value at A_3 or A_4 .



SIMULATION AND DATA

A total of seven algorithms were simulated and it was noted that they could be sub-divided into two main classes - those which did and did not attempt some form of line fitting.

When the formulae were applied to one hundred sets of points representing real data from reaction rate analysers all but two to three are satisfactorily calculated by any single method. Evaluation was continued using data specifically configured to represent different types of error occasionally encountered in enzyme analysis, and standardised to the same slope.

Data in this group was then randomly perturbed to simulate both minor imprecision and single gross errors.

Results for each algorithm are given with their descriptions.

SUMMARY OF RESULTS

The only line-seeking algorithm to consistently return the expected value of the straight-line portion of the curve was the linear regression calculation, based on a minimum of one-third of the line (at least 5 points).

CONCLUSIONS

Satisfactory algorithms should:

- 1) actively seek the linear portion of the curve
- 2) report deviations from the straight line in $\Delta A/\min$ or u/l
- 3) require linearity over at least $1/3$ of the curve.
- 4) be adaptable to real-time applications.
- 5) integrate the incoming signal where possible to avoid spurious points.

Satisfactory algorithms should not:

- 1) assume linearity
- 2) report deviations as percentages
- 3) consider less than $1/3$ of the line, or more than $1/2$ in a single segment.

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