Hospital pharmacy and the patient

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Edited by

Tom Bradley

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Preface

The development of new technology means that compromised patients previously confined to hospital may now be treated at home. Those patients receiving intravenous feeding, cytotoxic drugs and new insulin therapy, are fully trained by the health-care professionals (doctors, pharmacists and nurses) to encourage self-reliance and understanding which are vital to success.

There are hazards in treating these patients in the home environment, e.g. microbiological risks which are currently being evaluated, failure of equipment, and social problems as patients adjust to a new life in the community. Neverthless, the balance of benefits favour restoration of the patient to a self-reliant positive life at home.

The delivery of this important new dimension in therapy was described at a symposium held in the University of York by innovators in the field. Discussion enabled the core of knowledge and experience developed by multi-disciplinary teams to be shared. The problems of supplying parenteral nutrition and medication for the compromised patient in the home and the family situation were aired and solutions presented.

The special care for hospital out-patients receiving cytotoxic drug therapy and safe procedures for staff handling these agents was presented and together with responses to questions indicated the direction for UK hospital pharmacists to follow.

More information is needed and it is hoped that this account of these proceedings will stimulate interest in these aspects of health care.

T. J. Bradley

Opening Address

T D Clarke

I would like to welcome you to Yorkshire and to this symposium in York University. Having looked over the shoulder of the Chairman and speakers, I can promise you a full and stimulating programme. This symposium, as previous Travenol symposia have done, points the way to change. In the past, pharmacy has been labelled as a drug-orientated profession, both in its education and practice. The next 2 days will be devoted to confirming that pharmacy is becoming a patient-orientated profession, that hospital pharmacy is opening the doors of the hospital and carrying complicated therapies previously described as hospital only into the patient's home. It has happened with home haemodialysis and more recently with CAPD.

Now is the time to review the possibilites, the problems, the dangers and advantages of all forms of parenteral therapy for patients at home. The more difficult of these therapies concern the use of cytotoxic drugs, and parenteral nutrition, particularly away from the controlled environment of the hospital. The development of these techniques in the home will be discussed in the first session and the hazards, risks and responsibilities in the second. Consideration of the responsibilities for these services includes a discourse of the juxtaposition between hospital and community pharmacists, and here today are 230 hospital pharmacists and one community pharmacist.

An evening session will be devoted to the presentation by the '1981 Travenol Fellow' of his paper on the application of freeze-thawing. The extension of i.v. drug additive services within unchanged resources will require developments in technology of this nature and we look forward to

learning the details of the freezing process and subsequently the thawing process within the confines of stability limits.

The session on Friday morning will look at new developments in hospital practice, the development of a cytotoxic service, a case study in nutritional support and, I am very pleased to say, the pharmaceutical skills shown in stability studies of dilute corticosteroid creams.

I would like to take this opportunity to congratulate the authors of these papers on being selected from the numbers that were submitted, indeed in preparing their papers in such a short time, and to say how much we look forward to hearing from them.

In the final session the speakers will relate educational requirements of drug evaluation, pharmacokinetics and the application of new technology by pharmacists to the care of patients.

SECTION ONE

Parenteral Therapy for the Patient at Home

Chairman:
Professor J.E. Lennard-Jones

Chairman's Introduction

J.E. Lennard-Jones

Healthy people are active at home and a person who has been ill aims to take a normal place once again in a busy, outward-looking environment. In this symposium we are thinking not simply of treating illness at home, but of self-treatment at home; for most of the time the treatment is unsupervised and the person with the illness is responsible for it. During recent years it has become apparent that many patients do not take tablets and medicines and the word 'compliance' has been used to describe the efficiency of self-treatment. Compliance is a passive word and suggests obedience to authority. The parenteral treatments we are going to discuss require the patient to be an active and principal partner in a difficult technical regime.

Historically, such treatments began perhaps with the discovery of insulin. Those treating diabetics know about the problems a patient has in measuring doses, plucking up courage to plunge a needle through the skin, and in guarding against infection and other complications. The successful management of a diabetic patient largely reflects the quality of teaching given at the onset of the illness.

In the 1940s a treatment was devised for the temporary treatment in hospital of reversible renal failure. By the 1960s, chronic longterm haemodialysis was evolved to compensate for permanent failure of the body's excretory system. At first, and still to some extent, patients came frequently and regularly to hospital for treatment. To ease the pressure on hospital facilities, and the need for the patient to avoid travelling long distances, home haemodialysis was established. This is a technique which makes great demands on the emotional, mental and physical qualities of the patient.

Similarly, in the 1960s parenteral nutrition was developed in hospital as a temporary treatment for intestinal failure. In 1970 the idea was developed of using an arteriovenous fistula, not for removing waste products, but for introducing nutrients for the longterm treatment at home of patients with intestinal failure. Between 1971 and 1974, several papers were published from France, the United States and Canada, in which this concept was elaborated and new techniques introduced, particularly the use of a permanently placed catheter in the superior vena cava. The number of patients treated in this way now amounts to many hundreds in the United States, but to only about 40 in this country.

The same arguments, and the development of techniques for longterm central venous catheterization led to the development of cytotoxic intravenous therapy at home in the mid-1970s. The last few years have also led to the introduction of continuous insulin infusion as a special treatment at home for certain patients with diabetes.

We are thus going to discuss techniques of domiciliary treatment developed during the last decade. Like all recent developments, further improvements are possible and modifications are constantly being introduced. Also, since the techniques are relatively new, they are at present practised in relatively few centres.

I would like you to think what these new, relatively complicated and potentially dangerous treatments can mean for a patient. First of all, from a happy state of thinking little about health, he or she has become ill. If illness occurs suddenly it is much more difficult to cope with psychologically than if it occurs gradually. A relatively secure lifestyle suddenly becomes precarious and insecure. A person who needs cytotoxic therapy knows that this type of treatment implies a diagnosis of cancer and that the cancer may lead to early death. A person who needs longterm parenteral nutrition has to rely on an artificial life support system; someone who needs insulin infusions faces a lifetime of diabetes. In every case, the body on which they relied for healthy and vigorous enjoyment has failed in some way.

People who inject drugs or nutrients into their own body have, in one way to be more self-reliant, and yet in other ways to be more dependent than other people. He or she has to be an expert in difficult techniques which are potentially dangerous, yet, at the same time, be dependent on the efficiency and care of experts. Sturdy independence is no longer possible. It must also be remembered that patients are often not well when we ask them to learn about self-treatment. Patients with cancer often suffer from the symptons and debility caused by the tumour. Patients who need insulin infusion may suffer from diabetic neuropathy or other complications of the disease. A person who needs parenteral nutrition has often undergone more than one major abdominal operation, may be malnourished and weak, and may suffer severe diarrhoea or have an abdominal stoma, such as an ileostomy, to cope with.

Most patients are ignorant about the working and structure of their bodies. They are frightened at the prospect of injecting substances into themselves. They need teaching about matters they have never thought of before, such as the level of sugar in their blood, the need to avoid infection and the possible side-effects of drugs. They also need to learn about unfamiliar equipment like syringes, pumps and other devices. Education must be slow, painstaking and thorough. Imagine how you would feel if you were asked to inject a drug you knew to be dangerous into your own vein, or to infuse 3 litres of fluid into yourself overnight – would you sleep well?

Lastly, a patient asked to undertake any of these techniques feels different – different from friends and different from the family. To that extent he or she is isolated, not because others do not care, but because life no longer seems secure as it depends on a machine or a fluid or a drug.

What of the doctor? His role is still to make a firm diagnosis and, if possible, to recommend a treatment. He has to consider not only what is likely to be most effective, but what is most economic in terms of the patient's time, staff time and money. A complex regime should only be recommended when simpler measures fail or are not appropriate. With other members of the health team, he must assess the patient's mental capacity, manual dexterity and emotional stability. Patients and their relatives must not be asked to undertake more than they can cope with, and more than is justified by the likely outcome of the treatment. The doctor's role is to prescribe, helped by pharmaceutical knowledge and information; to watch for side-effects of treatment and to monitor its effectiveness. A doctor also has to cope with his own sense of inadequacy in the face of serious, and sometimes progressive, illness. He is glad that responsibility can nowadays be shared with other professions and greatly admires the efficiency, competence and confidence of other members of the health team in their special roles.

It has been said that happiness depends not so much on what we have but on how much we enjoy. The patients we are about to discuss have lost much and our aim must be to enable them to enjoy to the full what is left.

1

Cytotoxic therapy – developing a home intravenous service

R.W. Anderson

The University of Texas M.D. Anderson Hospital and Tumor Institute at Houston is a 504 bed comprehensive cancer centre for the in-patient and the out-patient. Comprehensive out-patient care is provided to over 300 000 out-patients seen each year in over 20 specialty clinics. There are approximately 1200 out-patient visits daily.

Pharmaceutical services are provided to the out-patient by three pharmacies in physically separate locations. Two pharmacies provide traditional dispensing and counselling services. A third pharmacy, known as the Station 19 pharmacy, prepares parenteral chemotherapy for administration to the out-patient within a specialized treatment and observation area of the clinic.

When chemotherapy is a part of the out-patient's treatment plan, the patient will normally receive at least the initial course of therapy at the institution. An average of 100 patients receive approximately 200 such doses daily. The Station 19 pharmacy is responsible for the preparation of all initial doses administered in this area. In addition, the pharmacy staff of three pharmacists and one technologist provides the pharmaceutical support base necessary for the institution's out-patient portable infusion pump programmes.

This programme was conceived as an alternative mode of chemotherapy administration for the out-patient, allowing the would-be in-patient the

advantage of at-home administration of a continuous infusion of chemotherapy.

The programme was initiated at the institution in 1975 with a prototype device known as the Alza® pump. Several portable infusors have since been tested – the Cormed® pump, the Auto Syringe® pump, and Travenol Infusor®. From the onset, the programme has utilized a multidisciplinary approach with the physician, nurse and pharmacist making up the infusion team. The physician determines the appropriate therapy, the nurse provides catheter care teaching and training on the use of the pump, and the pharmacist provides dose preparation and patient teaching for self-preparation of medication.

Some advantages of out-patient treatment over an in-patient stay include:

(1) The patient is able to lead a more close to normal life pattern, being allowed to return to his local community, to remain at home or go to work.
(2) The patient minimizes his in-patient hospitalization expense.
(3) There is less chance of the patient acquiring a nosocomial infection.
(4) Hospital beds are freed for the more acutely ill. M. D. Anderson Hospital occupancy currently exceeds 95%.
(5) The out-of-town clinic patient is saved the expense of repeated trips to the institution and interim living in the city.

The clinical advantages of continuous infusion over intermittent administration of certain chemotherapy has been documented by research data from both this institution and others. The two primary advantages are improved response rates and decreased toxicity. For example, a significant decrease in the severe nausea and vomiting associated with Adriamycin® (Legha *et al.*, 1982) has been noted with continuous infusion. Also, continuous Velban® (Yap *et al.*, 1979) and Cytosar® (Bodey *et al.*, 1976) infusions have been shown to produce significantly higher tumour response rates than with intermittent therapy.

The success of out-patient chemotherapy administration with the portable infusion pump is related in part to the use of a long-term silicone elastomer central venous catheter. The primary advantage to the patient for insertion of a central venous catheter is elimination of the need for repeated venipuncture. More than 7000 silicone catheters have been inserted at this institution, with 1700 patients currently having catheters in place. The median indwelling time is 30 days, although catheters have remained in place for up to 2 years.

The primary pump presently in use is the Auto Syringe pump, Model AS2F. This pump is powered by rechargeable batteries, weighs approximately 450 g, may be worn in a shoulder pouch or a belt, has alarm

capabilities, and provides an intermittent type of infusion. Medication flow is accomplished by a series of microinfusions at intervals of 4.28 s/infusion hour. The pump can be programmed to deliver over a time period of ½ to 49 ½ hours at a flow rate ranging from 0.01 to 100 ml/hour. For patient convenience, a 24 h infusion time is used, using either a 20 ml or 60 ml Monoject® Luer lock syringe. Essentially, any drug which has been approved for a continuous infusion protocol may be administered via the pump, within stability limits. Drugs which have been infused via the pump include Adriamycin®, DTIC®, Velban®, vindesin, 5-FU, bleomycin, Cytosar®, and Sprirogermanium. At the present time, the institution owns 66 pumps, which are rented on a rotating basis to the approximately 180 patients now in the programme. Over 2150 courses of therapy have been administered via these pumps. In addition, patients may also purchase a pump directly from the manufacturer. Approximately 65 patients have purchased their own pumps.

Shortly after the advent of the Auto Syringe pump programme 2 years ago, the pharmacy staff became aware of the need and opportunity for the involvement of the pharmacist in an additional patient teaching role. This need revealed itself by the fact that more and more patients wished to receive their treatment at home without returning to the institution. This required that the patient be instructed in how to prepare the necessary syringes of chemotherapy for insertion into the pump, a service normally provided by the pharmacy. Physicians were also requesting that some drugs with limited stability be infused via the pump. The need further grew as patients began to purchase their own pumps in an effort to maximize their personal convenience and minimize trips to Houston and to the institution. It was at this point that the department began to address itself to the need for a formalized patient education programme in this area.

In designing the criteria for such a teaching programme, the assumption was made that the pharmacist must train the patient to be a 'mini' pharmacist, i.e. to be able to prepare an accurate, parenteral dose of chemotherapy, sterile and suitable for use in the infusion pump for a specified number of days. It was determined that an appropriate means of accomplishing this task was to prepare a written instruction booklet (see Appendix to this chapter) that would accompany a verbal one-to-one teaching session. The booklet would provide needed information and reinforcement once the patient left the institution and would also provide consistency and a standard of teaching for any pharmacist performing the patient teaching session. The content would include a general discussion of aseptic technique, measuring drugs with syringes, understanding the pharmaceutical terms and calculations, and individual step-by-step instructions specific to each patient.

Patients to be entered on the programme are initially screened to determine their suitability as participants in the home programme. A patient

must be mentally and emotionally capable of handling the technical procedure. Therefore, in writing the text of the booklet, it was not necessary to tailor the vocabulary of instructions to the seventh grade language level normally used for medical information to the general public. Drawings would be used to illustrate difficult concepts. Each patient would have an individual instruction sheet, since drug and dose might vary with each patient. Finally, a section was needed for pharmacist documentation and assessment, to be retained by the pharmacy as a permanent record.

A close relationship exists between nursing and pharmacy to co-ordinate and schedule the actual teaching session. Prior to the patient receiving instructions of medication preparation, the patient should already have received instructions from a nurse concerning catheter care and pump operation.

Appointments for the pharmacy teaching sessions are normally made 24 h in advance. An infusion therapy nurse or the patient may contact the Station 19 pharmacy to arrange for the time. The teaching session is attended by whomever will be performing the medication preparation. In most instances, the patient will prepare his own medication. However, a family member may elect to prepare the medication. Family members are encouraged both to attend and participate in the teaching sessions for support and reinforcement.

The development of the teaching plan followed basic steps of defining and listing patient objectives, teaching content, teaching action, and outcome criteria. The session begins with the pharmacist confirming the chemotherapy ordered for the patient. The patient should know the name of the drug, the dose, and the number of doses that need to be prepared. The pharmacist introduces the instruction booklet to the patient, explaining each section. All aspects of medication preparation are covered in the booklet, including sections of definitions of basic terminology, steps required to obtain necessary drugs and supplies, how to store drugs both before and after preparation, what aseptic technique is, a review of the parts of a syringe and needle, how to measure drugs with a syringe, and a specific step-by-step instruction sheet for the patient.

The pharmacist will assemble all needed supplies for a demonstration and will then prepare the first dose of medication, carefully explaining each step to the patient and allowing time for the patient to ask questions. The patient then prepares the remaining doses directly under the supervision of the pharmacist. This instils confidence in the patient and allows the patient to develop the skills necessary to prepare the medications safely and accurately. The pharmacist evaluates the technique of the patient and advises the patient further when additional training is required.

When the patient completes the preparation of his doses, the pharmacist summarizes the procedures and reinforces major points or areas in which the patient may have problems. If the pharmacist determines that the

patient is a poor candidate for the self-preparation procedure, he will recommend that the patient seek out the nearest hospital pharmacist or his personal physician to assist him with the procedure. At the end of the teaching session, the pharmacist provides his name and the telephone number of the Station 19 pharmacy in case the patient has any problems or questions concerning the procedure after he leaves the institution. Finally, the Patient Teaching Check List is completed by the pharmacist to be retained in the pharmacy as a permanent record of the teaching session.

There have been approximately 75 patients taught self-medication preparation by our pharmacists. The time required for each teaching session has ranged from 30 minutes to 2½ hours, with an average of 1 hour. Patients who had prior experience working with syringes and needles or who demonstrated a superior manual dexterity required the least amount of teaching. The majority of patients required at least 60 minutes of teaching to fully understand and feel comfortable using the syringe and needle. The patients who lacked some confidence or who were being taught through an interpreter required the most teaching.

The outcome of our teaching efforts has resulted in no major problems developing with these patients preparing their own medication. Occasionally, a patient has called the Station 19 pharmacy several weeks after the teaching session to have their memory refreshed concerning a certain aspect of a procedure.

The teaching plan now includes the one-to-one session with the patient by the pharmacist, following the guidelines in the patient instruction booklet. The possibility of producing a videotape in English and Spanish to demonstrate the procedure is under consideration. Such a videotape would reduce the total amount of time spent by the pharmacist in the teaching session, although it would not replace the one-to-one interaction that has proven so successful with us.

Due to the success of this programme we feel that the basic format of the teaching plan can become a model for future applications. There is a number of other small volume portable infusion pumps that may be utilized in our institution and the development of a home intravenous hyperalimentation programme is underway.

Because of the distinct advantages of out-patient therapy over in-patient therapy and the greater convenience offered to the patient by use of the portable infusion pump, we anticipate expansion of the programme at our institution. Pharmacy involvement will continue to be an integral part of any expansion, with the patient becoming an even more active participant in his own therapy.

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Patient Instruction Booklet Medication Preparation for Small Volume Infusion Pump

THE UNIVERSITY OF TEXAS
M. D. Anderson Hospital and Tumor Institute at Houston
Department of Pharmacy

1

INTRODUCTION

The following information is provided so that you may learn how to prepare your own medication for your portable infusion pump. The pharmacist will be instructing you on the following major points:

1 DEFINITIONS
2 SUPPLIES
3 STORAGE OF DRUGS AND SYRINGES
4 ASEPTIC TECHNIQUE
5 MEASURING DRUGS WITH A SYRINGE
6 STEP-BY-STEP PREPARATION OF YOUR CHEMOTHERAPY

If you have any questions after you leave the institution, the pharmacist may be reached at the following number:

STATION 19 PHARMACY
(713) 792-2367
Hours: Monday through Friday, 9 AM - 9 PM

Pharmacist:_____R.Ph.

2

DEFINITIONS

You will need to understand the following words in order to perform this procedure:

1. *milliliter (ml)* and/or *cubic centimeter (cc)* = the unit of measurement for measuring the volume of drug solutions in syringes. Syringes usually have "cc" markings, but "ml" is used for writing purposes.

2. *0.9% Sodium Chloride* and/or *Normal Saline* = sterile solution used to fill your syringes.

3. *reconstitution syringes* = term used to describe all the syringes that will be used to mix your medications and obtain the correct dose. It is NOT the syringes that will be placed into the infusion pump. The syringes which are inserted into the pump are called LUER LOCK syringes. The caps that can be used to cover the ends of the syringes are called LUER CAPS.

SUPPLIES

A. Storage of Supplies:

Store all supplies together in the area where you will be mixing the medication. For safety purposes, keep all supplies out of the reach of children. Avoid excessive heat or cold. All supplies used are disposable.

B. Obtaining Supplies:

Be sure that you have all the necessary supplies before leaving the institution.

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1. Obtain prescriptions from your physician for the chemotherapy drugs and one 250ml bag of Normal Saline for each chemotherapy course.

2. Additional supplies should be obtained from Clinic Supplies:

_____ Luer Lock syringes
_____ Reconstitution syringes
_____ Luer caps
_____ Sterile alcohol pads
_____ Needles

STORAGE OF DRUGS AND SYRINGES

Before mixing drugs:

_____ Store at Room Temperature
_____ Store in Refrigerator
_____ Store in Freezer
_____ Protect from Light

Other_____

After preparing drugs in syringes:

_____ Store at Room Temperature
_____ Store in Refrigerator
_____ Store in Freezer
_____ Protect from Light

Other _____

4

ASEPTIC TECHNIQUE

"Aseptic Technique" is a term used to describe correct procedures that should be used in preparing the medications in order to avoid contamination with germs or bacteria. If germs or bacteria come in contact with the drug, the needle, or certain parts of the syringe, then contamination occurs. A frequent cause of contamination is through touching objects with the fingers. Contamination could possibly lead to infection in the body.

STEP 1. Wash hands thoroughly with soap and water. This will remove some bacteria from the hands but thousands will still remain. Therefore, it is extremely important in the following procedures that you do not touch the needle or syringe plunger (see syringe diagram) with your hands.

STEP 2. Clean working area thoroughly with alcohol gauze pads.

STEP 3. Remove tops of drug vials. Wipe rubber tops with alcohol pad. Also wipe rubber injection portals of intravenous Normal Saline bags.

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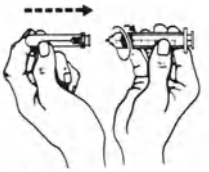
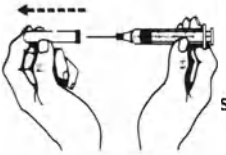
STEP 4. Preparation of syringe and needle using aseptic technique:

Disposable needles and syringes are supplied in individual sterile packages. Remove each syringe and needle from its protective package and attach the needle to the syringe as follows:

A. Insert tip of syringe into needle hub and turn syringe clockwise until tight. Remember, do NOT touch the hub of the needle. Since the hub of the needle will eventually come in contact with the drug, contamination with bacteria could result.



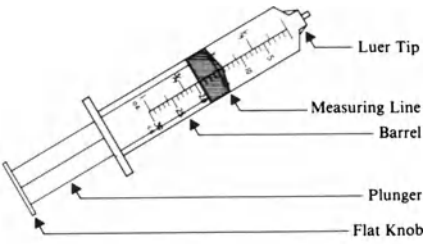
B. Leave needle guard in place until ready to use. To remove guard, pull straight off. Do not twist.



C. When pulling back the plunger of the syringe, the fingers should not come in contact with any part of the plunger except the flat knob at the end. The barrel of the syringe should be held in one hand as illustrated. Contamination of the medication could occur if the plunger is touched with the fingers.

5

Parts of a Syringe



Parts of a Needle

Needle with protective cover (guard)

Needle without protective cover

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MEASURING DRUGS WITH A SYRINGE

STEP 1. In order to withdraw a solution from the vial, inject an amount of air equal to the amount of solution to be withdrawn. By injecting air into the vial, pressure within the vial is increased, thus making it easier to withdraw the drug.

STEP 2. After injecting the air into the vial, turn the vial upside down and withdraw the solution. The tip of the needle should be positioned as close as possible to the rubber top of the vial to avoid getting air into the syringe.

STEP 3. A common problem in the filling of a syringe is that air may also be withdrawn from the vial into the syringe. The presence of these air bubbles or air spaces in the syringe will prevent accurate measurement of the solution.

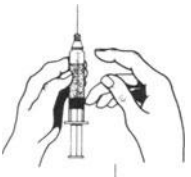
To remove air or air bubbles from the syringe:

A. Hold the syringe in a vertical position so that the needle is pointing upward.

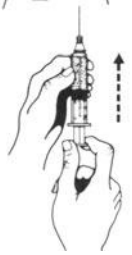
B. Pull the plunger back a short distance so more air enters the syringe.

8

C. Gently tap the barrel of the syringe with the fingers so that air bubbles clinging to the side are freed and float to the top of the solution.



D. Hold syringe in a vertical position and expel all the air in the syringe by slowly pushing the plunger in until the solution is at the tip of the barrel.



E. Read the volume of solution by aligning the measuring line of the plunger with the graduation marks on the barrel of the syringe.

F. If the volume read is too much or too little, insert the needle back into the vial and adjust the plunger again until the right volume is obtained.

G. When withdrawing solutions from plastic intravenous fluid bags, it is unnecessary to follow certain of the above procedures. Plastic bags, unlike glass vials, are flexible and will automatically collapse as solution is withdrawn. Therefore, when using plastic bags, do not inject air or any medication into the bag. Always **pull back** on the syringe plunger when withdrawing solution from the bag.

9

STEP-BY-STEP PREPARATION OF YOUR CHEMOTHERAPY

DRUG AND DOSE TO BE INFUSED IN EACH SYRINGE: _____

SYRINGES TO BE PREPARED _____

STEP 1.	Prepare _____ syringe(s) Normal Saline 10ml to be used as a manual flush.
STEP 2.	FOR ONE DRUG: Add _____ ml of Normal Saline to one_____mg vial of _____ _____. Shake well to dissolve all drug. The resulting DRUG CONCENTRATION is _____ mg/ml. Mix _____ vial(s).
	FOR TWO DRUGS: Add _____ ml of Normal Saline to one_____mg vial of _____. Shake well to dissolve all drug. The resulting DRUG CONCENTRATION is _____ mg/ml. Mix _____ vial(s).
STEP 3.	FOR ONE DRUG: Withdraw _____ ml into a reconstitution syringe from the vial(s) that you prepared in STEP 2. This equals _____ mg TOTAL DOSE, or your dose per syringe.
	FOR TWO DRUGS: Withdraw _____ ml into a reconstitution syringe from the vial(s) that you prepared in STEP 2. This equals _____ mg TOTAL DOSE, or your dose per syringe.
STEP 4.	Inject the contents of the reconstitution syringe obtained from STEP 3 into a Luer Lock syringe.

10

STEP 5.	ADDITIONAL DRUG TO BE ADDED (Omit if not needed): Add _____ ml (_____ mg) of _____ _____ to the Luer Lock syringe containing the drug(s) (from STEP 4).
STEP 6.	Fill the Luer Lock syringe from Step 4 or Step 5 further to a total volume of _____ ml with Normal Saline.
STEP 7.	Remove all air and air bubbles from the syringe and place a luer cap onto the "luer tip" of the syringe. (Note: If the syringe is to be frozen, do not remove all the air prior to freezing. Leave approximately 5ml of air space in the syringe to allow room for expansion. Remove frozen syringe from freezer to thaw out six hours before infusion. After the syringe is thawed, then remove all air prior to insertion into the pump.)
STEP 8.	Label each syringe with the name and the amount of drug.
STEP 9.	After preparing all syringes needed for your dose of chemotherapy discard all used needles, syringes, drug, etc.

11

PATIENT TEACHING CHECKLIST

(to be retained by pharmacist)

Patient Name _____

Patient # _____

Patient Address _____

_____

_____

Home Phone # _____

DRUG THERAPY REGIMEN _____

_____

The following information has been explained to the patient:

1. DEFINITIONS
2. SUPPLIES
3. STORAGE OF DRUGS AND SYRINGES
4. ASEPTIC TECHNIQUE
5. MEASURING DRUGS WITH A SYRINGE
6. STEP-BY-STEP PREPARATION OF YOUR CHEMOTHERAPY

Pharmacist assessment of patient understanding:

COMMENTS: _____

_____

Date _____ R.Ph. _____

Time taken for session _____

2

The current therapeutic role of continuous insulin delivery systems

J. Birtwell

INTRODUCTION

I have carefully selected the title of this review because, in my view, the current therapeutic role of continuous insulin infusion, by whatever route, should be limited. My reasons for this I trust, will become clear. Although my review must be brief and, therefore, incomplete, I must touch firstly on the background to the impetus for the development of continous insulin infusion systems.

Whilst the availability of insulin replacement therapy has been acutely life preserving for insulin-dependent diabetics, it is clear that the disease has been, for many, transformed into a chronic debilitating illness in terms of the long-term complications of retinopathy, nephropathy, neuropathy and cardiovascular disease. That these complications result from poor control of blood glucose, and other derangements of the metabolism of diabetics, has long been postulated. The lack of readily available methods for monitoring blood glucose, together with a therapeutic attitude biased more towards ease of treatment than good metabolic control, made it virtually impossible to test this hypothesis. The weight of evidence in longitudinal studies of complications in diabetic patients (Pirart, 1978) together with the results of animal studies (Crofford, 1975), clearly point in this direction.

Greater knowledge of the inadequate control of excursions in blood glucose and other parameters on an hour by hour, or day by day basis (Service *et al.*, 1970) has highlighted the deficiencies in using non-optimized, once or twice daily subcutaneous insulin replacement therapy. This knowledge has been increased with the availability of frequent and easy blood glucose estimations (Sönksen *et al.*, 1978; Walford *et al.*, 1978). Whilst demonstrating the possibility of improving blood glucose control by increased patient compliance, this facility has also demonstrated the difficulty in restoring the control of blood glucose in a number of insulin-dependent diabetics, particularly in those without evidence of continuing endogenous insulin secretory capacity. Small amounts of endogenous insulin can improve metabolic control considerably, despite inadequate exogenous insulin therapy. This knowledge has led to an increasing interest in improving the metabolic status of insulin-dependent diabetics.

The normal pattern of insulin secretion into the hepatic portal vein is of basal secretion at approximately 1 u/h, (half of which is taken up by the liver) primarily affecting hepatic glucose metabolism between meals and overnight with acute rises in secretion to above 10 u/h at mealtimes, causing both increased peripheral glucose uptake and decreased hepatic glucose production.

Approaches at obtaining a pattern similar to this in insulin-dependent diabetes can be divided into:

(1) Optimization of subcutaneous bolus insulin therapy.
(2) Electro-mechanical insulin infusion systems
(3) Pancreatic or islet cell transplantation by replacement of the failed organ.

GENERAL CONSIDERATIONS

The basic requirements for continuous insulin delivery are simply a reservoir for the insulin to be administered and a pumping system with the ability to deliver a basal level infusion and appropriate boost doses for meals. Refinements in this system are in the flexibility to pre-programme these levels separately. Further refinement involves provision of a glucose sensor feeding back to the infusion system to control the rate of infusion – "closing the loop". Therefore continuous insulin infusion systems can be divided into open-loop – without glucose sensing feedback – and closed-loop systems.

CLOSED-LOOP SYSTEMS

The closed-loop system presently available is a computer-controlled insulin and/or glucose delivery system using pre-defined algorithms and depen-

dent on virtually continuous glucose sensing by sampling from a peripheral vein. It has sometimes been called the artificial pancreas. The commercial system available is that developed by Miles Laboratories – The BIO-STATOR.

This system is effective in the restoration of blood glucose and other metabolites close to normality with appropriate algorithms. There are, however, considerable limitations to its use. See summary in Table 2.1.

Table 2.1 Closed-loop insulin infusion – Biostator

Description	Computer controlled insulin and/or glucose delivery based on preprogrammed algorithms and dependent on virtually continuous glucose sensing by sampling from a peripheral vein.
Drawbacks	size, cost, route (peripheral i.v.)
Applications	short term (days)
Research	e.g. glucose clamping estimations of insulin requirements
Patient treatment	feasible for surgery and labour

OPEN-LOOP SYSTEMS

Open-loop insulin delivery depends on pre-programmable insulin delivery with patient (or doctor) monitoring of blood glucose for appropriate dosage adjustment and ensuring continuing function of the system. The systems have been applied via subcutaneous, intraperitoneal and intravenous routes. Intramuscular infusion has also been used but is not considered of long-term value.

The principle of administration is the same for all routes but because of the differing pharmacokinetics of insulin for each route employed, different peripheral and hepatic insulin responses and blood glucose responses will be obtained. See summary in Table 2.2.

SUBCUTANEOUS ROUTE

The absorption of insulin from a subcutaneous depot or infusion is delayed by about 15 to 30 minutes before appreciable increase in peripheral insulin levels can be measured and, depending on the site of injection, peak levels may be delayed until 90 to 240 minutes. Studies using subcutaneous infusion of insulin either by Butterfly needle (Abbot Laboratories) or implanted catheter have usually used 30–40% of daily insulin dosage basally and the remainder divided between meal boosts, with a higher boost at breakfast time. Bolus doses or rapidly infused boost doses before meals

Table 2.2 Open-loop insulin infusion

Requirements		
Preprogrammeable insulin delivery		
Reservoir and pump		
Preferably variable basal rate	and boost rate	Patient 'feedback' by self-monitoring
Routes		
Subcutaneous		
Intraperitoneal		
Intravenous		
(Intramuscular)		

provide better control of prandial blood glucose excursion than square wave infusion. The steady-state depot during subcutaneous insulin infusion is probably about twice the basal hourly infusion rate but there is probably still considerable individual variation in this, as with the rate of absorbtion of a subcutaneous bolus injection.

The realisation that bolus dose pre-prandial therapy seems to be best via the subcutaneous route, together with the available absorption profiles for soluble insulin have led to questions about the necessity of the continuous element of subcutaneous insulin infusion, particularly diurnally. This will be discussed later.

INTRAPERITONEAL ROUTE

This route of continuous insulin administration has been the least studied, but it is potentially the most interesting physiological route of administration. Studies by Schade, Eaton and co-workers at the University of New Mexico, (Schade *et al.*, 1980) have demonstrated an apparently large degree of uptake of intraperitoneally delivered insulin by the portal system. The absorption by this route is apparently rapid and normalization of blood glucose response to a meal can be obtained without significant peripheral hyperinsulinaemia. Other workers have not been as successful with intraperitoneal insulin infusion, obtaining little benefit over subcutaneous insulin. The positioning of the catheter may be paramount in this context for portal uptake of infused insulin.

INTRAVENOUS ROUTE

Many workers have demonstrated near normalization of plasma glucose profiles with intravenous insulin infusion, over short periods of time (several days), in hospital using basal insulin infusion with simple square

wave increased infusion rates, or more complicated pulse delivery for meals. Bolus therapy is of course inappropriate because of the short half-life of insulin in the blood stream. There is no doubt that near normalization of plasma glucose can be obtained using continuous intravenous insulin infusion at the expense of considerable peripheral hyperinsulinaemia (as with subcutaneous infusion).

ACHIEVEMENTS AND DRAWBACKS

Short-term studies in hospital using all routes have shown restoration to near normality of blood glucose and other deranged metabolic parameters such as blood lipids, ketone bodies and other hormones, e.g. glucagon, growth hormone.

Longer-term studies on a continuous ambulatory basis have been concentrated on subcutaneous regimens. This is probably because this route is considered the safest, is the most accessible and resembles present conventional therapy most closely. Local complications and infections have been reported but are thought to be rare, provided the site is changed frequently with care and cleanliness and highly purified insulin is used. These studies have demonstrated continued improvement in mean blood glucose without necessarily complete restoration to normality, and improvement in other parameters of blood glucose control, e.g. reduction of glycosylated M haemoglobin to near normal range (Pickup *et al.*, 1979). Functional, as opposed to structural, improvements have been demonstrated, e.g. reduced glomerular filtration rate (usually abnormally high in poorly controlled diabetes), reduced microscopic proteinuria (Viberti *et al.*, 1979) possible improvement in capillary leakage in retinopathy (Steno Group, 1982), and improvement in nerve function (Pietri *et al.*, 1980). Additionally pristine control of blood glucose during diabetic pregnancy has been obtained using CSII. This route has been found not to be useful for treatment of so-called 'brittle' diabetes (Pickup *et al.*, 1981).

Long-term studies using open-loop intraperitoneal infusion (for greater than 5 days) have only been reported in individual cases, but further studies are in progress and this route must remain the most exciting for the future; providing sepsis can be shown to be avoidable.

There are some reports of long-term use of open-loop continuous intravenous insulin infusion using a catheter implanted in the subclavian vein via a subcutaneous tunnel, as is commonly used for long-term parenteral nutrition. This modification was necessary because of peripheral venous thrombophlebitis and the risk of sepsis. Many workers feel that potential risks of septicaemia and thromboembolism contraindicate the use of this route in the long term. Patient studies for up to one year have been reported (Irsigler and Kritz, 1979) to have shown good control of blood glucose without septicaemic problems. There have been problems of

insulin precipitation in catheters and of mechanical pump failure. The problem of immediate hyper- or hypoinsulinaemia is more acute with intravenous delivery and for this reason very careful monitoring is particularly necessary in ketosis-prone patients. My experience with this route has been one of recurrent septicaemia despite subcutaneous tunnelling.

CRITICISMS

Most of the initial studies using any of these infusion routes fail to compare treatment with what might be defined as optimized subcutaneous bolus injection therapy using soluble insulin 3 or 4 times a day and a modified insulin to provide basal insulin delivery overnight. Patient groups were not clearly defined in terms of residual insulin secretory capacity. Recent studies in the short term in hospital (Rizza *et al.*, 1980) comparing subcutaneous insulin infusion, subcutaneous bolus therapy and BIOSTATOR controlled blood glucose demonstrated no significant differences in control of blood glucose in insulin-dependent diabetes without residual insulin secretory capacity. Several long-term studies in a similar group of patients comparing subcutaneous insulin infusion with multiple daily injection therapy have shown no significant differences in control of blood glucose. (Schiffrin and Belmonte, 1982a; Reeves *et al.*, 1982). Other studies have demonstrated better control using CSII compared to multiple daily injections (Home *et al.*, 1982). It appears that frequent alterations of insulin dosage are necessary on the basis of frequent blood glucose estimations in order to obtain optimum control using either method (Schiffrin and Belmonte, 1982b). It may be, apart from patient preference, that in the majority of insulin-dependent diabetics continuous subcutaneous infusion may be no more efficacious than multiple bolus injection therapy.

FURTHER DEVELOPMENTS

In terms of infusion pumps mainly aimed at subcutaneous insulin delivery, refinements with regard to increased reliability, more fail-safe mechanisms, reduction in size, increased progammability and ease of use by increasing the time interval of recharging the reservoir are continuing. Some of these pumps are now available. Certainly these should be more cosmetically acceptable and perhaps more efficient, but only studies will tell if they hold other significant advantages. They are certainly more expensive.

The development of an implantable closed-loop system is dependent on the development of a sufficiently small, reliable glucose sensor. This is not presently available. Considerable progress has been made in the design and development of rechargeable externally programmable implantable open-loop systems. This has required great emphasis on reliability and bio-

compatability. A variety of measures have been taken to attempt to stabilize insulin in higher concentrations at body temperature and to prevent precipitation and fibrillation. This has usually included the addition of other materials, e.g. calcium ions in low concentrations. Individual patients have been supplied with implanted pumps but only on an experimental basis and not totally satisfactorily. Undoubtedly this work will progress but the cost is likely to be prohibitive for widespread use.

CURRENT THERAPEUTIC USES

Here I distinguish between experimental use and practical application.

It is quite clear that studies so far performed have been in the main with well-motivated, partly self-selecting patients who are compliant with the rigours of self-monitoring of blood glucose and are prepared to adhere to a fairly strict diet and exercise programme. It is to be hoped that with improved diabetic education, these patients will become the majority of insulin-dependent diabetics but at present this is not the case. Some authors even suggest that these attributes must be prerequisities for patient suitability to use pump therapy (meaning subcutaneous infusion). In my view this is probably correct at the present stage of development. Without extremely careful monitoring and patient compliance they cannot be expected to be efficient and could well be dangerous.

Goals of therapy have to be clearly defined. The establishment of the possible benefits in terms of reduction or abolition of diabetic complications and the degree of control of blood glucose obtained is essentially long-term work. The possible risks of persistent hyperinsulinaemia and long-term systemic or local complications of the routes employed have to be studied. In addition, present systems may well improve considerably in the not too distant future.

Certainly the means of improving the lot of the insulin-dependent diabetic in terms of control of blood glucose and therefore possible long-term complications are available but may not completely depend on continuous insulin infusion in its present form. As we have seen, it may be possible to achieve similar results with multiple subcutaneous injection therapy. In my opinion the therapeutic role of continuous insulin infusion is at present still as an experimental technique requiring further evaluation and improvement. I have summarised my indications for non-implanted open-loop insulin infusion in Table 2.3.

THE FUTURE

The mounting interest (and urgency) in the improvement in the metabolic status of insulin-dependent diabetics can only be to their benefit. The method by which this is ultimately achieved may be by continuous insulin

infusion using implantable infusion pumps, most probably via the intraperitoneal route, or in the development of islet cell or segmental pancreatic transplantation. Many more studies are necessary to assess precisely what is necessary to prevent the debilitating late complications of diabetes. The future of continuous insulin infusion is shown in Table 2.4.

Table 2.3 Therapeutic role of open-loop continuous insulin infusion

Intravenous route
Short term (days)
Diabetic ketoacidosis Labour Surgery Concurrent illness
Long term (limited) experimental "true brittle" diabetics
Intraperitoneal route ? Peritoneal dialysis "True brittle" diabetics
Subcutaneous route (1) "Patient preferences" – in defined groups (2) Long-term studies with regard to complications and hierarchy of metabolic control e.g. pregnancy/prepregnancy preproliferative retinopathy painful acute neuropathy

Table 2.4 The future of continuous insulin infusion

Intravenous route	– implantable systems
	– with glucose sensor
Intraperitoneal route	– as above
Subcutaneous may be superseded by (1) The above (2) Further developments in insulin modification, increasing predictability of absorption and/or duration or action	

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3

Care of the home parenteral nutrition patient

S.R. Wood

INTRODUCTION

Better understanding of nutritional requirements, improved methods of maintaining venous access and the development of safe nutritional products have led to long-term parenteral nutrition becoming a realistic therapy for those who have lost the ability to remain healthy by absorbing nutrients through the gastrointestinal tract. This loss of function may result from a chronic, debilitating illness such as Crohn's disease or a sudden, catastrophic event, e.g. mesenteric infarction. Some patients have the whole gut present but in a severely diseased state whilst others have undergone extensive resection. If parenteral nutrition needs to continue for many months or years it is usual for the patient to leave hospital and continue the therapy at home.

Individuals performing home parenteral nutrition must be provided not only with a regimen which meets their nutritional and clinical needs but also with a system of administration which is rational for home application. This may not be the most sophisticated available for hospital use, but because it is appropriate for the patient's physical abilities and social background, due to its acceptability, it will be well managed. It is likely that the therapy will be performed in a location isolated from immediate expert intervention, except that available by telephone, therefore not only must training be thorough but equipment selected for use must be completely reliable.

The doctor , nurse and pharmacist need to be aware of certain aspects of

the patient's life which may affect his ability to perform the therapy successfully. These are: the nature of the underlying condition, the patient's physical abilities and emotional response, relationships within the family, and the home situation. Support from health-care professionals close to the patient's home should also be considered and liaison between hospital staff and community personnel developed before the patient is discharged from hospital.

THE UNDERLYING CONDITION

Those who require home parenteral nutrition have undergone a profound physiological change. In addition to nutritional problems, other symptons, which affect the quality of life, may arise from the underlying disease. The short-gut syndrome, for example, is a common indication for longterm therapy. This can cause bloating and diarrhoea if there is continuity of the gastrointestinal tract or large, fluid effluent into a bag, if a stoma has been formed. The stomatherapist plays an important part in making the life of the latter more comfortable, by providing advice on the selection of large-capacity bags and on methods of securing the appliance to prevent the weight of the fluid pulling it away from the skin. Sometimes bowel problems are so severe that, unless the whereabouts of public lavatories are known, the patient feels insecure when out of the home.

THE PATIENT'S PHYSICAL ABILITIES AND EMOTIONAL RESPONSE

Manual dexterity and the emotional capacity to cope with parenteral nutrition at home are more important attributes than intelligence. Whilst it is possible to work and enjoy many activities, the patient must adapt to a changed pattern of daily living. This will include performing potentially dangerous procedures and infusing life-sustaining nutrients directly into a vein.

Emotional preparation begins immediately the decision is taken to institute home parenteral nutrition. Whilst everyone who comes into contact with the patient will influence attitudes it is important that one key person is identified who will take responsibility for the teaching programme. This will usually be a nurse, whose grade will depend on the nursing structure within the hospital. It is particularly important that this key person communicates fully to doctors and other nurses developments in the patient's emotional and physical skills, to achieve a cohesive approach.

Few people understand the working of their own body so early teaching will focus on basic physiology and metabolism, as related to parenteral nutrition, using the patient's symptons and procedures such as urine testing as illustrations. The language chosen should be simple and clear, and small amounts of information given at a time. It is helpful to provide an instruc-

tion manual, such as the one used by St. Mark's, for the patient to read at leisure.

The patient has to learn how to manage the infusion, look after the catheter and how to prevent and treat possible complications.

Management of the infusion

In the United Kingdom parenteral nutrition in the home is generally administered as an overnight infusion of 2½–3 litres of nutrient solution. During the day the intravenous catheter is filled with heparinized saline, to maintain patency, and closed by a Luer locking cap.

The frequently used hospital system of infusing nutrients from more than one container simultaneously is unsuitable because of the need for changes of container during the night. To overcome this problem patients are provided with a single, collapsable non-vented bag containing amino acids, glucose, electrolytes and trace elements. Vitamins are injected into the bag by the patient immediately before infusion and the bag is then covered to prevent their degradation by light. Fat emulsion is given separately at a rate of 125 ml/hour; half litre infusions are administered at least twice weekly to prevent essential fatty acid deficiency. In most hospitals the bags of nutrient solution are filled under laminar flow facilities and collected by, or sent to the patient, once or twice a week, depending on the storage space in their refrigerator.

To provide sufficient calories in a tolerable fluid load the bags usually contain a high concentration of glucose, therefore accurate flow control is important. It is vital to have a reliable, volumetric infusion pump with an alarm system which will alert the patient should a problem, e.g. catheter kinking, occur whilst he is sleeping. Such a pump is the Kontron 5000b which has the advantage of requiring a giving set which will allow gravity flow when released from the pump. The giving set can therefore be primed and flow maintained by gravity until the patient retires to bed, when the set is clipped into the pump which is kept at the bedside. This is especially important if the patient lives alone and must travel up and downstairs unaided.

The rate of infusion will depend on fluid and glucose tolerance. Some patients pass large amounts of urine during the night, which disturbs sleep, whilst others are unaffected. Generally the infusion will be given over 10–12 hours, requiring a rate of 250–300 ml/hour. To prevent reactive hypoglycaemia when stopping the infusion the rate should be reduced to 50 ml/hour for the last 30–60 minutes. Patients vary in the length of 'tapering' time required, and this should be evaluated during the training programme.

Practical teaching of procedures should not begin until the nurse is satisfied that the patient can achieve a sufficient span of concentration.

Frequently patients receiving parenteral nutrition look very healthy whilst still in the early stages of recovery from major illness. Starting practical teaching too soon leads to slow learning and frustration.

One of the first procedures to be taught, because it is so simple, is testing the urine for glucose in the morning and evening. A small amount of glycosuria, ½–1%, is acceptable in the morning following the large glucose infusion during the night, but this should clear by evening. Glucose in the evening specimen may be a sign of sepsis.

Before learning how to connect and disconnect the infusion and inject heparinized saline, the patient should understand the principle of asepsis and feel confident handling the necessary equipment. Gloves, syringes, needles and glass ampoules cause most problems.

The simplest method of practical teaching is for the nurse and patient to sit side by side in front of the working surface, performing the various techniques together until the patient is skilled enough to take over completely. This will require two, 1 hour sessions, daily for 1–3 weeks. During these sessions the experienced nurse will be alert to particular difficulties encountered by the patient and adapt procedures or substitute equipment to overcome them. For example a proprietary preparation of heparinized saline, Hepsal (Weddel Pharmaceuticals Ltd.), drawn into a syringe through a filter straw (Braun FS5005) reduces the number of manipulations required to prepare the injection and the risk of microbial contamination, and prevents the injection of glass fragments into the circulation, whilst simplifying the procedure.

Catheter care

As nutrient solutions are hypertonic, rapid dilution with blood is required to prevent damage to the vein. The tip of the intravenous catheter will therefore lie in the superior vena cava or the right atrium, having been introduced into the cephalic or subclavian vein. To facilitate self-care and isolate the skin entry site from that into the vein, the catheter will be tunnelled through the subcutaneous tissues to emerge at a convenient site on the chest or upper abdomen. This area should be marked with the patient sitting upright before the catheter is inserted. With the introduction of silicone rubber catheters it has become possible to retain one catheter in position for several years. Some of these catheters, for example the Hickman (Evergreen Medical Products, USA) and the Vygon 2191-17, incorporate a small cuff of Dacron felt which is positioned just inside the skin tunnel. The growth of fibrous tissue into this cuff fixes the catheter and is said to prevent ascending infection; however, scrupulous care must be maintained. The skin at the catheter entry site must be cleaned regularly with a suitable antiseptic, such as chlorhexidine 0.5% in 70% spirit, povidone iodine applied, (the dry powder spray, 'Disadine' D.P. Stuart

Pharmaceuticals Ltd., is easy for the patient to handle) and a sterile occlusive dressing applied. This skin care and dressing change should be performed weekly or if the dressing becomes loose or wet.

Potential problems

One of the major fears expressed by patients in the early stages of training is that dangerous problems, with which they cannot cope, will occur at home. A description of possible complications and methods of prevention and dealing with them, should they occur, relieves some of these fears. In addition, there must be 24 hour access to expert help. As such expert advice may not be available from the hospital during the night it may be necessary for the patient to have the home telephone number of the nurse, doctor and pharmacist who are most involved in his care.

Many patients receiving home parenteral nutrition are highly motivated in their self-care and complications are rare. Other patients who are unable to make the necessary emotional adjustment have difficulty maintaining satisfactory techniques and experience many problems. In addition to infection and metabolic disturbance, mechanical problems may develop related to the catheter and infusion system. Air embolism is one of the most serious of these. This will occur if air is allowed to enter the infusion system at any point. Non-vented bags, Luer locks on the giving set and proper taping of connections to prevent traction are important safeguards. Negative interthoracic pressure during inspiration may draw air into the circulation during changing of the giving set unless the catheter is first clamped. However, frequent clamping may fracture the catheter, therefore a short extension tube – such as Vygon 1155.01 – may be attached to the catheter for clamping purposes, the tube being changed weekly. The patient is instructed never to be without the clamp immediately to hand, in case of accidental disconnections.

Catheter blockage is an occasional problem, even with good technique for injecting Hepsal. The patient should be taught how to clear obstructions mechanically using a 1 ml syringe filled with sodium chloride. If this fails Urokinase 5000 Plough units in 3 ml sodium chloride instilled into the catheter, at the hospital, is often successful.

FAMILY RELATIONSHIPS AND SOCIAL CONDITIONS

Home parenteral nutrition affects all the people with whom the patient lives. To foster helpful, supportive attitudes in the family members, it is essential to understand their view of the therapy. Important information can be obtained during the training programme from the patient, the family and from home visits. Help from the medical social worker is very valuable in this respect.

The therapy can appear frightening, unless it is properly understood, and its effects can bring about changes in family relationships. For example, those patients who have suffered a chronic illness often become dependent on other family members. Suddenly gaining good health, due to being well-nourished, removes this dependence, causing resentment and anger in the family and a need to impose restrictions on the patient's rehabilitation.

Other families are very enthusiastic and, whilst this is supportive for the patient, can result in parenteral nutrition becoming their over-riding interest, rather than one part of daily life which needs careful attention. The nurse needs to be sensitive to these relationships when deciding how much practical involvement in therapy family members should have.

Patients being trained to perform home parenteral nutrition enjoy a special status in the hospital in that thay have an independence not experienced by other patients. However, when discharged home that status will change to one of a disabled person within a 'normal' family. This is especially obvious if the patient is unable to eat and cannot take an active part in mealtimes. The emotional discomfort this generates can only be overcome when the patient is able to accept himself as a valuable individual even though he is different from other people. The nurse should encourage the patient and his family to express their feelings openly and provide clear, honest explanations. The guidance of a psychiatrist is invaluable in this respect.

Poor social conditions do not preclude safe parenteral nutrition providing the patient has been well prepared. Aseptic procedures should be performed in a room where there will be no disturbance from other people and pets, but not the bathroom or kitchen. This is usually simple to arrange as skilled patients take only approximately 15 minutes to perform each procedure. A sheet of glass, stainless steel or some other material which will not scratch is used as a working surface and there must be adequate electrical points for the infusion pump.

The necessary equipment for home parenteral nutrition takes up considerable space, and patients are encouraged to store this in a spare room or cupboard where it is out of sight and not a constant reminder of the therapy.

LOCAL SUPPORT

The general practitioner will probably not have encountered parenteral nutrition in the home setting and he should be informed of the forthcoming situation before the patient is discharged from hospital. The health visitor and social worker also play important roles by providing regular contact close to the patient's home and help to prevent feelings of isolation. To ensure complete understanding between the patient, the hospital and

community staff, the nurse who has been responsible for the teaching programme should meet the general practitioner, the health visitor and the social worker within the patient's home, immediately the patient is discharged from hospital.

Home parenteral nutrition is a life-sustaining therapy, however it can only be successful with considerable organization, careful training, selection of appropriate equipment and attention to the many psychosocial aspects.

4

Is providing the regimen sufficient?

H. Doery

INTRODUCTION

Maximum benefit from drug treatment will be obtained when the best available product has been selected and administered in the most suitable manner, at appropriate intervals, for the correct duration. In the hospital this process is controlled by professional staff; however, if treatment is to be continued at home, the patient must assume this responsibility. Successful transition from hospital to home therapy can only be achieved when the consequences of patient self-care are fully understood, especially if the therapy is to continue for long periods. Parenteral nutrition is a particular example where treatment may be continued at home and in which considerable care is needed to ensure that it is carried out effectively and safely.

The customary role of the pharmacist is advising the patient on the correct use and storage of his drug treatment, the expected side-effects and observable changes which may occur as a result of this, as well as confirming his familiarity with the method of administration. However, the need for parenteral nutrition at home may also involve the pharmacist in the selection of the most appropriate form in which the regimen should be provided. The effectiveness with which these roles are carried out depends on good communication between doctor, nurse, pharmacist and patient. This is especially important in parenteral nutrition where the general exchange of information, appreciation of one another's problems and a co-ordination of advice to the patient, enable a return to as near normal a life as possible at home. In longterm therapy such as this, changes may occur

which make it appropriate to reconsider the treatment and its provision.

For the pharmacist involved in the support of patients on home parenteral nutrition there are three important areas under which such considerations can be made: the patient's underlying condition, administration of the therapy and the parenteral product.

The patient's underlying condition

An understanding of the patient's underlying condition which necessitated home parenteral nutrition is required, as the manner in which it affects the patient and how the patient copes with it, will influence the approach made to training and supply. If the disease state is one that is likely to recur at intervals, it may well affect the patient's ability to carry out procedures efficiently, or unaided, from time to time, or the steady progression of the disease may require changes in, or adaptions to, present equipment.

The patient will need to be advised that some drug treatment required, for perhaps recurrence of the underlying condition or isolated infections, may interact either with the therapy they are receiving, or with certain monitoring procedures, such as the possibility of cephalosporins giving a false positive reaction with certain urine testing agents.

In some special cases, the patient's condition may require adaption of usual procedures, e.g. a patient with a calcitonin secreting tumour received lower levels of calcium each day instead of the usual practice of alternate day dosage, or the inability of a patient with a urinary stoma to do urine testing for sugar (the ileal loop used to form the stoma absorbs dextrose).

Administration of the parenteral therapy

Successful administration of parenteral nutrition relies on a strict adherence to protocols laid down for the maintenance of aseptic technique in all procedures such as making additions to fluids, connection of the infusion, disconnection of the infusion and heparinization of the central line (and extension tube if one is used) and care of the catheter entry site. The pharmacist, if familiar with the requirements of the protocols, can play an important advisory role in assisting with the selection of the most suitable equipment and preparations, but to do this an awareness of the range or products available is required, e.g. the consideration of filtration devices. If an in-line filter is required, the choice will be affected by whether a particulate, or microbial filter is needed, whether the particular device is compatible with connecting equipment, whether the risk of making another connection to the line is less than the benefit gained from its inclusion, the effect of any added resistance to the flow rate or operation of the infusion control device used, and whether or not it will filter out significant levels of vitamins or micronutrients. The pharmacist should also

be aware of the need for particulate filtration of any solution drawn up from open ampoules, and that the passage of vitamin solutions frequently increases the resistance of many filters (both particulate and microbial). If the patient is to make the addition of vitamins to ready prepared solutions, the supply of equipment will be simplified if the filter chosen for drawing up heparinized saline is also suitable for filtration of vitamins.

The provision of preparations in the most suitable form is an important contribution that the pharmacist can make to the simplicity of the procedures. Examples of this are:

(1) Antibacterials. If chlorhexidine (0.5%) in spirit (70%) is required for the spraying of connections, a fine spray is essential so that even coverage is obtained and not irregular wet and dry patches. The supply of this in a refillable spray, rather than a pressure pack, means the solution can also be used for the removal of skin debris in the care of the catheter entry site. Povidone iodine is usually used in catheter site care due to its antibacterial and antifungal properties and so the provision of a dry powder spray may be welcomed instead of alternative procedures which require swabbing with a solution or the application of a greasy ointment.

(2) Heparinized saline. Heparinization of the central line after disconnection of the infusion is simplified if a ready prepared heparinized saline is provided rather than leaving the patient to make the correct dilution, and again the pharmacist should be aware of the various products available and could assist in the selection of the most appropriate one for the type of catheter used.

An appreciation on the limitations of the equipment used for administration is also relevant to the manner in which solutions are provided for the patient. The internal diameter of a fine bore catheter may well limit flow rate, especially if the infusion is run without the aid of an infusion pump. Appreciation of such factors is important when the patient needs to infuse large volumes such as 4–5 litres/day and still have time to disconnect (e.g. 16 hours infusion and 8 hours unconnected). On the other hand if an infusion pump is used, the pharmacist needs to be aware if the administration set used with that pump contains a filter chamber or not, and therefore if the final product to be infused will require refiltration if a core of rubber, or any other particulate matter, is found on visual inspection.

As well as being aware of how the infusion is performed, it is also important to understand just how the actual carrying out of the procedures affects the patient's lifestyle, as the main aim of the parenteral nutrition team is to return the patient to as near a normal life as possible. Most patients on home parenteral nutrition infuse approximately 3 litres of nutrients over 10–12 hours and infusion of such large volumes of fluid overnight can result in correspondingly large volume output, meaning that

sleep may be regularly disturbed. Supply to the patient of fluids in more than one container involves the patient in repeating the 'change of container' procedure on each occasion, which will require added time to wash, mask, and glove to enable the procedure to be carried out aseptically. An example of where the length of time involved acted as a deterrent to maintenance of the planned therapy, was a patient who rarely infused fat emulsion as it added 4 hours to the infusion time. This then resulted in the introduction of topical application of sunflower seed oil as an alternative supply of essential fatty acids.

Provision of all the separate ingredients of the regimen for the patient for aseptic compounding in the home would involve the patient in approximately ¾–1 hour of preparation time. Not only would the patient need to isolate himself from the demands of family life for that period each day, before carrying out the necessary connection procedures, but he would also need to be trained to recognize chemical and physical incompatibilities and to look for particulate contamination without all the aids available in the average pharmacy.

The parenteral product

On consideration of the objectives set out in the introduction, and the effect of the patient's underlying condition, the administration of the parenteral therapy and how it affects the patient's lifestyle, it becomes obvious that the ideal medicinal product, in this case, would be best presented ready prepared, in a single container. Before this ideal can be made a reality a number of factors need to be considered:

(1) Preparation,
(2) Compatibility and stability,
(3) Supply.

Preparation

As no single solution on the market contains the necessary ingredients in the correct levels for each patient, numerous additions will need to be made to the base solutions of amino acids and an energy source – glucose or glucose and fat. The additions will fall broadly into the categories of electrolytes, trace elements and vitamins. Maintenance of asepsis at all stages of parenteral nutrition is mandatory and so it follows that preparation, especially where multiple additions are required, should be carried out under strictly controlled aseptic conditions. At St. Mark's the additions are made sequentially via a 5 micron filter while the basic solutions are drawn into a 3 litre bag under vacuum; this ensures maximum dilution of each addition in order to prevent any concentration-dependent

incompatibilities. The complete procedure is carried out under laminar air flow conditions.

Compatibility and stability

Chemical incompatibilities

Factors which have been shown to affect many precipitation reactions of ingredients in parentral nutrition mixes are temperature, pH changes, concentration, the form of the particular salt, and/or the amino-acid profile. This indicates a need to assess the particular mix being used and not to just transpose information from one set of solutions to another. Many of these incompatibilities have been well documented (Earnshaw, 1980), but some of the more commonly encountered ones are the precipitation of:

(1) Folic acid with Ca^{2+} and Mg^{2+} in certain concentrations, e.g. 15 mg added to 500 ml Electrolyte Solution A (Travenol Laboratories Ltd.)

(2) Ca^{2+} with phosphate in certain concentrations (Nedich, 1978).

(3) Addamel (KabiVitrum Ltd.) with Synthamin (Travenol Laboratories Ltd.) giving a colloidal precipitate after 18 h in certain concentrations, and at certain pH (Farwell, 1982).

Physical incompatibilities

The most obvious of these will be the mixing of fats with amino acid/dextrose mixes, when coalescence of fat globules occurs. The tendency to coalescence has been shown to vary with the amino-acid composition and concentration, the concentration of electrolytes, particularly di– and trivalent cations, and it will also vary with the concentration of dextrose and with pH[6]. This then indicates the need for testing whatever mix is to be used, and will also necessitate re-testing for stability with changes in any of the variables mentioned above.

Chemical stability

Stability data on a number of different dextrose/Synthamin mixes used at St. Mark's has enabled a 28 day life to be given for mixes not containing vitamin additives and 3 days for those with vitamins (Multibionta – BDH Ltd.) providing the solutions are stored under refrigeration and in the dark (Farwell, 1982). Light protection has been shown to be important for stability of vitamins in short-term, and amino acids in the longer term. Further studies on the stability of vitamins in parenteral nutrition solutions in 3 litre bags have shown that longer than 24 hours can be given to Multibionta in certain parenteral nutrition solutions and that some vitamin

preparations are unsuitable for use in 3 litre bags (Allwood, 1982). Hence the need to choose products carefully, and to obtain stability data for each particular mixture to ensure that what is added is present in adequate levels by the time it is infused.

Microbiological stability

A number of parenteral nutrition mixes using different amino acid solutions have been tested microbiologically and it was shown that the different solutions support bacteriological and fungal growth to varying degrees (Farwell, 1982; Duffett-Smith and Allwood, 1979) so, when choosing solutions, an awareness of their individual advantages and disadvantages is required.

The effect of refrigeration at 4 °C has been shown to inhibit the growth of microbiological contamination whereas a rise in temperature brought about a corresponding rise in levels of contamination (Farwell, 1982).

Expected levels of contamination during preparation in the hospital environment should be relatively low and so the detection of micro-organisms would require the testing of the contents of a whole container. Considering the cost of the contents of a 3 litre bag, the ideal situation would be to apply a non-destructive test to give the assurance of a non-contaminated product. This assurance is important as once the product leaves the hospital, control of the product is relinquished to the patient and, considering the varying storage conditions that may occur when the patient wants to take a holiday abroad or even on a boat, it is important to know that the product supplied is as near to the ideal as possible.

Quality assurance

The need for chemical testing of the product has been mentioned but the need to view the final product against both light and dark backgrounds while passing a light source through the solution, both after preparation and before supplying to the patient, cannot be too heavily emphasized, if particulate contamination or delayed chemical reactions are to be detected. Standards of preparation can be maintained by concentrating on staff training in the teaching and maintenance of good aseptic technique, and also in the use of 'broth runs' before allowing any preparation of solutions for patient use.

Supply

The frequency of supply will be dictated by the stability of the solutions and the patient's refrigerated storage capacity. At St. Mark's supplies are made on a weekly basis, where possible. The maintenance of lower

temperatures during transit is achieved by the use of cool boxes (Camping Gaz Isotherm 964) with cool packs which, on testing, showed only a 2 °C temperature rise over a 5 hour journey. Owing to the large distances and the widely separated areas in which the home patients live, the use of British Rail Red Star Parcel Delivery was found to meet the same day delivery requirement and gave flexibility for short and long distance supply. The same system of supply is used for the associated disposable dressings and administration equipment, thereby involving the pharmacy in the time-consuming task of collecting, and packaging in suitable containers, extra items that the patient may require from time to time.

The support of patients on home parenteral nutrition is an extremely heavy commitment and one that, once undertaken, has to be maintained, even sometimes at the expense of the same standard of supply to in-patients. The commitment will continue to challenge the pharmacist's limits of knowledge in the area of compatibility and stability as different additions may be requested, and of storage requirements as the patient attempts to resume a normal life and may wish to travel abroad or follow previous interests. The understanding of how the patient's lifestyle is affected by his underlying disease and by the adminstration of parenteral nutrition at home, as well as continued communication which seeks to resolve problems as soon as they arise, all provide an ongoing stimulus to ensure that the pharmacist supplies the best product possible and makes the most positive contribution of which he is capable, to the home patient's care.

In the light of the above, is just providing the regimen sufficient?

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Discussion

Professor Lennard-Jones: Now, we have been hearing in the last two papers about what can be done for the patient at home. We admire the work in America, teaching patients to give themselves cytotoxic drugs and hearing about the pros and cons of continuous intravenous infusion. As a practising clinician, I point out to myself the need for close monitoring of the side-effects of these treatments. We have heard about recurrent septicaemia with continuous insulin infusion and I would like to ask Dr Anderson what instructions the patients are given about looking out for possible side-effects of their cytotoxic drug therapy, as the duty of all of us is to monitor these treatments to make sure they are doing what we hope they will do.

Dr Birtwell took pains to point out that continuous insulin infusion is very much in the experimental stage at the moment, and we don't know whether it is better for most patients than the current insulin regimen or perhaps, more frequent insulin injections. I have not been following insulin in the literature because it is not part of my speciality; I have been interested in developments of pumps and am very pleased to be brought up to date. There is a very interesting article in the current *British Medical Journal* which provides a nice summary of the pumps.

We are going to have a short period of discussion now and I shall lead by asking Dr Anderson to explain who talks to the patient about side-effects?

Dr Anderson: This is a very important topic. It all starts with the physician in discussing the overall therapy with the patient. They do spend a considerable amount of time on the side-effects because it is so critical with this type of therapy. The patients are fully informed about this aspect. As far as monitoring side-effects, I think patients are in constant contact with the principle physician, with the nurse and with us in the pharmacy. As we dispense these doses, we go over a drug data sheet with the patient and we go over all the possible side-effects; the chief ones, the ones they can't do too much about but have to contend with and other ones that need to be brought to the attention of the attending physician. It is extremely critical that patients know as much as possible about the drugs, and each is given a drug data sheet, a monograph of their particular therapy. In the case of multiple drugs, they would have a monograph on all the drugs so it is ex-

tremely critical that all members of the team are involved with this and the patient knows what to expect and what to report.

Mr Webb: Dr Anderson, your slides showed a patient being taught how to reconstitute the drugs and measure doses, and she was working under a laminar air-flow cabinet. Clearly, when she is at home, she will not have one of these. Do you have any problems with patients being worried about the absence of this facility?

Dr Anderson: No! The most convenient place in that particular pharmacy to do the preparation is the laminar-air work station. We do emphasize the aseptic nature of the environment and in part of the description in the little booklet, we talk to them about how to clean off the general area of the counter top where they are going to be working, realizing that they are not going to have a biological safety cabinet. It is pointed out that they should make the total area as clean as possible. But, no! We do not have any apprehension shown by the patients. To do the teaching on a regular counter top would be better, and in some cases we do that, but in most cases we work in the hood area.

Mr Dean: I would like to ask both speakers about infection problems, because obviously these exist. Perhaps they could indicate what infection problems occur, what organisms cause problems and how the patients monitor these problems themselves and what the treatments usually are.

Dr Birtwell: Using the subcutaneous insulin infusion route, problems of infection are minimal because the patient has to change the site of his continuous infusion very frequently. Experience of the intravenous route has been severly limited. Our problems with infections have often been with gram-negative organisms and we also have had combinations of gram-negative organisms. I think one of the basic problems with using this type of system is the kind of patients to use it on. Our patients have been true brittle diabetics who in addition to the brittleness of their diabetes, have brittle personalities, and I am afraid that we have had some suspicions that they haven't been as careful as they should have been. In terms of monitoring septicaemia, you simply can't. The patient comes in prostrate.

Dr Anderson: Our monitoring method relies on return visits by the patient to the Institution and we have not really experienced a particular problem in this area. I think it relates more to technique and patients are so thoroughly instructed that we have not been aware of problems.

Mr Tallett: Could the speakers tell us about the cost and in the case of the cytotoxic drugs, how the patient copes with the cost?

Dr Anderson: The pumps that we use are provided in one of two ways. One is by rental. Our daily rental charge for this is 20 dollars per day. The other choice is to buy one of the pumps, now costing about 1200 dollars. Many of the patients have purchased these pumps and donated them back to the Institution at a later time. The cost of buying a pump is so much less than being in the Institution or even staying nearby at a local hotel. The insurance companies in the United States approve of treatment on an out-patient basis because of the overall reduction in the total cost to the patient. The costs of the drugs are just about the same as if they were received as an in- or out-patient.

Dr Birtwell: The same applies to Insulin using these systems. The costs are the same whatever you use. The variety of insulin pumps available are the two that I showed you: the Pye Dynamics Pumps costing £200, and the Siemens Pumps costing between £1600 and £2000. The later developments in insulin pumps are costing about the same. There is one made by Auto-Syringe and Travenol on the market at £600. In addition you have the cost of syringes and catheters so in fact, it is quite an expensive business! What will be cost effective in the long run can only be accepted if it is cheaper in terms of complications for the patient. All diabetics, apart from those that I discussed, are treated on an out-patient basis.

Ms Jennings: Could I ask Dr Anderson how he instructs patients on disposing of unwanted solutions and empty vials etc?

Dr Anderson: That's a very good point and we are going to discuss that in more detail this afternoon. Following our recent studies, we are much more aware of what advice we should be giving on the disposal of these particular agents. At the present time, the patients are disposing of the agent in the normal way. We do not have them isolating their supplies for disposal. This will become part of our overall recommendations which are not finalized at this point. Most likely we will be having some provision for patients to isolate those items for return to the Institution. We will talk more about disposal and that type of information this afternoon.

Miss Day: How much work has been done on the stability of these drugs? I noticed that you mentioned the use of dicarbazine with which we have no end of problems for in-patients. The other point is that you mentioned mixing drugs in a syringe. We have difficulty with different people trying to mix certain drugs in syringes and obtaining stability data on what is permissable is well nigh impossible; in fact nothing seems to be documented.

Dr Anderson: The accumulation of stability data is a very big task and we are now working on that in our department supported by industry, in fact

Travenol. We are in the process of determining long-term stability of approximately 15 different agents in both a plastic disposable syringe and in the new Travenol Infuser. We will include data at room termperature, refrigeration and frozen. We will soon be publishing this data. We have been fortunate in our department in obtaining the services of an organic chemist, Dr John Benvenuto. In fact, he visited Great Britain about a year ago and presented some of his data on stability in the Mini-Bag. We are now extending those to include cartridges for the pump. So we are very much interested in the stability, both singular agents and in some cases multiple agents in the same small volume cartridge.

At the same time, on an in-patient basis, we are studying concurrent administration of these agents through the same line. This is a real problem for us, having patients with vein compromise situations with only one line being available and up to 30 different doses having to go in during the day. The situation of having them not going simultaneously is almost impossible. So we are going to do some dynamic studies on the stability of solutions of cytotoxics as they flow through the same line. We have a new manifold system with six ports down through one line which we have implemented at the Institution, so we are getting back into the multiple mixtures, even though years ago we tried to get away from that. Only with stability data can this be made possible.

Dr Fish: Could I ask about the mechanical dependability of the gadgetry. I think both speakers have hinted at the fail-safe features. Do they have experience of problems with failure, and if so how do they advise patients?

Dr Birtwell: There have been problems with mechanical failure, particularly syringe drive pumps. The fail-safe mechanisms are really alarm systems, and the more the better. This means that if the catheter becomes blocked, the pump will alarm; or if the pump stops for any other reason, it will alarm for example if the battery is failing.

We have experience of these things failing. Obviously, via the subcutaneous route, an immediate insulin lack is not so much of a problem because there still is a residue amount. Experience gained by intentionally removing the system and then seeing what happened to the patients, suggests that although they start becoming ketotic in less than 12 hours, they have sufficient time to recognise there is a problem. It means that, if they get up during the night they are not going to be at death's door, although they will have to reinstate their system.

With the intravenous route, there is much more of a problem because the half-life of insulin in blood. Unless they have sufficient antibodies this is between two and five minutes. So patients, especially those that are ketosis prone, rapidly become extremely ill. This is a significant problem

and will remain one, particularly for the implantable systems, which is why they have to be as reliable as possible.

Dr Anderson: With the auto-syringe which has been our principal pump up to date, it has been extremely accurate. We pre-set that and actually take off the dials in some cases so that the patient does not mess around with it. It is extremely accurate. When each pump is returned, after use by the patient, we send it to our biomedical engineering department and they check any recalibrations that are necessary. With the new Travenol Infusor, it is also accurate, but it is much more dependent upon temperature because we have viscosity changes with temperature changes and therefore the flow rate alters. There is still quite a bit of research and development being done on this one to make it less dependent upon temperature. Reliability: the alarm systems available with the auto-syringe have pleased us and we have not experienced any difficulties.

Dr Birtwell: I think that the real difference in using continuous insulin delivery and either parenteral nutrition or cytotoxic administration, is that it has to be continuous; and nothing less than continuous will satisfy, particularly by the intravenous route. I wondered if the problems we have run into with septicaemia may not be related to the duration of time we are having to use the systems. Could Dr Anderson tell us for how long patients are having to use their systems and for how long are they infusing?

Dr Anderson: The different courses of therapy would vary from a five day to a 15 day course. We have a new sperigominuim course of 42 days which will be our longest course although it is known that catheters have remained in place for up to two years. Normally it is a five to seven day course. The lines are kept in depending upon the total duration of the patient's treatment protocol.

Unnamed Speaker: Heretical comment for Dr Birtwell. He says it must be continuous infusion, but on the other hand you pointed out that one of those pumps is giving small booster doses with meals. Why can't the patient put in a butterfly catheter in the morning and then put repeated doses of insulin through that six times a day?

Dr Birtwell: That is exactly what has been done in France, for instance, and we have also used that system reasonably well. You are quite right because then the patients would not have to inject themselves more frequently.

Ms Hodges: Very early on, a mention was made that continuous cytotoxic therapy had greatly diminished side-effects and I know that one of the

major problems that has to be coped with in the case of large but intermittent doses, is combatting the fear of the patient in coming up for this therapy. Would Dr Anderson like to comment as to whether in talking to patients and counselling them he has got to cope with this problem. Presumably whether they use the therapy or not is entirely their own decision.

Dr Anderson: That is very true. As I pointed out earlier, the amount of discussion with the patients concerning the side-effects is substantial. We do not try to over-alarm. By the time they begin their therapy, they have accepted it to the extent that psychologically it does help in their overall therapy and response to the drugs. The patients that are going back into the home environment seem to be able to cope with this better. I am sure it is being away from the Institution and the out-patient chair area with people in a line. I don't think that is a very good design. When they get back in the home environment, somehow psychologically expectations concerning the side-effects might be minimised. Every patient who gets the chance to be a home patient welcomes it and they do come back saying that they are handling their therapy in a much better way.

Mr Hitchings: I would like to ask Miss Doery a point which she touched upon in her presentation. She mentioned the deleterious effect that vitamins have on the integral filters in some of the giving sets and I must admit that this is an effect I have not heard of. I wonder if she could elaborate on that and also indicate which filters are suitable for use in this situation.

Miss Doery: Perhaps I have given the wrong impression. I am not sure about filters in the giving sets. Vitamins definitely effect the filters that we have used in the preparation; one particular one is an Argyle 5 micron and we normally pass all the additions for one bag through the one filter connector with a spigot in the end just for speed of addition. We found that the resistance to that was altered so much that it became difficult to get all our additives through in the time that it took the bag to fill. We use a Braun filter straw now for this purpose and find it much better.

Mr Beaman: Miss Doery, you mentioned that an alternative to 'Intralipid' was sunflower oil. Could you elaborate on that?

Miss Doery: Sunflower oil is a source of linoleic acid and it is absorbed very well if it is applied topically on the forearms.

Miss Wood: The women patients love using it. The hospital patients will tell you about their dry skin to get to use it because it really makes the

skin soft. It is fairly controversial about the amount of absorption that occurs. If you have a patient who won't give himself Intralipid, you have to find some sort of compromise and we can't make anyone have Intralipid. It is their lives after all.

Mr Purkiss: You mentioned that there was a colloidal precipitate with Synthamin-17 and Addamel. We have added those two together many times, we have always got bright solutions and we do regular particle counting on the solutions which we prepared. We have never seen a precipitate, a colloidal solution or cloudiness. It is a concentration effect because I noticed that you used a vacuum means of filling?

Miss Doery: I have not seen it because we don't use it. It has been well documented. At what stage after preparation do you check your particle count? Is it over 18 hours later?

Mr Purkiss: The particle count is done on unused bags. For instance, if a bag is not used for some reason and is returned to us, we normally split it into two; one part is for retrospective microbiological testing and the other one has retrospective particle counting. So those bags can be anything from 3 days to 3 weeks old and the particle counts are always within the BP limits for infusion fluids.

Mr Cairns: The first question is to Miss Wood. A problem in our wards is the trouble the nursing staff have with the lines attached to parenteral feeding – everything from the catheter out, and I wondered if your patients have problems with that. It is a problem which gives our nursing staff the most concern.

Miss Wood: I think it is important to have a set policy for what is going to be used and what is not going to be used and to make sure that the hospital supplies department don't arbitrarily change what is supplied. The problem is that everyone becomes accustomed to one system and all of a sudden a different giving set arrives on the ward. Then it becomes a matter of education. I showed a slide of the two-bottle systems and that is a total nightmare as far as nurses are concerned. If any of you would like to experience what it is like, I would ask you to come and do a shift at St. Marks with a couple of patients on a two-bottle system and experience what it is like to control one of those infusions. You have two containers of fluid of totally different density in each container and you are trying to get it through one catheter. A lot of problems arise, especially when you are setting up the administration set because if you are not careful, you get back pressures and fluid escapes. You have to be very careful with the clamps on the airways, especially when you are setting up Intralipid with

the two-bottle system. Many clamps on airways are not very efficient. You do have to be very careful with the Travenol airway because you have to close it right to the end and then open up the flow control valve on the giving set before you open the valve on the airway. The vacuum in most bottles, especially Intralipid, is so great that if you open the airway vent first, the whole thing will shoot out through the airway. The equipment is not easy to handle. I spend a great deal of my time in testing different pieces of equipment and then using them with the nurses on the ward to get their acceptability.

Mr Cairns: I got the impression that you used a standard regimen on your patients. How relevant is all the testing? We use a different regimen on every patient and grade them up and down, etc. It would be impossible to relate the stability data that you have for your regimen to ours and it is not possible to produce stability data for every regimen that we use. We find it impossible to precipitate anything in a bag anyway, no matter how long you keep it.

Miss Wood: All I can say is that when we started, because we didn't know stabilities we gave everything a 24 hour life. We have to run a 7 day service from a 5 day week department and so stabilities were something that we had to look into. It was something that had to be done before we would supply home patients. The work was undertaken by Dr Farwell and involved different concentrations of dextrose, amino acids and different electrolytes. Our trace elements are more or less standard and from that, because we do use a relatively narrow range of formulae, we are happy. The potassium and sodiums added will be different, but as they showed no deterioration, we are happy in accepting that. The thing is that you would have to test every single mix if you are going to include fat in the bag because the electrolyte concentrations will vary. Some will cream and reconstitute on shaking, and it depends on how happy you are with that arrangement. At St Marks we are rather conservative before we step into something new that we are not sure of.

Mr Simpson: Why is it that when you involve some members of the Primary Health Care Team, mainly the GP and the Social Worker, you don't involve the District Nurse? Do you find this causes any problems on account of the distance that you are away from the patient and also because patients might well be accustomed to looking to the District Nurse as their first port of call with any problems they have?

Miss Wood: What we are trying to do is to get the patient to become as independent as possible. My personal feeling is that if you are sending patients home on parenteral infusion and they need to have a District

Nurse, they shouldn't be at home on parenteral nutrition, they should be in hospital. You are not sending anyone home for the convenience of the hospital; you are sending them home because they need long-term care and therapy and to live normally. Now the General Practitioner has to know what is going on because he referred the patient to the hospital in the first place and he has got the closest involvement with the patient, or may need to prescribe drugs for the patient. He is going to be seeing them, so it is obvious that one has to involve them. The problems that arise with patients are social problems. They should not be problems of the patient needing nursing care from the District Nurse at home. We have found that all the problems that arise are social ones. The person you want is either the Health Visitor or a Social Worker and we have found the Social Services to be invaluable, as long as they understand exactly what is involved in home feeding. Again, meeting them and explaining to them exactly what is happening – they are trained to work with people in their own homes, to adjust their social setting and so on, we have found most helpful. But District Nurses, I think, should not be involved – there are other reasons, but I don't particularly want to go into those.

Mr Hughes: I was concerned about the statement made by our first speaker about the absence of compatability between different brands of luer-lock fitments. How serious is this and have you taken it up with two organizations most involved: the British Standards Institute and the DHSS Supplies Branch?

Miss Wood: Yes it has been taken up. Dr Peters at UCH is on their heels all the time about this. It is something that people often don't recognize and it is a particular danger where you can use a piece of equipment from one manufacturer, and the next piece of equipment down the line will be from another manufacturer. For example, the extension tube and the giving set come from two different manufacturers. You just have to ensure that those systems are compatible before you try them on the patient. This is terribly important when it comes to supplies because one of the things we have found is that the supplies department will try to order the cheapest piece of equipment they can with that label. You ask for an extension tube and they will order the cheapest extension tube, whether it is suitable or not. This is why it is important that someone who is sending supplies to the patient knows what they should be using and sends out safe equipment.

Mr Wozniak: This is a very interesting title that Miss Doery has used – "Is providing the regimen sufficient?" and at the start of her talk she posed questions on the pharmacist's knowledge of the surgical sundries involved. Is the answer in learning about catheters, cannulae, dressings and everything else supplied via hospital supplies departments?

In Scotland hospital pharmacies handle these supplies but they do not train their young pharmacists about their use so the situation is almost as bad as in England where pharmacies do not handle these items.

Would you care to comment on how important you thought the first part of your talk is?

Miss Doery: I feel the first part is very important. With the new Basic Grade Pharmacists that I have through, none of them have any idea about the management of infusions, even how to prime an ordinary giving set. I find that most of them are totally unaware of the nursing and practical problems. We all know that you reconstitute ampicillin with water for injection; do we know how long it takes to dissolve, do we know how difficult it is? I think we need to carry through an appreciation of the administration of the product as well as the preparation and supply of it. I do feel quite strongly about that. I don't say we should take over the nurses or doctor's role, but I think we need to appreciate what goes on.

Miss Wood: I think one of the other important things to note is that the patients who are at home from St. Marks have a list of telephone numbers and they work their way down the list until they get someone who is available to speak to them if they have a problem. Now, the person they get; it might be myself, it might be Helen or it might be the registrar or professor, *but* the problem may be related to a pharmacy problem or a nursing problem. Each one of us has to be able, on the spot, to deal with that difficulty. I don't have any deep pharmaceutical knowledge, but I can give immediate advice about what to do, because I have learnt from Helen. Again, Helen can give immediate nursing advice if a nursing problem comes up, because she has learnt from me. I mean to emphasise that we all have to help and teach each other. There is a vast amount of knowledge and expertise available and we have to pass it on.

Mr Bolton: Two questions for Miss Wood. The first is how often do these patients on long-term TPN have to come back to the hospital for assessment? The second point I was interested in, is that it is now being reported from some workers in Canada and the United States, that patients on long-term TPN undergo some form of personality change and I wondered if you have seen this and could comment on it?

Miss Wood: When they are first discharged, I do a home visit on their first day at home, then we see them in the hospital after two weeks and then again after two more weeks, thereafter maybe monthly, or less frequently. It depends on the individual patient. You have to really understand the individual. Often the patient will tell you everything is going very well, but you have to be able to read what they are really meaning. A lot of these

patients have a debt of gratitude towards you because you have given them a new life, and whilst you don't want them to feel grateful towards you and you do everything you can to make them feel they have control of what is going on, they do tend to try and present a good face to you. You have to be skilful in assessing the situation as to how frequently you need to get them in, also you have to do home visits every couple of months to see how the family are interacting etc. and what is going on. Patients will adapt their techniques, we all do it unconsciously, it is part of how to carry out procedures.

As far as personality changes are concerned, they do undergo personality changes. They are extremely difficult to cope with and we now have a psychiatrist actually on the nutritional support team working with us. He has been very helpful in so far as he has been able to explain some of these personality changes and they are different in different patients. He has said that there are many analogies with home dialysis. As with home dialysis, there is a visible manifestation that something is wrong; eg. there is the catheter there! Even if they are not connected up all day, the catheter is still there! Certainly, patients get very bored with carrying out their therapy after a long period of time. They get fed up with it and so don't carry out their procedures well enough. Other changes also occur. But there is *a big difference between parenteral nutrition and home dialysis,* in dialysis you are taking some waste away from the patient! Food has far more emotive and behavioural connotations. You are actually putting something into patients to keep them alive and what is going into the patient is coming from the hospital. So the hospital is acting as a mother-type figure: supplying life to the patient. What tends to happen is that they develop more allegiance to the hospital than they do to their own family and you see quite peculiar changes in the relationship they have with the people around them in their own home. This is something which doesn't stop when parenteral nutrition finishes. If a patient adapts, and they are able to finish parenteral nutrition, you can often have quite bad problems. We have one patient who, three years after coming off home parenteral nutrition, still has not adapted to feeding herself. She got gratification from this procedure going on in that she was rather special. This again is very important, not to make the patient feel that they are a special person. They are different, but they are not special and taking this out of her life has left her quire bereft. She is totally maladjusted in society.

Ms Wild: In general, can you say how long it takes to get a patient stabilised on to your standard solutions? Do you have any problems where you can't get a patient stabilised and you have to make a specific solution for them?

Miss Doery: We don't just provide standard solutions. We do prepare

individually for each patient, although there does tend to be a patient norm. Particularly with St. Marks having a relatively narrow range of patients; it is all gastroenterology and they are all tertiary referrals. There is a similarity to some degree. The formulation depends on the patient's condition and after they come in for their monthly check-up adjustments may be made. We find calcium and magnesium a problem with a lot of them; also the sodium and potassium will vary, so we make adjustments on a monthly basis. But with the home patient, it is not critical that something has to be changed that day and so we just phase it in to their next supply of fluid. No, it doesn't present a great problem because we prepare individually for each patient.

SECTION TWO

Hazards, Risks and Responsibilities

Chairman:
Dr Shirley Ellis

Chairman's introduction

S. Ellis

This morning we were discussing the provision of parenteral therapy at home using drugs and techniques which, within the memory of some of us, were regarded as experimental even within hospitals. I think this afternoon we have to think about what these changes imply in the context of the risks and hazards that we have to deal with within the home and the responsibility of the pharmacist in alleviating those risks.

We are moving from an environment which we can control, to some extent, and certainly monitor, to one in which we can do neither and which was not designed for any such purpose. We are transferring many tasks from the professional, or trained personnel, to the amateur and with very little time, in some cases, to train the patient to undertake those tasks. As we heard this morning when things do go wrong, expert help is not available on a call button but at the end of a telephone. The advice that is given may be very much 'do it yourself' rather than expert practical help and so the patient must be more self-sufficient. The patient is in the community, surrounded by the general public who may be fit or they may be ill with unknown bacteria whereas in the hospital one can at least monitor the illness or know what is wrong with the patient in the next bed. Do these factors actually increase the risks to the patient? I hope that this afternoon we shall hear the opinions of our speakers as to whether the risks are increased or decreased. I think one thing we can be sure of is that they are different to the ones that occur in the hospital ward. Hazards are often implicit in the drugs themselves and this is especially so with cytotoxic drugs and our first speaker this afternoon will discuss the hazards of handling cytotoxic drugs. Much of Dr Anderson's work is related to the hazards of hospital personnel, but I think we must ask ourselves the question 'is the

young mother who prepares medication for a child every day at the same sort of risk and is her unborn child equally at risk because she has handled cytotoxic drugs on a regular basis?' Are spills and waste more difficult to handle in the home or perhaps in the nurse's car than in a controlled hospital environment? I think we must remember that our responsibility does not end because the Health and Safety at Work Act does not apply to the patient's kitchen.

Other risks may be associated with the techniques rather than the drugs and Dr Noone will deal with microbiological hazards. The product may be prepared under very controlled conditions, but it can easily be compromised during administration and those of us who have been taught to work under class 1 laminar flow conditions must react adversely to the fact that the patient has to deal with these in the open room.

The third and fourth speakers will discuss the pharmacist's responsiblity. We must play an active part in ensuring that home parenteral therapy is as safe and effective as possible. As discussed this morning, some contributions that can be made are obvious. We must ensure that the highest possible quality of material is supplied and that it is as near to 'ready-for-use' as possible. We cannot over-emphasize other aspects which are equally as important. We must make sure that our instructions to patients are clear and understood and that they cover all aspects of use and destruction and not just administration. One should always be ready to discuss the problems and not just supply the information we think the patient will need. Patients being treated at home are much more isolated and we heard this morning how they must have confidence in the equipment. They also must have confidence in all the health-care professionals with whom they come into contact. We must take an active part in participating in team work and also in supporting the team, so that whoever they contact gives the same information with the same emphasis. I think it is easy to make sure that everyone gives the same answer to a specific question, but it is surprising how the emphasis or the way in which the answer is given can alter the patient's response to what is said. We need to be more closely involved with teams if we are going to do this type of work adequately.

I hope that all these aspects are going to be expanded on by the speakers this afternoon, but before handing over to the first speaker I would like to make one final plea. These patients are being treated at home. Why? To save the NHS money, because we don't have sufficient beds or because we want to free acute beds? The answers to those is 'yes' but the most important reason is because we wish them to live as normal a life as possible. When we talk about the risks of therapy we can no longer just look at the risk/benefit ratio of the actual therapy. We have to look at the degree of reduction of risk we obtain by changing the way in which patients do things and balance it against the effect that the change has on the patients' approach to normal life.

5

Handling cytotoxic drugs – health and safety hazards

R.W. Anderson

INTRODUCTION

Occupational exposure to cancer-causing chemicals in not new. Clinical observations by astute physicians in the 18th century were among the first methods for detecting carcinogens *in vivo* (Haddow, 1974). Assay systems were developed in the early 20th century to detect potentional hazards from needless occupational exposure. Clinical observation methods are at best subjective and are often anecdotal. Human epidemiology studies are limited in sensitivity because of the high incidence of cancer in the general population, the difficulty in defining exposure groups, and the very long latent period (often more than 20 years) in the development of cancer. Animal cancer tests are also limited in sensitivity due to the relatively small number of animals (often 50 or less) that can be included in carcinogenisis bioassays and because these tests may detect only the more potent carcinogens. Animal carcinogenicity tests are also costly (now almost $300 000 per substance tested) and time consuming (about 3 years) (Hollstein and McCann, 1979).

In the past several years such an enormous number of chemicals have been tested by many test systems (in the Salmonella/Ames test alone, results on over 2600 chemicals have been published (Hollstein and McCann, 1979) that these tests have been incorporated as toxicological screening procedures by all regulatory agencies of the US Government. Carcinogen detection remains a tremendous task, as over 60 000 chemicals are presently in widespread use in our environment, with an estimated additional 1000 new chemicals introduced in significant quantity yearly

(Weinstein, 1981). Medical concern over handling cancer chemotherapeutic agents was expressed in the literature over a decade ago (Ng, 1970). Several articles have proposed various guidelines to minimize direct contact with the drugs and equipment during chemotherapy preparation, administration, and disposal (Harrison, 1981; Hoffman, 1980; Gousse *et al.*, Zimmerman *et al.*, 1981; Ladik *et al.*, 1980; Davis, 1981; Knowles and Virden, 1980). Only recently, however, have studies appeared that attempt to identify and measure the risk of exposure to personnel involved in the preparation and administration of these agents. Falck *et al.* (1979) were among the first to demonstrate evidence of mutagenicity in the urine both of patients receiving chemotherapy and of nursing personnel in an oncology unit. Waksvik *et al.* (1981) also demonstrated evidence of mutagenic activity through chomosome analysis in a high-exposure group of nursing personnel in a oncology ward. Other direct chromosome studies, such as measurement of sister chromatid exchange frequencies, have been used as indications of mutagenic activity in lymphocytes of nursing personnel (Norrpa *et al.*, 1980). Of particular importance to hospital pharmacists was a study that demonstrated airborne levels of medications prepared in a horizontal laminar flow hood (Kleinberg and Quinn, 1981). At least one mutagenic study to date has produced negative results. A recent letter by Staiano *et al.* (1980) related no mutagenic activity in intermittent urine collections of hospital pharmacists preparing chemotherapy admixtures in both horizontal and vertical laminar flow hoods. Clearly more studies are necessary before the issue is resolved.

OBJECTIVES AND STUDY DESIGN

Concern over the potential occupational exposure of pharmacy personnel at the University of Texas M.D. Anderson Hospital resulted in the development of a research proposal approximately 3 years ago. After protocol development and approval by human experimentation review channels, the study was begun in early 1981, with the first phase being completed late that year.

The objective of the study was to assess the exposure of pharmacy personnel to cancer chemotherapeutic agents during their normal work routines. If the study methodology demonstrated the uptake of mutagenic substances by the personnel, various intervention methods were to be tested for their ability to prevent such exposure. The study was a collaborative effort between the Department of Pharmacy at the University of Texas M.D. Anderson Hospital, School of Public Health and Graduate School of Biomedical Sciences. M.D. Anderson Hospital is a 504 bed oncology specialty hospital, clinic, and research institute located in the Texas Medical Centre in Houston, Texas. The Department of Pharmacy employs 200 personnel, including over 80 pharmacists, to provide both

in-patient and out-patient pharmacy services and to support the research efforts of the institution.

Every attempt was made to have the study reflect the work cycles, methods, and environments normally encountered by the personnel. The study design used was a longitudinal study with the test subjects serving as their own controls. Eight day continuous urine collections in 24 hour sample lots were to be obtained from persons who prepared intravenous admixture solutions containing cancer chemotherapeutic agents. These persons worked in the normally used horizontal flow clean air benches. Urine samples were also collected from persons who worked in the pharmacy but did not admix or handle cancer drugs. A temporal correlation between the appearance of mutagenic activity in the urine and the time of potential exposure would provide evidence that exposure has actually occurred. Should exposure be demonstrated, the study would be repeated in the horizontal flow environment using masking and gloving as simple methods of intervention, and in a vertical flow biological safety cabinet as a stronger measure of protective intervention.

METHODS

The test method chosen for the M.D. Anderson Hospital study was the Salmonella/mammalian microsome mutagenicity test developed by Professor Ames *et al.* (1975). The basis of the Ames test is the organism *Salmonella typhimurium*, in particular histidine auxotrophic strains sensitive to reversion back to prototrophy by a wide variety of mutagens (Ames *et al.*, 1975; Frantz and Malling, 1977). Since histidine is required for cell growth, the test indicator is the appearance of a number of colonies beyond a background level in an agar medium lacking a full supplement of histidine. That is, the tester strains contain a mutation in one of several genes governing the synthesis of the amino acid histidine, and they cannot grow unless histidine is present in the growth medium. Different doses of the substance being tested are combined with the bacterial tester strain on an agar plate. A trace of histidine is added, which is not enough to permit colonies to form fully, but which will allow sufficient background growth to permit expression of newly induced mutations. Background growth afforded by a limiting amount of histidine permits one to determine the toxicity of the test drug: a normal hazy background of microcolonies becomes granular in appearance with toxicity. The number of bacteria reverted by mutation back to an ability to synthesize histidine is measured by counting the revertant colonies on the plate after 2 days incubation. Quantitative dose–response curves, with few exceptions, are linear. The method is extremely sensitive, and usually micrograms, and in some cases nanograms, of mutagen can be detected. Positive test results are almost always clear-cut, with numbers of mutagen-induced revertant colonies

usually two or more orders of magnitude greater than the relatively low spontaneous incidence of revertants as background growth (Hollstein and McCann, 1979; Ames *et al.*, 1975).

The test has been adapted for use in detecting chemicals that are potential human carcinogens or mutagens by adding homogenates of rat (or human) liver directly to the test mixture on the agar plates. (The liver microsomal enzyme preparation is called S-9 since it is the 9000 × *g.* fractionate of the liver homogenate.) Thus, an important aspect of mammalian metabolism can be duplicated in an *in vitro* test. In this way, a wide variety of carcinogens requiring metabolic activation can be converted to active mutagens as well (Hollstein and McCann, 1979; Ames *et al.*, 1975; Ray, 1979; McCann *et al.*, 1975a). Two other features of the tester strains of the *Salmonella* organisms have been developed by the Ames group that further increase the sensitivity and versatility of the test. All of the standard tester strains contain additional mutations that cause alterations in the outer lipopolysaccharide (LPS) permeability barrier, facilitating diffusion of large organic molecules (e.g. polycyclic hydrocarbons and aromatic amines) into the bacterial cell. These alterations of the LPS barrier give a marked increase in sensitivity to some mutagens over those strains without these alterations (Hollstein and McCann, 1979; Ames *et al.*, 1973). One of these mutations affecting permeability also causes a loss of the excision repair system. The loss of this major DNA repair capability (excision repair-negative organisms) further increases the sensitivity of the test to the presence of many mutagens (Hollstein and McCann, 1979; Ray, 1979; Ames *et al.*, 1973).

The Ames/Salmonella mutagenicity test detects almost all of the known organic chemicals that are human carcinogens. McCann demonstrated a 90% correlation between known carcinogenicity and a positive Salmonella test for mutagenicity in a study of 300 chemicals (McCann *et al.*, 1975b; McCann and Ames, 1976). Purchase *et al.* (1976) demonstrated a 93% correlation in tests of 120 carcinogens and non-carcinogens (Ng, 1970). The Ames/Salmonella assay is the best validated of any microbial assay and is used routinely in genetic toxicology screening programmes as part of a battery of different short-term mutagenicity tests and as a reliable predictor of carcinogenic potential (Hollstein and McCann, 1979; Frantz and Malling, 1977; Ray, 1979; McCann and Ames, 1976; Purchase *et al.*, 1978).

24 h urine samples were collected for 8 day periods from nine persons, some over multiple test weeks. Each urine collection period began on a Sunday at 7.00 p.m. and ran for 8 days through to the following Monday at 7.00 p.m. All of the personnel worked normal shifts, either Monday–Friday or, occasionally, Monday–Saturday. Six persons composed the 'exposed' group – five technologists and one pharmacist – whose jobs all involved admixing cancer chemotherapy drugs each day. Doses prepared by each ranged from 12 to 90 on days worked, and none on days off. Three

persons acted as controls and went through the same urine collection methodology. They worked in the same pharmacy environment each day but did not admix any drugs.

Initial testing was performed in horizontal laminar flow hoods using all traditional methods of handling and preparing intravenous admixture preparations. Various intervention methods, including masks, gloves, and the use of a biological safety cabinet, were introduced in subsequent testing. Over 150 tests were performed, covering 19 test weeks of urine collections. Diet, tobacco, beverage, and drug intake of all subjects were recorded and monitored. The Ames/*Salmonella* mutagenicity assay was performed on each 24 hour urine sample.

RESULTS

All test organisms were not sensitive in every test with each subject. However, all subjects demonstrated a positive response to at least one of the test organisms. Figures 5.1, 5.2, and 5.3 illustrate mutagenic activity in six exposed controlled subjects with test organisms TA 98, TA 100, and TA 1535. Results from the exposed subjects indicate mutagenic activity levels exceed two times background between the third and fourth day of exposure and return to background level by the eighth day. The control subjects illustrated no mutagenic activity throughout the study period. Several intervention methods were considered to minimize the exposure liability demonstrated by these studies. Principle attention was given to the prevention in ingestion, inhalation, and absorption through the skin. A special respiratory mask designed to prevent inhalation of aerosolized particles was worn by two subjects. Figure 5.4 illustrates that this method alone did not result in a reduction of mutagenic activity. Next, two subjects were tested while wearing disposable gloves. Figure 5.5 illustrates that these gloves likewise provided no additional protection. The third method of intervention involved four subjects preparing antineoplastic admixtures in a Class II Biological Safety Cabinet. Figure 5.6 illustrates a major reduction, if not total elimination, of mutagenic activity.

DISCUSSION

The use of horizontal laminar flow hoods has become a standard of practice in most centralized i.v. admixture programmes (Joint Commission on Accreditation of Hospitals, 1981; National Coordinating Committee on Large Volume Parenterals, 1975). Many hospital pharmacists use these horizontal laminar flow hoods with relatively few extra precautions for the mixing of antineoplastic drugs. At M.D. Anderson Hospital the exposure potential to persons handling antineoplastic agents is considerable. Of 2700 i.v. admixtures prepared daily, approximately 300 are antineo-

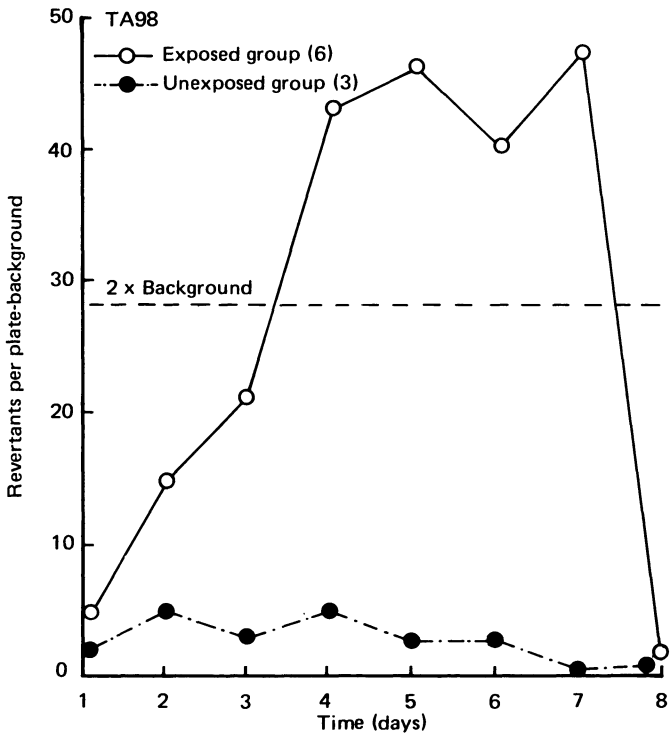
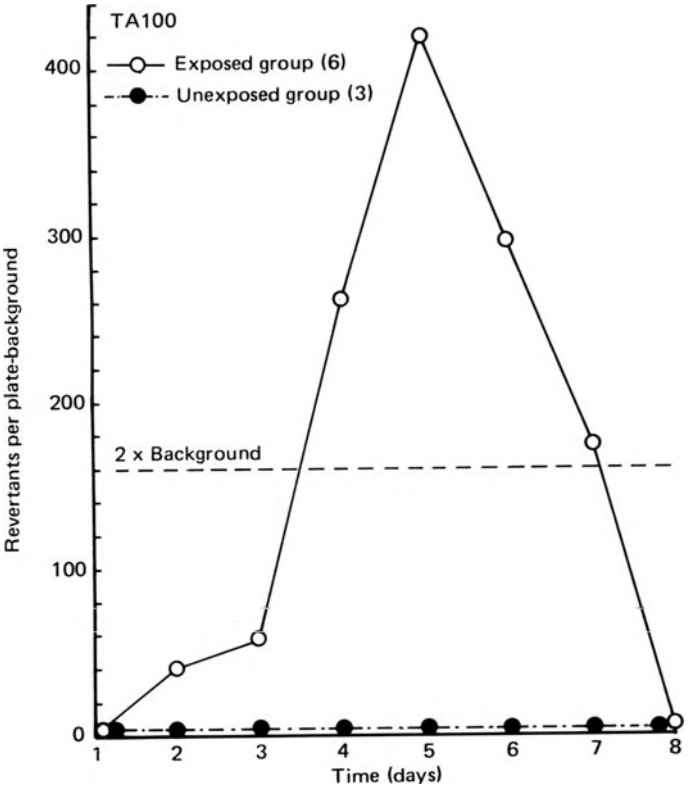


Figure 5.1 Mutagenic activity in the urine of pharmacy personnel using *Salmonella typhimurium* test strain TA 98

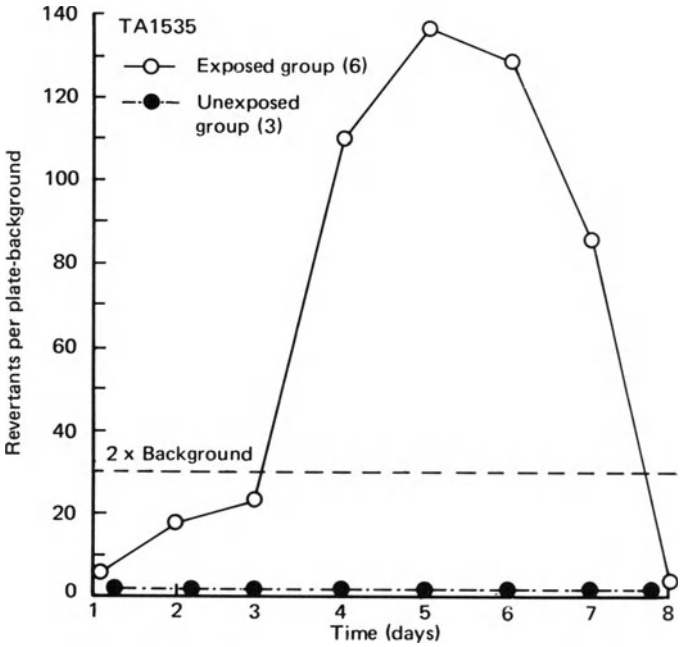
plastic drugs. During the study, the number of antineoplastic i.v. admixtures per pharmacist or technologist ranged from 12 to 90 daily.

A longitudinal approach in this human monitoring study of exposure was taken for two reasons. First, with the small study population available for this investigation, the demonstration of temporal variation in mutagenic activity of the urine samples coinciding with the time of potential exposure to these agents would be the most convincing illustration of exposure. Second, a longitudinal approach takes into account the pharmacology of the drugs to which the study population was exposed. With each agent having a different rate of absorption and excretion, total urine collection for 8 consecutive days is the most effective way to collect different drugs or their metabolites, which may be excreted at different times during the work week. The positive response with excision repair-negative strains in all test subjects prior to protective intervention demonstrates an exposure liability to these persons routinely handling such agents during the preparation of i.v. admixtures in a horizontal flow hood. It is generally accepted that



Figures 5.2 Mutagenic activity in the urine of pharmacy personnel using *Salmonella typhimurium* test strain TA 100

urine mutagenic activity levels determined by the Ames test in excess of two times background are significant (Hollstein and McCann, 1979; Ames *et al.*, 1975; Anderson and Styles, 1978). The selection of intervention methods was considered on the parameters of compliance, ease of use, cost, and effectiveness. Respirator masks were used to prevent the inhalation of ingestion of aerosolized particles, as standard surgical masks are unable to prevent uptake of this material. In our study, however, mask intervention alone failed to reduce exposure. This was attributed to poor compliance because the mask was bulky, hot, and generally uncomfortable. Smudge marks on some of the masks indicate touching and other adjustments by the workers, which no doubt lessened the effectiveness of the respirator mask. While the studies of persons wearing gloves proved negative, further studies are essential to determine more specific specifications for gloves and glove materials (Thomsen and Mikkelson, 1975) (e.g. latex, polyvinyl chloride, etc.). Limited reports have been published concerning the effectiveness of polyvinyl chloride and latex



Figures 5.3 Mutagenic activity in the urine of pharmacy personnel using *Salmonella typhimurium* test strain TA 1535

gloving material. The results with the combination of the Class II Biological Safety Cabinet and the wearing of latex gloves were dramatic.

Kruse (1981) has recently described biological saftey cabinets and their use in pharmacy practice. Since Kleinberg has demonstrated the detection or aerosolized drugs following manipulations in horizontal laminar flow hoods (Kleinberg and Quinn, 1981), it would seem feasible that the inhalation of particles or the absorption of drug through the skin would be the method by which personnel are exposed. It logically follows that any method of intervention preventing inhalation, ingestion, and absorption would provide maximum protection.

CONCLUSION

In projecting the significance of this study, one must keep the following considerations in mind. Many cancer chemotherapy agents handled by health professionals have been shown to be both mutagens and carcinogens (Weinstein, 1976, 1980; Harris, 1979; Wall and Calisen, 1975; Sieber, 1975; Rosener, 1976; Reimer *et al.*, 1977; Krikorian *et at.*, 1979; Bergsagel *et al.*, 1979). The significance of exposure to these personnel is not known. Effects may be subclinical and not become evident for several years following exposure. With this in mind, protective intervention seems to be the prudent course to follow.

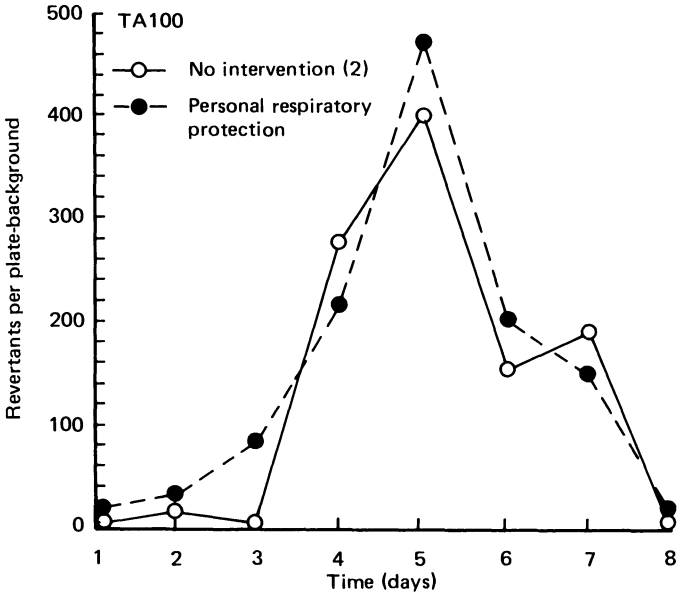


Figure 5.4 Effect of personal respiratory protection on mutagenic activity in the urine of pharmacy personnel

As stated before, relatively few guidelines for handling antineoplastic agents have been published. Over the past 3 years, however, guidelines have been published in Sweden (Department of Drugs, 1978), Norway (Directorate of Labor Inspection, 1980), Australia (Davis, 1981), and Canada (Canadian Society of Hospital Pharmacists, 1981). The National Institutes of Health have published recommendations (Zimmerman *et al.*, 1981) and several hospital pharmacists throughout the United States have developed and implemented similar guidelines (Harrison, 1981; Hoffman, 1980; Honda *et al.*, 1981). These guidelines routinely specify the use of specialty hoods and wearing apparel. Of the most stringent precautions, the Norwegian Directorate of Labor Inspection (1980) specifies that pregnant women should not handle antineoplastic agents. They also conclude that other high-risk persons are those who plan pregnancies, have allergies, previous abortions, previous history or congenital malformations, previous cancer treatment, and those who work with ionizing radiation.

Guidelines for handling antineoplastics have been developed by M.D. Anderson Hospital. These guidelines include basic recommendations concerning biological safety cabinets, protective clothing, compounding and administering techniques, disposal, personnel policy recommendations, and monitoring methods. The guidelines are included in the Appendix.

Results of this study represent a beginning for further studies at M.D.

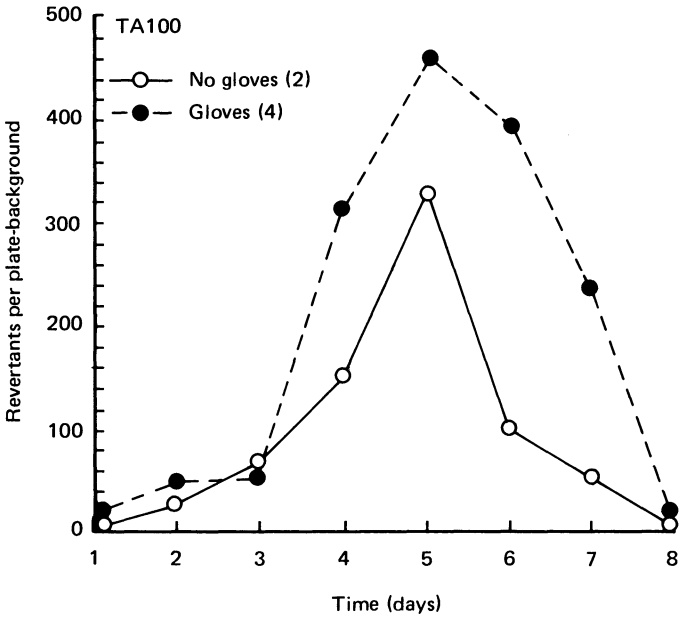


Figure 5.5 Effect of wearing gloves on mutagenic activity in the urine of pharmacy personnel

Anderson Hospital. On a continued co-operative basis, the Department of Pharmacy, the University of Texas School of Public Health, and the University of Texas Graduate School of Biomedical Sciences are actively involved with the following research protocols:

(1) Study of exposure liability in hospital personnel who administer, but do not mix, antineoplastic agents;
(2) Exposure liability of personnel who perform waste disposal;
(3) Chromosomal studies of personnel who prepare antineoplastic agents;
(4) Epidemiological studies of past, present, and future employees who now work or worked with antineoplastic agents;
(5) The deactivation of antineoplastic drugs in human waste, including general sewage treatment implications.

The guidelines developed from this study at M.D. Anderson Hospital are definitely rigid and will cause major changes in both compounding and administering methods. It is our opinion, however, that the evidence determined to date leaves little choice for the prudent practitioner. Our recommendation is that protective intervention methods must be followed by all persons handling these agents.

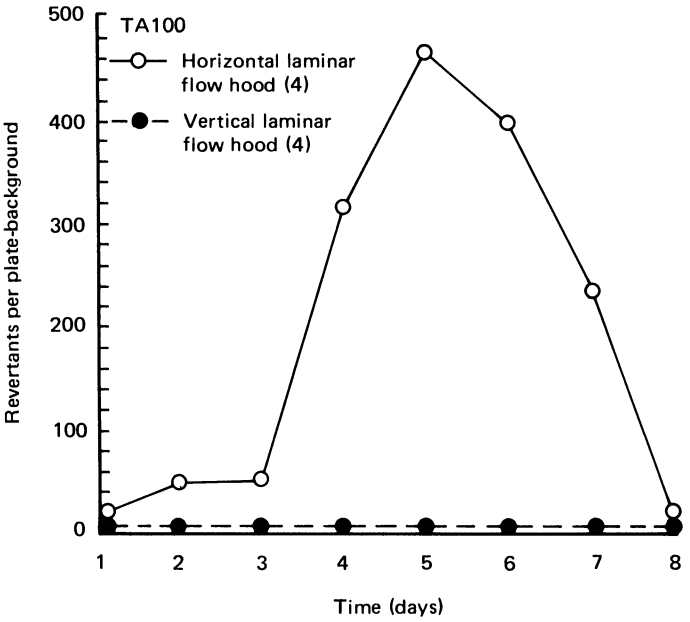


Figure 5.6 Effect of preparing drugs in a Class II Biological Safety Cabinet on mutagenic activity in the urine of pharmacy personnel

APPENDIX

GUIDELINES FOR HANDLING ANTINEOPLASTIC DRUGS

Biological safety cabinets

(1) All mixing of antineoplastic drugs shall be performed in a Class II Biological Safety Cabinet.
(2) Special aseptic techniques and precautions must be utilized because of the vertical (downward) airflow.
(3) No other i.v. admixtures should be prepared in biological safety cabinets designated for the mixing of antineoplastic agents.
(4) The biological safety cabinets should be certified by a qualified technician biannually, or any time the cabinet is physically moved.
(5) The exhaust plenum of the biological safety cabinet should contain a charcoal filter in addition to the HEPA filter.
(6) The biological safety cabinet must be operated with blower on, 24 h per day – 7 days per week.
(7) Drug preparations shall be performed only with the viewing window at the required access opening.

Gloves and protective gowns

(1) Disposable gloves must be worn for all procedures involving antineoplastic drugs. Double gloving is recommended when cleaning up spills.
(2) Disposable protective barrier garments should be worn for all procedures. These garments should have closed front, long sleeves, and closed cuff (either elastic or knit). Disposable protective aprons may be worn as a barrier in lieu of closed front garments.
(3) All potentially contaminated garments must not be worn outside the work area.

Compounding techniques

(1) Hands must be washed thoroughly before gloving and after removal.
(2) Care must be taken to avoid puncturing of gloves and possible self-inoculation.
(3) Syringes and i.v. sets with Luer-lock fittings should be used whenever possible.
(4) A sterile plastic-backed absorbent drape should be placed on the work surface during mixing procedures. The drape should be exchanged whenever significant spillage occurs, or at the end of each production sequence.
(5) Vials should be vented to eliminate internal pressure or vacuum.
(6) Before opening ampoules, care should be taken to ensure that no liquid remains in the tip of the ampoule. A sterile gauze sponge should be wrapped around the neck of the ampoule while opening.
(7) Final drug measurement should be performed prior to removing the needle from the stopper of the vial.
(8) A non-splash collection vessel should be available in the biological safety cabinet to discard excess drug solutions.
(9) The external surface of final i.v. containers should be wiped with alcohol-soaked sponges prior to removal from the biological safety cabinet.
(10) Special procedures shall be followed for major spills or acute exposures.

Administering techniques

(1) Disposable gloves shall be worn during all antineoplastic drug administration activities.
(2) Syringes and i.v. sets with Luer-lock fittings should be used whenever possible.
(3) Special care must be taken in priming i.v. sets. The distal tip cover must be removed before priming. Priming should be performed into a sterile gauze sponge, which then is disposed of appropriately.

Disposal recommendations

(1) All disposable items that have potentially come in contact with antineoplastic drugs during compounding or administration must be disposed of in specifically designated containers. These cardboard box containers shall have plastic liners containing an absorbent substance. All box seams shall be taped before removal from the work area. Designated content description labels and a 'Biohazard' symbol shall be placed on each container.
(2) All hazardous waste containers shall be disposed of by proper incineration.
(3) General cleaning of the work area must be performed using dust containment procedures. If vacuum cleaning is used, it must be through a central filtered system.

Personnel policy recommendations

(1) All personnel must receive special training in working with antineoplastic agents.
(2) The number of personnel working with these agents should be minimized.
(3) Eating, drinking, smoking, application of cosmetics, or similar activities are not permitted during compounding or drug administration procedures.
(4) Access to the compounding area must be limited to only necessary authorized personnel.
(5) The personnel working with these agents should be observed regularly by supervisory personnel to ensure compliance.
(6) Acute exposure episodes must be documented. The employee must be referred for professional examination.

Monitoring methods

(1) Routine urine analysis testing for mutagens should be performed to monitor the effectiveness of protective measures.
(2) A permanent registry shall be maintained of all employees who handle antineoplastic drugs.

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6

Microbiological risks for the compromised patient at home

P. Noone

I accepted your invitation to speak on this subject with some trepidation as I really did not know a great deal about it, in any quantitative, concrete way. Having researched possible sources of information I have come to a strong conclusion that nobody knows much about it in any overall, scientific way. Comparative surveys of hospital-acquired versus domiciliary-acquired infection in compromised patients have not been done and in any event are not strictly comparable. Compromised patients in hospital are generally more critically ill and/or more immunocompromised than those at home. Moreover, there is microbiological continuity between hospital and home for many of these patients in so far as a compromised host acquiring a colon full of hospital Gram-negative rods may well continue to be colonized with these organisms at home, especially if he/she continues taking antimicrobial therapy (e.g. co-trimoxazole prophylaxis against pneumocystis infection). Moreover, patients bring their own domestic and personal flora into hospital with them and these organisms may become invasive if the patient is subjected to cytotoxic therapy or invasive procedures.

But I think that what lies behind the title of this talk is the invitation to examine a generally held belief, which is part of conventional wisdom, or at least hospital folk-lore, that hospitals are dangerous places from a microbial point of view with multiresistant opportunist pathogens lurking everywhere ready to invade the immunocompromised host whenever

hospital staff are sloppy or overworked or both. On the other hand, home is safe – if only you can survive to get there. Colonized by old-fashioned, 'commensal' bacteria of low virulence and universal sensitivity – indeed they could even be looked on as friends.

But is this a true picture? Hospital certainly can be a dangerous place with regard to opportunist pathogens – we know about the food and medicines we eat, the intravenous infusions, the contaminated equipment, humidifiers, incubators, disinfectants; the dirty hand; the carriers and disseminators of pathogens and so on. But do those same risks or at least some of them apply at home? The truth is we do not know enough about the home environment. I will give some examples hopefully to disturb any complacency that may exist but first I must point out that since risks of the hospital environment are fairly well known we can take steps to contain them. But as we are ignorant about much in the home situation we are unable to give much scientific advice on preventing infection and hence we leave the compromised patient vulnerable.

Nevertheless, there are good reasons for going home – the quality of life is better (usually) and the costs of treatment tend to be much less. But at present, I must object to a 'lessened risk of infection' as being a major reason for going home. It needs to be proved.

Where are these reservoirs of opportunist bacteria and other micro-organisms outside of hospital? Well the usual list applies – fomites, food, water, the patient's own microflora, other people (especially children!), pets and livestock (whether four or six legged) or their 'products'. These reservoirs may be at home, at work, in institutions, restaurants, hotels – all the places we go to in the course of a 'normal life'.

Some of the obvious risks which spring to mind include *Streptococcus pyogenes* – a virulent pathogen – which is not uncommon in domiciliary and family settings. A small percentage of healthy people may be carriers and others will have minor sepsis, sore throat, sinusitis, infected fingers and the like. A recent report of 'scrum strep' (Dorman, 1981) illustrates how well this pathogen spreads by physical contact. The compromised host can be killed very rapidly by such infection.

Enteric pathogens such as *Salmonella* and *Campylobacter* are more invasive in debilitated hosts. Salmonellae are commonplace in frozen poultry, sausages, meat pies and other meat products. The risk of acquisition in undercooked or institutional food is appreciable.

But there are other infections spread via the gastrointestinal route and in a recent prospective survey of bone marrow transplant recipients, Yolken *et al.* (1982) found that 40% of 78 patients were infected with enteric pathogens including adenovirus, rotavirus, coxsachievirus and *Clostridium difficile*. The mortality in infected patients was 55% as opposed to 13% in non-infected patients ($p < 0.001$). These enteric pathogens are *not* associated with high mortality in normal patients.

But viruses of this kind are commonplace in the home situation. Viruses may also be a major cause of respiratory infection. About 20% of patients with radiologically confirmed primary pneumonia who were investigated showed evidence of viral infection (Editorial, *Lancet*, 1981). A further 20% had had mycoplasma infection. Secondary bacterial infection with *Streptococcus pneumoniae*, *Staphylococcus aureus*, and *Haemophilus influenzae* may also ensue.

In recent years Legionellosis has become well recognized and more readily diagnosed. Something of its epidemiology is also being elucidated. It is known that *Legionella* infections are more likely in the compromised host and carry a higher morbidity/mortality in that group. Certain hospitals have been associated with epidemics or sporadic cases of Legionnaires' disease but the agent can be found in many hotels and institutions particularly those recently built with humidified air systems. Dennis *et al.* (1982) in a recent review revealed *Legionella pneumophila* in 17 of 52 hotels examined in the UK, often associated with hot taps or hot-cold mixer shower heads. What do you tell your compromised patient? Don't stay in hotels?

Another opportunist bacterial pathogen recently recognized as a respiratory pathogen possibly associated with humidification systems is *Acinetobacter.* For long thought to be non-pathogenic, *Acinetobacter* became recognized as an ITU-kind of pathogen, often associated with pneumonia and catheter infections and with a high mortality (40% plus). Later, it was associated with pneumonia in alcoholics (outside of hospital) and more recently an outbreak of fatal pneumonia in iron foundry workers with silicosis (Editorial, *Lancet*, 1982).

But perhaps one of the most important opportunist pathogens in the domiciliary environment is *Mycobacterium tuberculosis.* A recent paper in the *Lancet* (Spencer Jones, 1982) indicates just how infective this agent can be and how devastating for compromised patients. Over a 16 month period 212 people (34 years or less) in a rowing club in Deal were exposed to a 66-year-old man, apparently healthy, who was president of the club. 74% remained Mantoux negative. Of the rest, active tuberculosis developed in three young people, all unprotected by BCG. There were two other cases in older people too. This may seem a low rate of infection. However, there were two fatalities – a 17-year-old with tuberculous meningitis and a 41-year-old alcoholic – a compromised patient. *M. tuberculosis* remains a particularly important opportunist in our compromised patients and one which it is difficult to detect at an early stage. A high index of suspicion is perhaps the safest reflex response to this risk.

Another respiratory opportunist is *Pneumocystis carinii.* In the past we have considered this agent to be a commensal which turns pathogenic in compromised hosts – a typical endogenous infection. But is this true? Masur *et al.* (1981) have described an outbreak of community-acquired

Pneumocystis carinii pneumonia between 1979 and 1981. The patients infected included drug addicts and homosexuals. Immunological testing showed that lymphoproliferation, T-cell counts and absolute lymphocyte counts were depressed but humoral immunity was intact. One patient had Kaposi's sarcoma, another angioimmunoblastic lymphadenopathy. Eight patients died. This study suggested not only that cell-mediated immune function was important in preventing pneumocystis infection but also that cross-infection may play a part. If this suggestion is accepted as possible, we are left with enormous grey areas of risk for all kinds of patients including children in remission from leukaemia. It also highlights the possible cross-infection problems from sexual liaison. What do we advise our compromised adult patients – not to compromise themselves? Not to have sexual liaisons? But otherwise lead a normal life?

I referred to foundry workers contracting *Acinetobacter* pneumonia but there are many other occupationally-linked infections. One example from the recent literature is Leptospirosis in trout farmers (Robertson *et al.*, 1981). Of course, the whole operation was plagued by rats; and rat urine in the ponds and around the trout food storage sheds was thought to be the vehicle of contamination. In the study four workers had flu-like illnesses, one had jaundice and one died. None of the workers were thought to be immunologically compromised. But I think this paper emphasizes another of the possibly unknown areas of risk – what would appear safer occupationally than trout farming? How would such risks affect compromised hosts?

But let us leave exotica and return to the bread-and-butter of hospital opportunist infection – *Pseudomonas aeruginosa* and *Klebsiella–Enterobacter – Serratia.* Surely here we are on safer ground at home than in hospital? Young *et al.* (1981) have written an excellent review of Gram-negative pathogens in septicaemia. As they point out, *Ps. aeruginosa* is the Gram-negative rod with the highest mortality (about 40–60%) in bacteraemia in neutropenic hosts (in hospital). The usual pattern of infection is that septicaemia is preceded by gastrointestinal colonisation (up to 6 weeks prior to septicaemia). In the absence of good immunoprophylactic measures, these workers point out that detailed attention to infection control measures (to prevent colonisation – as it is well known that *Ps. aeruginosa* is an epiphyte and a common contaminant of tomatoes and salads for example) and aggressive antimicrobial chemotherapy at the suspicion of the onset of septicaemia is the best approach. Although this approach is possible in the hospitalized patient, is it so feasible in the domiciliary patient?

I have no doubt that *Ps. aeruginosa* and *Klebsiella* infections do occur in domiciliary settings in compromised hosts. Prior to the 1950s perhaps alcoholics were the chief type of patient in that category. But advances in

haematology, oncology and renal transplantation have altered that situation.

In a prospective study in our intensive therapy unit over a 6 month period, two of four severe *Ps. aeruginosa* infections and two of three severe *Klebsiella* infections were acquired in a domiciliary setting – all in compromised hosts. There was little *Pseudomonas* or *Klebsiella* infection acquired by hospitalized patients during this period.

Ninane and Chessells (1981) reviewed 168 children with acute lymphoblastic leukaemia treated mainly at home over a 3 year period. The risk of fatal infection was most high in the first 2 years, and in younger patients, 8.3% (14 of 168) died from infection. Four of seven children admitted with bacterial septicaemia died. The deaths were caused by *Klebsiella*, *Ps. aeruginosa*, *Clostridium* species and *H. influenzae*. In each instance the patient had been ill for 48 h or more and were shocked on admission. Such a delay in diagnosis and treatment would not be likely in hospital. Respiratory tract infections (59% of all) were the most common reason for admission to hospital in this group and the agents responsible were very varied. Nevertheless, the agent with the highest mortality was measles, probably accounting for 36% of all deaths. None of these patients had been immunized against measles. It is worth noting that the death rate in this series is considerably lower than that quoted in comparable studies.

But although recognizing the high mortality associated with Gram-negative rod bacteraemia, it is worth discussing that changes may be occurring in the nature of agents causing bacteraemia in leukaemic, neutropenic and bone-marrow transplant patients. Own own review of positive blood cultures at the Royal Free suggest that Gram-positive bacteria now account for 60% plus of positive blood cultures and *Staphylococcus epidermidis* in particular (45% plus of total) has become significant. It is probably due in part to better prevention of Gram-negative sepsis, but no doubt also related to the advent of the Hickman catheter and total parenteral nutritition.

The problem is that we know very little about *Staph. epidermidis*. It is not a single species and we have no reliable means of typing strains so that we can study its epidemiology. Is there cross-infection with certain strains? It is certainly ubiquitous on the skin of patients and staff and shows an amazing ability to become resistant to antibiotics. It also seems to exhibit a predilection to colonize foreign bodies (especially plastics) in the human body and to cause low grade but debilitating infections. Spitz-Holter valves in neurosurgery, prosthetic heart valves and prosthetic hip joints all fall prey to *Staph. epidermidis*. Mehtar and Taylor (1982) examined 55 patients undergoing total parenteral nutrition at a district general hospital over a 29 month period. The introduction of an 'i.v. catheter policy' was associated with a reduction in septicaemia from 75% to 15%. Overall the rate was 27.6%. i.v. cannulae (50%) and 3-way taps (70%) were contaminated and

correlated with positive blood cultures. *Staph. epidermidis* was implicated in over 50% of cases although *Staph. aureus*, *Klebsiella*, *Ps. aeruginosa* and *Candida* were also involved.

Holmes and Allwood (1979) have reviewed comprehensively the microbial contamination of intravenous infusions during clinical use. As they point out, there are a whole range of ways in which contamination of i.v. fluids may occur. Sterile manufacture is obviously important but it is not unlikely that contamination of fluids will occur during use. *Enterobacter-Klebsiella* species show an ability to multiply in simple i.v. solutions but *Candida* species are the most important contaminants of TPN solutions. Whether administered in hospital or at home candida septicaemia is a significant risk with TPN. The diagnosis and treatment of candida septicaemia are difficult, putting it mildly.

Although *Staph. epidermidis* is a frequent contaminant of i.v. fluids and cannulae it shows little ability to multiply to large numbers. Nevertheless, it may colonize indwelling central lines and Hickman catheters and then cause a pyrexial and debilitating condition. Among other ill-effects this may lead to overtreatment with broad spectrum antibacterials and antifungals with possibilities of toxicity.

Fleer *et al.* (1982) reported recently on *Staph. epidermidis* bacteraemia in a neonatal intensive care unit. They found that 18% of intravenous feeding fluid was contaminated with the organism. In premature infants with deficiencies in activation of the alternative pathway of complement, bacteraemia with *Staph. epidermidis* was more likely.

Another group of compromised hosts with a high rate of *Staph. epidermidis* infection are those patients with end-stage renal failure undergoing continuous ambulatory peritoneal dialysis (CAPD) (Gokal, 1982). Over 800 patients are currently being treated by this method in the UK. The most important complication is peritonitis usually resulting from contamination of fluid, lines or an infected catheter site. *Staph. epidermidis* accounts for at least 40% of all infections and can be difficult to eradicate, as occasionally highly resistant strains are involved. In the hard core of patients with repeated resistant *Staph. epidermidis* infections it is important to ascertain whether their infections represent re-infection or relapse. As with all *Staph. epidermidis* infection much more detailed epidemiological information is needed so we can understand how it occurs and thus how we can better prevent it. *Staph. epidermidis* is a supreme opportunist pathogen because of its widespread habitat on people both at home and in hospitals, its undoubted capacity to develop antimicrobial and antiseptic resistance and its ability to colonize prosthetic and foreign materials in tissues.

At the moment all we can do is advise compromised hosts and their attendants at home to be scrupulous in their hygiene when handling intravenous or intraperitoneal fluids and cannulae and wherever possible

develop no-touch techniques; to avoid infectious contacts – including especially those with viral infections; also to have a low threshold for calling medical help if an infection is suspected. Prompt and aggressive antibacterial therapy is necessary to avoid fatality with several opportunist bacteria including streptococci, staphylococci and the Gram-negative rods.

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7

Home parenteral therapy and the general practice pharmacist

J. Kirby

May I first of all say how pleased, but apprehensive, I am to be here. As far as I know, I am the only community pharmacist here, and there we have an example of rapid progress in our profession. When I was asked to give this paper, I was indeed a general practice pharmacist, and was labelled as such, but now I am a community pharmacist! Just to prove that I'm not really a Daniel in the hospital lion's den, I did work in a hospital pharmacy for 2 years.

At the start my approach was simple – 'Find the problem'. As some of you may have seen, I wrote to the *Pharmaceutical Journal* in May, asking my colleagues for any experiences in the field under discussion. The result was disappointing – even given the ever present disease of apathy we live with – one letter, and this from an elderly and retired hospital pharmacist with whom I had been associated many years ago. In fact it was basically sentimental, and of no practical use in the preparation of this talk.

To illustrate the problem further, may I quote three examples from my own business. I was handed an FP 10 script one morning for a Mr B., who had received in the past Ventolin inhalers, Becotide inhalers and the normal treatment for an asthmatic or bronchitic. Although he was not a regular customer, one had built up a vague feeling of knowledge of the patient. This particular prescription on the morning in question was for a domicillary oxygen outfit. This I duly delivered later on the same day, as there was no urgency, and on arrival at the patient's home, discovered he

had a small suite of rooms to the rear of the house, with a kidney dialysis unit installed and functioning. This was completely unknown to my staff and myself. Secondly, a Mr G., presented regular prescriptions for low-protein foods and high-carbohydrate drinks, which was not unusual; as it has become a normal duty of the community pharmacist to give advice and supply dietary products. It was only after a discussion on a cooking detail with his wife that we learnt, by sheer accident, that Mr G. was a prospective kidney transplant patient. Thirdly, there was a Mr C., who had an aortic replacement; we only discovered this by noting with interest the medication prescribed, reading an article in the local paper and putting two and two together.

I mention these three cases in order to show the difficulty of the community pharmacist, in discovering the domicillary, chronically ill patient. We do not work as part of a permanent team with a formalized structure. There are no established lines of interprofessional communications.

Due to the financially stringent times we are facing, the fact is that more and more patients are going to be discharged from hospitals even more quickly than in the past. As we shall see (or are seeing) the one crucial question is, 'Who's responsibility is the patient going to be?' I hope to put forward a case for contribution to that care being available from the community pharmacist.

We have the precedent of diabetics originally obtaining supplies from hospitals; ostomy patients were first of all given all their appliances from hospital – and indeed we still have the situation of some manufacturers being appliance contractors and encouraging patients to order direct by sending FP 10s to them. This situation was not in fact helped by the attitude of some Community Pharmacists of not wanting to know – due in fairness to the niggardly payment to pharmacists for ostomy supplies by the DHSS. One can also use the community pharmacist's position in the supply of special dietary products for coeliacs, patients with pancreatitis and not least the domicillary oxygen service. Incidentally, here is a service which has become far more widely used and appreciated since the hospitals have been discharging patients more rapidly.

More recently, as a direct result of hospital policies, there has been a vast increase in catheterization of home patients, with the attendant new role of the community pharmacist in providing catheters. We all had our little drawer, containing one or two Jacques rubber catheters, but now it is a whole new ball game. There is also the spin-off of bladder washes, condom attachments and Uri-bags; areas in which the community pharmacist was ignorant both as to function, form and supply, but with which he has now come to terms.

The Drug Tariff, which defines the eligibility of appliances for supply on FP 10, has been reasonably quick to adapt to new needs and advances in

technology, although it did fight against 'Micropore' for many years, and one does have a little sympathy, because now no one uses zinc oxide plaster at all! Could everyone be allergic to zinc oxide plasters? I feel that a word of explanation may be called for here. The DHSS specifies that the doctor may determine what drugs and foods may be prescribed. If there is any query the DHSS takes it up with the doctor. However, for appliances and testing materials the responsibility of supply is with the pharmacist.

I am taking rather a long while to reach the kernel of my topic, but I feel that it is essential to develop the framework within which the community pharmacist works, so that you may grasp where and how problems may arise.

With the increase in the numbers of domicillary patients with needs for home i.v. therapy, will the routes outlined in the precedents quoted be followed? Will transfusion solutions of nutrients be supplied to the patient by the discharging hospital, or, since they have become available from commercial sources, may pressure be applied by the patient and the family to obtain supplies from the local friendly chemist? The great advantage of the community pharmacist is his availability – with respect to my hospital colleagues – they are not on everybody's doorstep. Research has shown that the community pharmacist is very often the first stop for requests for health information.

The major problem is, and I will grasp this contentious nettle at the start, 'Does the community pharmacist know enough to cope with the problem?' We belong to a scientifically-based profession. I qualified when Mersalyl and ammonium chloride were the accepted most efficient means of inducing diuresis and when acid acetylsal. 600 mg t.d.s. was the first treatment for rheumatism and gold injections second and last. I worked in a hospital where, in 1959, we had a jar of leeches, although I don't think we ever dispensed any for hypertension. We did have the new drug from India known as Rauwolfia. We took part in clinical trials for para-aminosalicylic acid and isoniazid. These have now virtually disappeared from the scene. Community pharmacists and hospital pharmacists have learnt to live with broad-spectrum antibiotics, beta-blockers (selective and not so selective), methyldopa, bendrofluazides, its derivatives and the benzodiazepines (several generations). We, all of us, have coped.

Not all community pharmacists deal with colostomy patients, catheters, oxygen, etc. and not all pharmacists are going to have a total parenteral nutrition patient presenting FP 10s. In fact, I understand that the DHSS predict an upper limit of four patients per 1 000 000 of the population over the next 5 years (DHSS, 1982). There is also an argument that TPN, is not always necessary or beneficial (Editorial, 1981). A further point, and one that may be controversial, is put by A.M.J. Woolfson (1981), 'is the expense of £250 daily for a TPN patient justified?'

We now come to specific problems.

(1) Supply of transfusion solutions. It is impractical for manufacturers to make solutions available to wholesalers, who are the main sources of supply for the community pharmacists, because the manufacturer must keep strict records of where any particular batch is at given time in case of the need for recall.

Direct supplies to the community pharmacist would require an availability of 24 h a day, 7 days a week and 52 weeks a year. If supplies come from the discharging hospital, the mechanics of payments would need to be formalized. The costs involved would make a mockery of the present informal exchanges and settlement that go on between many hospital and community pharmacies.

(2) Supply of the 'hardware', cannulae, pumps, tubing, etc. are not at present in the Drug Tariff. Arrangements would have to be made for their inclusion or for the supplies to be made by the discharging hospital.

(3) Any additives to be made to the transfusion, either rebalancing dietary intake or the addition of medication would require action. With the introduction of the improved type of 3 litre flexibag with its comparatively easy and trouble-free facility for making any additions, a community pharmacist should be capable of making the necessary changes, as they arise in a domicillary situation.

(4) Sterility and bacterial contamination. This is a major problem, as we know that no community pharmacy has a 'sterile' working area. This problem will arise when additions need to be made to existing solutions. However, I understand from an article in the Pharmaceutical Journal (1982) that this problem will recede as manufacturers like Travenol market more comprehensive formulations. Patients, I presume, would only be discharged for domicillary treatment after careful screening and any changes of treatment would be minimal. Bacteriological contamination would be kept to a minimum by good domestic hygiene.

(5) Other medication. Here, as I mentioned earlier, the community pharmacist suffers from being isolated from his professional colleagues. Nevertheless he is in ready contact with the patient's immediate support team, the family. Over the past decade more and more emphasis has been placed on the pharmacist's responsibility for the medicines he sells. Maybe there is the vested interest that if we show we care, then the Valhalla and monopoly on the sale of medicines will come more easily. This is not the forum to discuss that one, but this session is titled 'the responsibility of the community pharmacist'. Should we make sure that every vitamin preparation sold, every laxative sold, every analgesic asked for or every cough

medicine recommended is not for a patient on total parenteral nutrition?

Finally, I hope that I have shown you the problems that the parenteral nutrition patient or parenteral medication patient might present to the community pharmacist. I hope that I have persuaded you that the community pharmacist can adjust to change, and that if in the future we are asked to take this one on, or even share it with our hospital colleagues we will not be found wanting. The crux, and the title of this symposium is well chosen. It is not, '*who thinks they are best suited to do the job,*' but '*who will perform that job best for the patient*'.

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8

Home parenteral therapy and the hospital pharmacist

F. Gibson

The concept of home parenteral therapy has in common with all innovations, be they in science, art, or pharmacy, three stages of reaction. As these reactions are universal and predictable they have been made into a law, called Clark's Law of Innovative Ideas. It may be described in three phrases which are distinquished by the passage of time and success. The first phrase is 'It is impossible, don't waste time'. In the field of home parenteral therapy, this stage was passed years ago when home dialysis achieved what many assumed was an impossible dream. In fact, we would not be at this symposium today had it not been for those who ignored this typical reaction and went on to achieve success.

The second phrase, 'It is possible, but it is not worth my doing', is uttered at a later stage when those who issued the first statement acknowledge the inevitability of a success but strive to rationalize their own inertia. As pharmacists, we seem to be stuck at this stage in our professional development. But having said that, after listening to today's informative and exciting presentations, I am sure you can now envisage the tremendous opportunities for pharmacists in the delivery of this health care. I would like to discuss some of these opportunities, and to stress the advantageous position which hospital pharmacists are in to develop them.

I would like to challenge the pioneers in the audience to cast aside the second phase of Clark's Law and actively to pursue an innovative role

for hospital pharmacists in this field so that we can reach the third and final stage of Clark's Law which is 'I said it was a good idea all along'.

The information provided in the literature on hospital pharmacists' involvement in home parenteral therapy was searched by computer which reviewed the last 10 years of scientific and professional literature and I identified over 30 published references on this topic that were authored or co-authored by hospital pharmacists. The majority of this information appears in the American literature, 28 of the total being published in the United States. I am more familiar with the American system, nevertheless having worked in hospitals in Manchester for 3 months and for 3 months at St George's Hospital in London, I believe that much of the American experience can be applied in the National Health Service.

Table 8.1 Parenteral therapy administered by home therapy patients

Antihaemophilic factor
Cytarabine and other cytotoxic drugs
Analgesics
Parenteral nutrition
Antibiotics
Dexamethasone
Insulin

Table 8.2 The pharmacist's role in home parenteral therapy

Direct patient care
Provisions of drugs and supplies
Patient education
Indirect patient care
Co-ordination of transition to home care
Testing and evaluation of equipment
Educating other members of the home health team
Administrative activities
Inventory control
Research

Surprisingly, there is a wide spectrum of therapy which is being administered in the home and these are shown in Table 8.1. Three of these therapies, parenteral nutrition, insulin and cytotoxic agents, have been highlighted today. The rationale for these parenteral agents being administered in the home is twofold. The patient's quality of life improves because of the independence and mobility which is gained by the return to the home environment, and the cost of treatment is reduced. As an example, let us review the antihaemophilic factor programmes. Hospital pharm-

acists at Ohio State University train patients with haemophilia and their families in the proper administration of Factor VIII (Nold and Patrick, 1977). This training includes instruction in the reconstitution, storage and potential adverse effects of Factor VIII, as well as instruction in the technique of administration and record keeping. The pharmacist provides assistance to the patient in obtaining drugs and supplies, plus assistance on a 24 h basis regarding questions or problems with the therapy. This home therapy has led to an improvement in the patient's productivity in society, increased convenience and speed of treatment and a reduction of anxiety within the family. A 74% reduction in absenteeism from work and a 45% decrease in health care cost were recorded in a similar programme at another institution (Levine and Britten, 1973).

Pharmacists have contributed a great deal to the success of other home parenteral programmes (Schad *et al.*, 1979; Stiver *et al.*, 1978; Swenson, 1981; Ivey *et al.*, 1975). These contributions can be described in terms of direct and indirect patient care activities (Gaffron *et al.*, 1980), as shown in Table 8.2. In terms of direct patient care activities, the most *significant* and *innovative development* by pharmacists in home parenteral therapy has been in assuming part of the responsibility for patient education and training. It is this role as *educator* which holds the key to our future as hospital pharmacists in home parenteral therapy. This is the ideal opportunity to combine our technical expertise and our pharmaceutical knowledge with our professional responsibility for educating patients. In no other therapeutic endeavour is the persistent co-operation and interaction of nurses, pharmacists and physicians so crucial to the success of patient management as in home parenteral therapy. Hospital pharmacists can also make significant contributions behind the scenes. These include co-ordination of transition to home care, testing and evaluation of equipment, educating other members of the home health team, administrative activities, inventory control and research. All of these activities have been discussed throughout today's sessions.

I would like to make a plea to pharmacists involved in training patients for home care. They should be involved in documenting activities if they are involved in the training. They should also determine the cost savings that result from administering treatments at home versus in the hospital. The benefits that these patients receive should be evaluated by measuring end points such as the ability to return to work. These findings should be published and the results utilized for securing additional administrative support.

The literature supports what we have already heard today, that pharmacists can and do play an innovative role in home parenteral therapy. Many of you by now are saying, 'but all that is based on the American system, it'll never work here'. I'm convinced that this statement will soon become a corollary of Clark's Law. In considering what motivates individuals, my

theory is that 'people who do things' are adaptive to change, have the facility to implement the change and are committed to success. This chain of events is catalysed by certain behaviour patterns. I refer to these patterns as the p's of change, the t's of implementation and d's of success. The p's for change include the ability to *plan*, the talent for *politics* and the virtue of *patience. Timing, tenacity* and *tolerance* are an integral part of the t's of implementation. Finally, the individuals who possess the d's of success exhibit *desires*, *diligence* and *dedication*. The point of my theory is that at the end of each day it will be the pharmacists who exhibit these characteristics and skill, either individually or collectively, who will prove the fallacy of parts one and two of Clark's Law. I would like to leave you with one thought – 'I said it was a good idea all along!'

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Discussion

Mr Beaman: I would like to ask Mr Kirby if there is really a role for the community pharmacist in parenteral nutrition, until we get patient registration with community pharmacists?

Mr Kirby: When I was first asked to talk, my answer was "I don't see how there is a role" and then I read up about what was involved and now I feel that there is a role. But it is a minor role and I feel the role would be advisory, in an emergency, rather than playing any major part. The point I made at the beginning about diabetics and colostomy patients, if you had asked these questions a number of years ago, people would probably have said there is no role for the community pharmacist and yet now we are very much involved. I feel this will take place even more because of the third major issue of the talk, the financial restrictions that the hospital service can carry. I know that the money all comes from the same place in the end, but the community pharmacist will need to subsidise it for a few months and that the DHSS have to pay the final bill. The point is that at the moment I don't see all community pharmacists doing it; however, some may.

Mr Wozniak: I believe that the future holds a role for the community pharmacist in that more people will be treated at home by TPN, and that commercial companies will have developed acceptable products. Patients will be at a distance from the hospital, they will need delivery of supplies, they will probably need to hire refrigerators etc. and the community pharmacist is right on the spot. The question is will he, in view of the financial outlay and negotiation for items of service with the DHSS? I think it is refreshing to be given the chance to develop his service!

Mr Swallow: Could I direct a point at Dr Noone? This morning Suzanne Wood said that with their patients on home TPN, they don't recommend that their temperature is routinely monitored. Presumably, if patients are going to get septicaemia, they need treating quickly.

Dr Noone: I would take her point. Obviously, monitoring a temperature doesn't necessarily stop one getting septicaemia. If you do get septicaemia,

you are going to feel very ill. If you are feeling ill that is a good time to take your temperature. There may be other reasons for feeling ill than having a temperature, the trouble is when you have something like this wrong with you, you tend to blame everything upon it. Your hair falls out because you are getting on in years and you think it must be because of the condition you have – you have a scapegoat, and I think you have to be careful about that. One of the things you have to avoid is making people into hypochondriacs and I feel that this would be a great pity. Just like in hospital, you don't want people involving themselves in needless ritual which doesn't solve the problem at all and many people think that by involving themselves in ritual, they are avoiding the real problem. The first talk this afternoon illustrated that very well, people donning gloves and wearing uncomfortable masks and all the time they were getting poisoned.

Mr Tallet: I would like to ask Dr Anderson, with the benefit of what he now knows and with the benefit of hindsight, can he think of any staff at the M.D. Anderson Institute that have suffered illness, injury or anything of that kind from handling cytotoxic drugs.

Dr Anderson: Based on some of the anecdotal reports that have been published, we have tried to go back and determine if there have been any indications of a problem and really we have found nothing. We have mixed a lot of chemotherapy there and the exposure was there, but we have not experienced these kinds of side-effects. We go back knowing about mutagenecity and knowing about the fact that we were going to have perhaps delayed responses and the fact that it is not dependent on the quantity of dose or whatever the exposure, and even though we have not had these indications, we still feel that because of what we documented, we must minimise every possible chance.

Miss Day: One comment for Mr Kirby. North-West Thames Regional Pharmaceutical Committee are having an active battle with the Department of Health about the very slow way in which new items are getting on to the drug tarriff. You will probably have seen correspondence in the Pharmaceutical Journal on this matter and we have done quite a lot of looking into it. Tomorrow we are opening a domiciliary care unit and I am interested in how Mr Kirby would like prescriptions presented to him for 100x30mg diamorphine hydrochloride ampoules. Would Mr Kirby comment on what form of consultation there should be when such a script emanates from a visiting GP acting from a hospital clinic.

Mr Kirby: Do you mean professionally?

Miss Day: What I actually meant was, we have arranged that the domiciliary nursing staff from the hospital will call in to the community pharma-

cist with this prescription and explain the background to it. Would you have felt this was the right way?

Mr Kirby: It is really what I am asking for! It is co-operation between the two services involving the community pharmacist. I can't think of a better way of doing it.

Mr E. Howard: I would like to ask Dr Noone if he knows of any work done on common home disinfectants to replace hospital antiseptics for patients discharged from hospital. Such as using diluted 'Domestos' instead of chlorhexidene which the patients can use in their own home so they don't have to become reliant on hospitals.

Dr Noone: I would be interested to learn about it. 'Domestos' is really hypochlorite and it doesn't matter about the trade name. I think there may be dangers in handling Domestos and I think it is best to supply the users of disinfectants with the disinfectants at the in-use strength, rather than getting them to dilute down more concentrated disinfectants. This is certainly true in the hospital service and probably just as true in the community. One should use antiseptics and disinfectants which are easy to use, but I would be shocked if you suggested we should use 'Dettol' instead of chlorhexidene.

Mr Williams: One just wondered about the specificity of that test for mutagenecity. Whether drugs which are thought to be relatively harmless would ever give rise to false positives. What happens to people who have been taking antibiotics or perhaps steriod hormones. Do these give false positives in that kind of test?

Dr Anderson: Yes, there can be some outside sources which give false positives. It is one of the reasons why all staff maintain a log of their food, smoking etc. and we advise those doing the testing of this background. The one thing that was pointed out by the longitudinal study was that all this was taken into consideration and still we had the peak occur, corresponding exactly with the exposure to the work environment. Those would have ruled themselves out as a control against themselves, but there needs to be a better testing methodology than just 'Ames'. We realise that and we are working on those kinds of studies right now. It has a lot of drawbacks and yet it is one of the most respected tests for mutagenecity and carcinogenecity. It was a simple system for us to use; it is still very expensive to do on a routine basis, but at the time it was a good system to document the exposure. At this point, it is all we claim to have done. To really assist the health hazard inquiry it will need another set of studies.

Dr Capps: I was very interested by Dr Anderson's comment on the chemical treatment of sewage. I know that thiosulphate reacts very rapidly with certain alkylating agents to break them down. Have you done any other work on chemicals which might be effective in rendering both alkylating agents and anti-metabolities less reactive?

Dr Anderson: We have not done too much now. We have contacted all of the major manufacturers and asked them for methods that they know of for the deactivation of their particular products, but what we want to do in the Institute is to develop a process which can be used universally. We would like to have one agent that would do everything but I doubt if it will be found. We really want if for two purposes. One, to react with the materials as we collect them from the patients and also some system that we might be able to use in the home environment. Some chemical that can be packed in a small container and used on each occasion – that is one of the projects that is barely under way at the present time. We don't expect to come up with a universal treatment, but we feel the need to explore it because the quantities we are talking about are much greater than the kind of exposure we are talking about here, and they do have an exposure to the entire community.

SECTION THREE

New Approaches in Practice

Chairman:
Mr D.R. Knowles

9

An evaluation of the use of case studies in clinical pharmacy training

E.A. Aston and S. Hudson

In offering a clinical pharmacy service, one of the major limitations is the ability and experience of the participating pharmacists. In 1978, when it was decided to adopt a more clinically orientated approach to the pharmacy service in the Leicester area, the training of staff was seen as the first priority. The training programme devised then has been described previously (Tobin, 1980; Godfrey *et al.*, 1979). The course was based on formal lectures held weekly, immediately after work. The course provided background information on common disease concepts and was designed to stimulate course members to undertake private study.

The attendance on this course was remarkably high and we were pleased with the general enthusiasm shown by all grades of pharmacist to develop the clinical approach to pharmacy. In order to exploit this enthusiasm, meetings continued on a fortnightly basis with pharmacists presenting case studies based on patients from their wards. Pharmacists benefitted from the preparation needed before the presentation and from the opportunity to present their views and experiences to other professionals.

However, in 1981 it was decided to 're-formalize' the meetings and to offer a structured course of seminars based on case histories. The use of case histories meant that staff who had joined the area since the formal course ended would gain knowledge of the basic concepts involved in each disease state, whilst more experienced staff could see examples of how and where to apply pharmaceutical knowledge in patient management. The

structured programme encouraged members to attend regularly and the format made private study essential.

Course members were given case histories, with specific questions to answer, before each meeting. Two case histories would be discussed at each meeting, with the members divided into two small seminar groups to encourage participation by all members. Each meeting ran from 5.30 p.m. to 7.00 p.m. with refreshments provided. The course lasted from March, to June, 1981. Table 9.1 shows the completed programme.

The attendance on the course was again high, with members from all grades involved, as shown in Table 9.2. Table 9.2 also gives attendance figures for the course. Considering that the course was held out of working hours, it is gratifying to see that pharmacy staff are so motivated to improve their contribution to patient care.

With any training programme it is important to assess its effectiveness. At the end of the lecture course in 1979 an unannounced test paper was given to the course members. The average mark on a paper of 34 multiple choice questions was 40%. Unfortunately it was difficult to assess the significance of this result in the absence of a pre-course test. However, in a similar American study (Sula *et al.*, 1979) test scores before and after an intensive education programme had been shown to be significantly different.

Table 9.1 Programme of case studies used in a clinical pharmacy training programme

Week	*Case study 1*	*Case study 2*
1	Unprepared test	Hypertension
2	Diabetes	Neoplastic disease
3	Overdosage (iron)	Asthma
4	Depression	Peptic ulcer
5	Ulcerative colitis	Bronchitis
6	Epilepsy	Schizophrenia
7	Liver failure	Cerebrovasular disease
8	Meningitis	Overdosage (Distalgesic)
9	Unprepared test	Anaemia
10	Renal failure	Thyrotoxicosis

Accordingly, at the start of the new seminar course, and again after 11 weeks (15 case histories), an unprepared multiple choice question paper was given. Question papers were submitted anonymously, but coded to enable comparison of results for individuals. In order to exclude any difference in the two test papers, the course members were divided into two groups. Whilst the first group received Paper A initially and then Paper B after 11 weeks, the second group received Paper B followed by Paper A. Results for the two groups are shown in Table 9.3.

Table 9.2 Membership and attendance for a clinical pharmacy training programme

Grade	*Number (% of grade)*
A.Ph.O.	1
D.Ph.O.	2 (67)
Principal	1 (50)
Staff	6 (60)
Basic Grade	19 (63)
Pre-reg	9 (100)
Total	38
Attendance	
Mean	27 (71%)
Minimum	20 (53%)
Maximum	30 (79%)

Table 9.3 Results of two unprepared tests before and after a course of case studies

Group	*Test sequence*	*n*	*Mean score % (±SE) before*	*after*	*Mean difference in score % (±SE)*
1	A – B	10	34 (±5.4)	41 (±4.9)	+ 7.7 (±2.1)*
2	B – A	12	25 (± 5.2)	32 (±3.9)	+ 7.1 (±2.2)†

Using '*t*' test between paired samples, t, = 3.62* and 3.19† ($p<0.01$)

Analysis of the results showed that 19 out of 22 (86%) course members improved their test score. Analysis using a '*t*' test for paired samples showed that the improvement was highly significant ($p < 0.01$). It is interesting to note that the average post-course score was 36% which correlates well with the result from the 1979 course. The average score in both cases was apparently low and we feel this illustrates the need for most pharmacists to study regularly. The course members varied considerably in age and experience but the improvement was seen in all grades.

We feel these results illustrate the usefulness of case studies as a means of training staff in clinical pharmacy. The advantages of case studies compared with formal lectures were:

(1) The increased involvement of course members. Staff could contribute experiences from their ward work to the seminar group.
(2) The preparation necessary by course members encouraged them to undertake private study.
(3) More pharmacists were willing to contribute a case history and lead a seminar group on that subject than to lecture on the subject. This meant the teaching load was spread. The 18 case histories were submitted by 11 pharmacists.

(4) The format was acceptable to both experienced pharmacists wishing to see more practical application of clinical pharmacy, and to new pharmacists wishing to learn basic concepts.

In conclusion, we have shown the effectiveness of a clinical pharmacy training programme using case studies. We hope both the enthusiasm of pharmacy staff and improvement in their clinical knowledge demonstrated here will encourage other areas to organize similar training schemes.

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Discussion

Mr Clark: You raised a small point which may not be pertinent to your main course and that is that medical students are trained to continue learning and pharmacists are not. Could you say something about that?

Mrs Aston: I think the training of medical and pharmacy staff altogether is completely different. One of the things that we found about pharmacy staff is that they are reluctant to stand up and defend their actions and they are not used to being put on the spot. Medical students are put on the spot right from day one all the way through the course, because of the viva system that is used and because they are thrown into the consultant's ward round. I think it would be a big help if we started training pharmacists at the college level in that kind of system. The other thing is that there are other qualifications doctors have to obtain if they are going to go on any further in their careers and at the moment these don't exist in pharmacy. Hopefully, the College of Pharmacy Practice will change this and people will be committed to continuing education if they want to get any further in their careers.

Dr Shaw: This is obviously the second part of an ongoing part of pharmacy training. Can you elaborate your ideas on the third part in terms of what happens next?

Mrs Aston: Because of the turnover of staff, there are always new staff who need to be trained in the basic concepts. Case studies were the way to continue. We found that we could get over basic concepts without boring the pharmacists who were already there and who had been doing the job for 2 or 3 years. We found, when we let the meetings become more informal, that the attendance dropped off and that people were not committed. I think you have to have the boost of another formal course, perhaps every 18 months. We couldn't organize this kind of programme on a regular basis within working hours, much as we would have liked to have done it as this would have been the ideal answer.

Mr Beaman: The third instalment of what they are trying to do is to programme this training into normal working hours. We have had a lot of

problems in trying to find the time and convince pharmacy managers to give us the staff time to do this. It is now up to the pharmacist managers to agree to the appropriate arrangements.

Dr Fish: The mark at or about 40% would in normal degree terms be a bare pass. They would all be borderline. Also the spread of results was not very great although, of course, your numbers were small and one might have expected this, but as I recall it was, plus or minus, about 5%. Can I ask you if you validated the MCQ (multiple choice question) tests that you used, and if so, how?

Mrs Aston: No.

Dr Fish: It is essential to validate MCQ tests.

10

An integrated approach to ward pharmacy

R.D. Swallow

INTRODUCTION

The project described in this paper was carried out in a teaching hospital of 705 beds with patients staying, on average, 10.5 days and having an annual discharge/death rate of approximately 24 000. The pharmacy department provides a full 24 h service including a full i.v. additive service, backed up by a drug information service. Ward pharmacy commitment consists of 20 wards being covered by the equivalent of six in-patient service day pharmacists and ten wards being covered by pharmacists from other areas of activity.

The situation existed, however, whereby the approach to ward pharmacy was in need of change and development. The interaction of the pharmacist on the wards with medical and nursing staff was somewhat weak and that with patients virtually non-existent. Also the old system of non-stock drug distribution was rather haphazard and both pharmacists (especially 'out of hours' staff) and nurses had a low level of confidence in the old system.

The pharmacists' role on the ward tended to follow a repetitive and time-consuming routine with relatively little positive feedback on what they had been doing on their ward visit. This consequently widened the segregation between the day and night service and thus work was either duplicated or the night pharmacist was not readily aware of how problems with a particular patient had been dealt with by the ward pharmacist.

In short, the pharmacists' role on the wards was largely uncoordinated;

also, time-management was very poor and as a result clinical areas of activity were underdeveloped.

THE 'NEW' APPROACH

It was apparent that a totally new approach to ward services was needed and the following objectives needed to be met:

(1) Better integration professionally with ward staff (medical and nursing).
(2) Streamlining of the drug distribution system.

(3) Establishment of close working links between the ward pharmacy service and the pharmacy department as a whole.
(4) Improvement of patient awareness of ward pharmacists.

(5) Better co-ordination of ward pharmacists by the staff pharmacist responsible for ward services, make them more accountable and responsible for their actions on the wards.

Several approaches to these problems were considered but eventually it was decided to explore the possibility of introducing a system utilizing ward pharmacist-maintained patient medication profiles.

PATIENT MEDICATION PROFILES

The idea of patient medication records is not new; in fact several papers have been published discussing the advantages and disadvantages of such systems in principle (Kradjan, 1974; Sloas *et al.*, 1975; Erskine *et al.*, 1978; Toal, 1973), including a very extensive survey published by the American Pharmaceutical Association (Brown and Sommers, 1973). However, the majority of work was concerned mainly with hospital out-patients or patients in the community (Visconti, 1969; McCarron, 1975). Our proposed system was felt to be fairly unusual in that the profiles would be maintained exclusively by the ward pharmacist; it would be totally separate from any prescription or administration record and it would be concerned only with hospital in-patients.

Pilot study

The proposed scheme was put to the other pharmacists in the department and, on the whole, most were keen to give it a trial. The counter arguments included the feeling that it would be too time consuming to maintain such records and that the hospital was too busy, i.e. such a system would not be suitable for an acute general hospital.

To put the idea to the test a pilot study was set up on three medical and three surgical wards using photocopied profiles in small ringbinders. This concept of a record of individual patients' drugs was very well received in principle, but the ring binders proved cumbersome in use. There was a need for a good, easy-to-use portable filing system.

Kardex system

Ultimately it was decided to try a portable version of the filing system much used by nurses, the Kardex system (Figure 10.1).

When designing the patient medication profile card to fit in the Kardex, four basic requirements had to be fulfilled, namely:

(1) Patient's name,
(2) Consultant's name,
(3) Facility to record drug details,
(4) Facility to record clinical details,

Several prototypes were drawn up before the final one was submitted to the printers (Figure 10.2). The initial evaluation of the Kardex units was carried out on two medical wards and one professional surgical ward using 'loaned' Kardex units and photocopies of the printer's proof of the card.

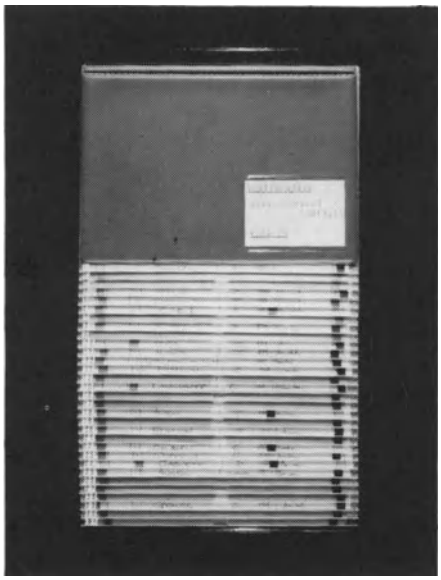

Figure 10.1 Portable Kardex unit

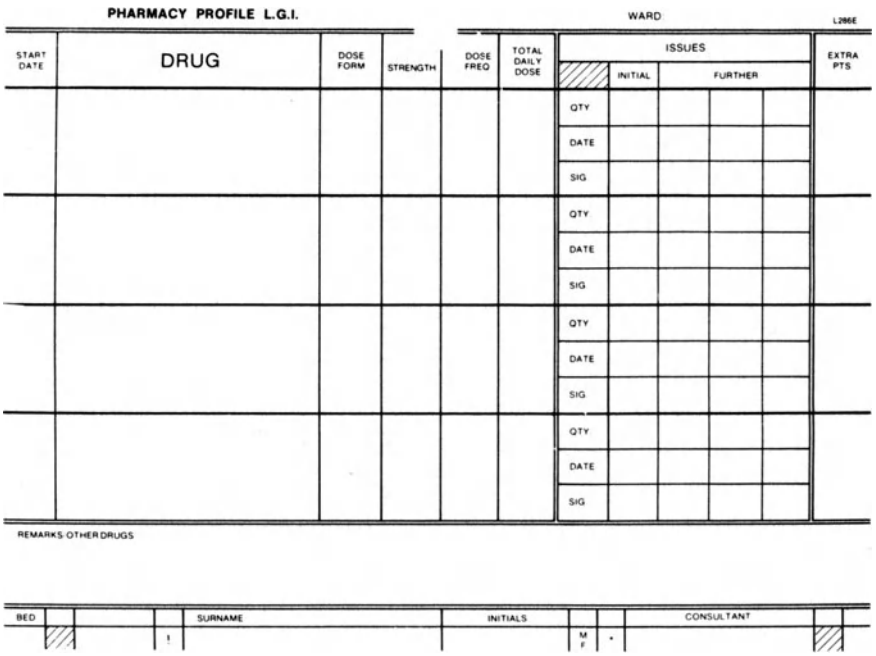

Figure 10.2 Leeds General Infirmary patient medication profile

The system was very well received and was subsequently accepted properly. Kardex units were gradually introduced onto all wards (except on the intensive therapy and neonatal care units) and cards were printed commercially. Patient medication profiles have now been widely used at the Infirmary for over 18 months and several advantages are readily apparent. The units are very easy to use as they include special indicator 'flags' to bring any one card to the user's attention. There is now a permanent record of each patient's drugs (only non-stock drugs are recorded in absolute detail) for each ward. This is extremely useful, for example, for queries concerning discharge drugs and problems encountered by the out-of-hours pharmacists. In fact, the pharmacists' records of a patient's drugs and drug problems are often more accurate than those recorded in the patient's notes. The drug distribution of non-stock drugs is much more efficient and reliable (dispensing is carried out directly from the profile). The ward pharmacists are much more patient-orientated and a great deal more time has been made available on the ward to look into and sort out patient problems (Figure 10.3).

One of the few disadvantages is that not all the drugs are recorded *in detail* (only non-stock drugs); this was felt to be a reasonable compromise

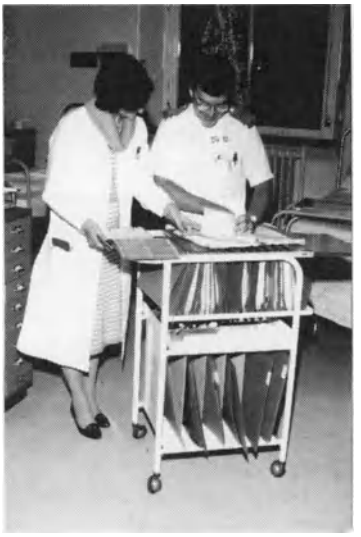

Figure 10.3 The system in action

in a busy acute hospital. Also on the present card there is possibly not enough space to record all the necessary clinical data. A check-list format of age, weight, serum creatinine, other relevant laboratory results, drug levels, etc. is under consideration. There is still room for development!

The attitude of the ward pharmacists is subjectively better and it is probably fair to say that they are more fulfilled by having a positive role to play on the wards.

The ward pharmacists are much more accountable for their actions on the wards and guidelines are rigorously laid down to cover such items as drug-dose monitoring problems, parenteral nutrition, etc. The ward pharmacists are also expected to be fully responsible for problems arising from their wards and such problems are referred to the relevant pharmacists who are expected to follow them up in full. Undoubtedly, a higher standard of practice is now expected of all our ward pharmacists.

CONCLUSION

The ward pharmacy service at Leeds General Infirmary has been more highly integrated with the service as a whole and confidence in drug supply has been greatly enhanced. Clinical awareness and job satisfaction of the ward pharmacists is better, and liaison with both patients and ward staff has greatly improved.

No system is perfect, but this one has evolved to cover the whole of a

large teaching hospital and work is being carried out to design a suitable patient medication record for the Intensive Therapy Unit.

Some problems of motivation of staff exist as in most hospitals, but now that the basic system is firmly established, training and monitoring the role of the ward pharmacist is already proving to be easier to organize.

Stevens and Wolfert (1969) reported the use of a system of patient medication profiles and stated, 'In our experience and judgement, such a system of (in-patient) medication profiles is warranted to bring the pharmacist closer to the patient'.

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Discussion

Mr Purkiss: We have tried patient profiles on and off for two years now, and we have great trouble in getting the pharmacist to fill them in because they say they are transcribing data which is already on the prescription sheet and which is already in the patient's medical notes which they see regularly.

Mr Swallow: We felt that we needed in the pharmacy a record of what drugs the patients were on and to link this type of record with the drug distribution system. I take your point, the information is already there. We wanted to have a system whereby we had a record in the pharmacy of the drugs the patients were on as well as other information about the patients. Short of having a photocopy of each prescription on the wards, we felt that a patient medication profile was one step towards the ultimate utopia of having a system whereby the prescription is directly transcribed on to a record that is transmitted down the phone to the pharmacy. The question of encouraging the pharmacist to fill them out fully did occur with one or two pharmacists, I am pleased to say not with the grade 1 pharmacists; the problems arose among pharmacists of higher grades, for example, those involved in areas other than patient services. We seem to be ironing out these problems and I think that this type of system needs someone who is motivated to co-ordinate it. This system does work of its own accord.

Mr Nunn: Patient profiles have been an integral part of our paediatric pharmacy service for the last three years and I reinforce what you have said about them. They do contain a lot of important information. Can I ask if they form a permanent part of your patients' record?

Mr Swallow: At the moment, no.

Mr Nunn: Why not?

Mr Swallow: It is something we had not really considered putting in the notes. At your hospital, do your patient records go into the paediatric notes?

Mr Knowles: (Chairman) Does that imply that you have a formal agreement for the keeping of profiles by pharmacists with the medical staff and the administration and other people so that it becomes part of the patient record?

Mr Swallow: I think you see from what has been said this morning, about the type of information that a pharmacist is collecting, that often it is collected and integrated in a far better way than most current medical notes and so we would say that a lot of this information is essential. I think pharmacists in general are poor record keepers and we ought to be keeping a record of our interventions and this is one way of doing it.

Mr C. Cairns: We have been using a similar system for the last couple of months for slightly different reasons. We have found some other benefits from it. One is that when prescriptions come down from the wards, they are checked against the medication profile for the patient and a high amount of error has been detected between what the patient was getting on the ward and what the resident has written up for the patient going home.

Mr Swallow: I did intimate in my talk that one of the very important benefits from this system is that discharge queries can be more easily handled and I feel the pharmacist is probably more careful in keeping a note of exactly what the patient is on from the prescription. Much more so than from the discharges which are written out separately.

11

Ward and clinical pharmacy – a comparison with Holland

D.R. Forbes

The Department of Clinical Pharmacy, St Raboud Hospital, Nijmegen, with 900 acute beds, employs 60 staff of which seven are pharmacists giving a ratio of 0.1. Bristol Royal Infirmary and associated hospitals employ 45 staff of which 15 are pharmacists; a ratio of 0.3. With a lower ratio of pharmacists to total staff, Nijmegen provides a more active clinical service than we do at Bristol Royal Infirmary. I visited Nijmegen, Holland, to investigate the reasons for this difference.

The criteria that showed a more active clinical service were therapeutic drug monitoring, unit dose, cytotoxic reconstitution, total parenteral nutrition solution preparation and drug utilization reviews. These were the outward signs of the service at Nijmegen that differed from ours. It can be debated whether these contribute to better patient care.

I would normally consider that to implement these changes would represent a claim for more pharmacists. So, how had Nijmegen achieved their development with so low a ratio of pharmacists to other staff? Their success must first be put into perspective. The Netherlands has been a wealthy country although things may now be turning sour. From what I have seen, their hospital buildings are most impressive and spacious but clearly revenue intensive. There has been money to upgrade departments and personnel, the like of which has never been seen here. But there is an underlying and fundamental difference in attitude that explains much of their success. I identified two philosphical reasons for this success.

The first is that the pharmacists concentrate on drug and patient orientated pharmacy. This seems too obvious to mention but the attitude that

the pharmacist cannot be a jack of all trades was clear. The Dutch pharmacist aims to be a master of a few and these are the drug-orientated areas mentioned earlier. A computer needs a computer expert, not a pharmacist playing at computers. Engineering needs an engineer, not a pharmacist playing at it. Administration needs an administrator not a pharmacist playing at it. But the management of the pharmacy needs a pharmacist to manage it; to decide priorities to ensure the department is drug-orientated. In Holland this management is carried out in a structure almost totally devoid of the strict pyramidal hierarchy which we have struggled to build. There is one pharmacist registered with the Hospital Board as the Pharmacist and 6 further pharmacists graded by length of service and experience and not rewarded by titles in the hierarchy.

The clear message to me is that we must unlearn traditional attitudes of career structure. We must concentrate on improving what we are employed to do, do it well and employ specialists to do the other tasks for us. To do this we must create 'space'. Most of us will not have access to development money for some years to come, so we must create it ourselves. This 'space' may be time, it may be money, but it will mean rethinking our departmental structure. This has been achieved at Nijmegen by ensuring that as posts fell vacant, the best use was made of the available revenue to buy a specialist. Further 'space' may be created by deciding no longer to develop the pharmacy service to meet developments created by medical staff but to develop the services for our own benefit.

The second philosophical approach is that Nijmegen gives pharmacy technicians greater responsibility than we currently allow. Whereas in the past we may have found this difficult to accept professionally, the TEC training of technicians will give us the opportunity to match increased skills with increased responsibility. There can be little doubt that the hospital service has 'supervised' dispensing as defined by the PSGB. We may now have to move to a more relaxed attitude as exists in the community.

Most of the ward pharmacy at Nijmegen is carried out by technicians. Pharmacists cover the high dependency wards of ITU, cardiac surgery or where there is a greater pharmaceutical involvement such as in the neurological unit. The dispensing of presciptions however is done and checked by technicians. The ward supply is totally unit dose from a distribution centre/dispensary. The nursing staff on all but a few wards fill the medication trolleys from the unit dose stock supplied. Pharmacy technicians do fill some medication trolleys directly but this is seen as too time consuming to extend to all wards. This means that all requests for oral medication are met by a unit pack.

I have no doubt that we will move to unit dose as a cost saving manoeuvre. We must agree early on a standard package. In Europe there is already agreement for oral dosage forms on a standard blister format and packaging for them. We must urge manufacturers and colleagues to accept

this so there can be no excuse for manufacturers to opt out as they often do and perhaps rightly, by claiming hospital pharmacists cannot agree on what is wanted.

But, most important of all, is Nijmegens's quest to evaluate what they do. The therapeutic drug monitoring system is one aspect of this. We have talked for long in the UK about statistics and how to measure workload in pharmacy but little about drug utilization research. Can I recommend that we adopt a uniform system for evaluating drug utilization, that is used in many European centres. It exists, it works and would give us useful inter-authority and inter-European comparisons.

I refer you to Chiel Hekster's paper to the *Clinical Pharmacology and Therapeutic World Conference* at Wembley (1980), 'Record Linked Audit of Drug Utilization Data in Hospital' using the concept of defined daily dose, originally proposed by Lunde *et al.* (1979). The defined daily dose is the estimated average maintenance dose for the main indication of a drug as established by the Nordic Council of Medicine. This is modified by taking into account bed occupancy, number of beds studied, the period in days and the total daily divided dose. The relevant equation provides a term called the adapted Daily Divided Dose. This is expressed as the probability that a patient is treated with the particular drug or the percentage of patients who receive that particular drug. Using this method of data collection, Nijmegen have been able to show the effect of policy decisions on areas such as microbial use in a urology ward and the reduction in the use of albumin.

Any requests for an extemporaneous medicine were sent to the production unit via a VDU terminal link after being checked by the technician for accuracy. The dispensary and distribution centre were run by technicians and the only pharmaceutical involvement was to check at the end of the day how the requests had been coped with.

These are then two philosophical approaches which we might need to look at further; greater use of specialist non-pharmacist staff, and increased responsibility for technicians.

There are some visible, practical differences to couple to the philosophy. Total parenteral nutrition solution preparations and cytotoxic reconstitution are, I know, done to some extent by many centres now. These areas are again, essentially run on a day to day basis by technicians. Pharmacists in particular have a close involvement in therapeutic drug monitoring service based on 'Emit' analysis and backed by computer interpretation of results.

The service offers stored medication history and drug concentration values with three main objectives. Firstly, it provides a written report and case history of the individual patient supported with laboratory drug plasma concentration values and reference values where applicable. Secondly, it accumulates data that allow epidemiological studies and

statistical identification and determination of variables in drug clearance. Thirdly, it provides a computer recommended prescription, medication history and instruction service for anti-convulsant drugs.

There are some features of hospital practice at Nijmegen that would not meet our standards. For example, ward pharmacy being run by the technicians means little contact with the medical staff. Any prescriptions requiring interpretation are relayed to the nurse, then to the doctor and back. On one ward, the prescriptions were not signed and this appeared to be reasonably common. What was worse, was that on one occasion, the ward clerk brought the prescription in and wrote it, 'on the instructions of a doctor'. Perhaps this is added reason for a pharmacist to visit the wards personally.

The comparison of ward and clinical pharmacy between Nijmegen and Bristol Royal Infirmary highlighted some positive advantages that we should consider.

(1) The need for hospital pharmacy to concentrate on the drug orientated approach.
(2) To employ specialists where specialist advice is needed.
(3) To give technicians greater responsibility.
(4) To use proven research methods to show how effective drug control measures are.

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Discussion

Dr Shaw: Could I ask if there are any salary differences between technicians and pharmacists and what sort of scale they have?

Mr Forbes: The pharmacists' salaries are twice mine and their standard of living is about the same as ours. They are well paid, there is no doubt about that. The pharmacists think they are on a par with solicitors and barristers. The technicians similarly are slightly better paid than we are. It would be the same as technicians' and pharmacists' differential.

Mr Clarke: I went to Nijmegen a little time ago and obviously things have developed. Two things came out as far as I can see. One is that we have a much higher standard of finished buildings when we do get around to building them, particularly in aseptic areas. The other is that I think you have rather underwritten the level of education of those technicians. They were more like the old C & D level of person rather than our present technicians who are considerably below that. I welcome the development of TEC, but I don't think TEC will lift us anywhere near that sort of level. I would also like to support the idea that technicians ought to be better used.

Mr Knowles: Would you agree, Mr Clarke, that with TEC there is the possibility of moving in the general direction that they have in Nijmegen, as Mr Forbes has been saying?

Mr Clarke: I think this is the whole purpose of TEC, is it not, that we should be able to move on from TEC?

Mr Forbes: But I think many pharmacists have seen TEC as a 'threat'.

Mr Clarke: I have been in hospital pharmacy for a very long time and all through my life and my time on the Guild Council, the great threat was that the technicians would take over the pharmacists' jobs. I have never believed this and I never will.

Mr Forbes: Yes, I am sure you are right, but education of itself doesn't mean that the technicians are any more effective. I thought it was dis-

appointing that with their apparent excellent training, they weren't using it to the optimum advantage. They weren't contacting doctors and they weren't intervening in the same way that the pharmacists have been reporting here this morning. Whether there is a role for using the TEC Technicians in this way is a matter of debate.

Ms Wild: From your statistics, you said approximately 0.01 pharmacist per patient, which in one pharmacist per 100 patients. At our hospital, we have 17 pharmacists and in excess of 1500 beds which approximates to 1:100, and we seem to operate a much more clinical service the pharmacists in Holland seem to do. From my reading of it, they were actually just based in the dispensary and there was very little clinical input.

Mr Forbes: The ratio in fact is the ratio of pharmacists to the total staff in the department and not meant to represent the number of pharmacists per bed. I think I am saying that it is a government decision that they won't have more pharmacists; it is not that they can't get them and they do make the most effective use of the available staff. I think that is the prime message. We talk about needing more pharmacists, but we need to make more effective use of the staff we have got.

Mr Harrison: There are a number of British firms providing those unit dose packs to Dutch hospitals and it should be possible to put pressure on the ABPI to get a standardized unit dose pack. Can you confirm that the technicians can dispense controlled drugs unchecked? The next part of my question concerns the academic links that Eppo Van der Klein and his staff have. Are there lessons here that we ought to have more academic links in the teaching hospitals with schools of pharmacy and schools of medicine?

Mr Forbes: The answer to the first question on controlled drugs is 'I think you are wrong'. The technicians do not dispense the controlled drugs on their own. The second part is the academic link. There is not a school of pharmacy in Nijmegen so they don't have a direct link with a school of pharmacy. Also the link they have with the medical school is very tenuous. They have a very interesting, clear rivalry between the clinical pharmacology and the clinical pharmacy department; each of them have gone their own separate ways and compete in the sense of selling their service.

Mr Pate: Do you think that, because employing outside experts is liable to be very expensive, it would be appropriate to send our technicians away on specialized training courses to learn computer technology etc?

Mr Forbes: Personally no. I think that you need to employ specialists with

their specialist knowledge and if it costs you more, you are going to have to make provisions for that. We want technicians, yes, but they have specific jobs to do.

12

The stability of diluted betamethasone 17-valerate topical preparations

K.R. Middleton and R.F. Haines-Nutt

The newer potent fluorinated corticosteroids have revolutionized the treatment of many inflammatory skin disorders. Unfortunately, excessive or prolonged use of these drugs often results in atrophy of the skin. In attempts to minimize such unwanted side-effects, physicians have resorted to the questionable habit of diluting commercially available topical corticosteriod formulations with supposedly inert bases.

The most widely used topical corticosteriod is betamethasone 17-valerate. This is relatively unstable and readily rearranges under non-ideal conditions to form the more stable betamethasone 21-valerate (Gardi *et al.*, 1963). Bundgaard and Hansen (1981) have shown that this isomerization in aqueous solutions is subject to specific acid and base catalysis as well as to a spontaneous or water-catalysed reaction. The 21-valerate has only one fifteenth the activity of the 17-valerate (McKenzie and Atkinson, 1964) and is in turn hydrolysed to betamethasone (Li Wan Po *et al.*, 1979a, 1979b). Many of the commonly used diluents for Betnovate (Glaxo Laboratories Ltd.) have been shown to produce a rapid breakdown of the active steroid (Li Wan Po *et al.*, 1979a, 1979b; Mehta and Calvert, 1982; Yip and Li Wan Po, 1979) and in complying with a physician's request for a diluted Betnovate preparation, the pharmacist should ensure that a stable preparation is being presented to the patient. In Devon some dermatologists wished to semi-quantify treatment with topical steriods by directing that a specific length of a tubed preparation be applied to the affected area.

In order to prepare tubed dilutions efficiently the pharmacy wished to have a stable preparation which could be made in quantity. Unguentum Merck (E. Merck Ltd.), an ambiphilic base containing approximately 60% fat and 40% water, had been shown to have certain promising properties.

Other workers had already shown that the delivery profile of 1 in 4 dilutions of Betnovate cream in Ung Merck and in the recommended diluent Cetomacrogol cream (formula A) are equipotent (Woodford, 1981) and that Betnovate cream 1 in 1 and 1 in 4 in Ung Merck passes the USP XIX Antimicrobial Preservatives–Effectiveness test (E. Merck Ltd., product information). Also, Ray-Johnson (1981) has shown that 1 in 1 dilutions of Betnovate cream in Ung Merck are chemically stable for at least 8 months.

There is little demand for 1 in 1 dilutions in hospitals in this area, the most commonly requested preparations being 1 in 4 and 1 in 10 dilutions of Betnovate cream both with and without the addition of 1% clioquinol, a potent antibacterial and antifungal agent. Chemical stability data obtained with the 1 in 1 dilution cannot be extrapolated to the 1 in 4 and 1 in 10 dilutions, although it might be expected that these weaker preparations would be far less stable than 1 in 1 dilutions. In view of this lack of data, a study was undertaken to determine the stability of Betnovate cream in Ung Merck at the 1 in 4 and 1 in 10 dilution levels and Betnovate ointment 1 in 10 in white soft paraffin. The effect of clioquinol on the stability of these preparations was also investigated.

Apart from Betnovate in aqueous cream which was tubed (see later) all the Betnovate dilutions were made in the hospital pharmacy and the preparations were stored in transparent glass jars with screw-capped lids.

EXPERIMENTAL

A reversed phase high pressure liquid chromatography method was used to assay betamethasone 17-valerate and 21-valerate. The equipment included an Applied Chromatography Systems pump, an ultraviolet detector (Applied Chromatography System) equipped with a 254 nm interference filter and set to a sensitivity of 0.02 aufsd. Chromatography was performed with a 25 cm × 4.6 mm ID column packed with Spherisorb 5 ODS preceded by a guard column containing the same packing. The mobile phase was acetonitrile – 0.1 mol acetic acid (45:55) delivered at a flow rate of 1 ml per min. Standard solutions of betamethasone 17-valerate and 21-valerate were prepared in dimethyl sulphoxide, chromatographed and calibration lines plotted on the basis of peak area measurements. A 20 μl loop was used for all determinations and gave good reproducibility.

The preparations under test contained large amount of excipient which had to be removed as far as possible before chromatography. It was found that a clean-up method similar to that used by Li Wan Po *et al.* (1979a) to

remove excipients from ointment bases worked moderately well with Betnovate cream/Ung Merck preparations and was used throughout. The method consisted of weighing 2 g preparation into a separating funnel and partitioning the mixture between 20 ml hexane and 10 ml dimethyl sulphoxide. The lower dimethyl sulphoxide layer was removed and re-extracted with 20 ml fresh hexane and a 20 μl aliquot of the dimethyl sulphoxide extract was then used for chromatography without further treatment.

RESULTS AND DISCUSSION

All the preparations studied contained large quantities of excipient and this precluded the use of a simple dissolution and injection technique for assaying the steriod content of the various formulations. Li Wan Po *et al.* (1979b) state that the partition coefficient of betamethasone 17-valerate, 21-valerate and betamethasone between dimethyl sulphoxide and hexane is in excess of 1500. This suggests that with the extraction procedure employed in this study almost all of the steriods remain in the dimethyl sulphoxide layer whilst the majority of the hydrocarbon excipients in the formulations will be removed by the hexane.

The chromatographic conditions described gave well-resolved peaks for both betamethasone 17-valerate and 21-valerate. Unfortunately, betamethasone left the column at the same time as the remaining excipients and was therefore undetectable. It was found that the normal phase system described by Li Wan Po *et al.* (1979a) gave good peak resolution for betamethasone but relatively poor separation of the 17-valerate and 21-valerate. This system, which employs a mobile phase of ethyl acetate–chloroform–methanol (71:28:1) saturated with water, was used on all the samples under test but no quantifiable amounts of free betamethasone were detectable in any of the preparations, indicating that betamethasone 17-valerate in the samples had not degraded past the 21-valerate stage.

Reference to Table 12.1 indicates that approximately 10% of the 17-valerate is lost after 12 months in the case of dilutions made with Ung Merck and white soft paraffin. Clioquinol did not affect the stability of the 17-valerate. Betnovate in aqueous cream is a tubed preparation and comprises Betnovate cream 1 in 4 in aqueous cream which has been prepared with yellow soft paraffin. The finding that only 17% of the active steriod is lost after 12 months came as a surprise in a view of the reputed instability of betamethasone 17-valerate in such bases. However, the fact that the aqueous cream is made with yellow soft paraffin could be an influencing factor.

In addition, there was no apparent cream demixing over the 12 month period of the study and no micro-organisms were detectable in any of the preparations despite the inadequate containers.

The benefits derived from this pharmaceutical response to a clinical

Table 12.1 Stability of betamethasone 17-valerate in various bases

Preparation: *Betnovate cream+*	*% 17-valerate remaining after* *6 months*	*12 months*
Ung Merck 1 in 4	100	–
Ung Merck 1 in 10	98	91.5
Ung Merck 1 in 4 + 1% clioquinol	101	92.5
Ung Merck 1 in 10 + 1% clioquinol	96.6	89.5
Betnovate ointment + white soft paraffin 1 in 10	97	90.1
Betnovate in aqueous cream 1 in 4	94.3	83

request are manifold, benefiting clinician, patient and pharmacist. A formulation of known stability can be tubed and hence the dermatologist can direct that a specific quantity of the preparation be applied to the affected area. The patient knows how much to apply and is assured that the potency of the cream is maintained over the period of treatment. Lastly the pharmacy can prepare large batches of these preparations thus saving time and money.

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Discussion

Mr Williams: There was a dermatologist at University College Hospital, London many years ago who would never use white soft paraffin because he believed there was some bleaching process at some stage in its manufacture and he always felt there may be a residual agent of some kind that might be harmful. Dermatological preparations were made up in yellow soft paraffin, and now looking at the loss of activity of this compound in the white soft paraffin base, do you think this may be due to a constituent of white soft paraffin and if so, do you think it could be the bleaching agent that this dermatologist once suspected?

Dr Middleton: I believe I said that BAC cream was made locally by a hospital in Devon and was made with aqueous cream. BAC is 1:4 in aqueous cream. The cream is made in the hospital with yellow soft paraffin. For the same reason which you were talking about, the dermatologists don't like using white soft paraffin. Even then, we lost 17% over a 12 month period and I would have expected to lose a lot more than that. So the answer is, I don't really know, but I don't think so.

Mr Bolton: Concerning the assay – I wondered if you could tell us approximately what percentage of extraction you were getting using that technique and also if you had considered using an internal standard in the assay?

Dr Middleton: We did use standards but we got such good extraction with this procedure that we didn't have to use them after we had once validated the method. I have full details if you want them, but I thought in this meeting I would not bore the audience with such finer points.

Dr Calvert: We have done quite a bit of work on betamethasone stability in a similar manner to yourselves. One of the interesting facts we have found is that when the potency was compared with 1:4, 1:8 and 1:16 dilutions the dermatologist reported they all had the same potency. There was no dilution effect in a pharmacological sense and we came to the conclusion that we were much better questioning the need for these dilutions than spending a lot of time looking at stability.

Dr Middleton: All I can relate to is the paper by Woodward who showed these preparations were equally potent with the approved diluents which is just a matter of cream formula.

Dr Calvert: They are equipotent and what we found was the 1:8 and 1:16 are also equipotent. You really have to go to a 1:32 dilution before you obtain the effect the dermatologists are seeking. The other interesting fact that the dermatologists put forward to us was that they preferred it in emulsifying ointment because they knew it degraded and it saved them having to tail the dose.

Dr Middleton: I have heard the same comment in Torbay. They thought that Betnovate and BAC were very unstable and that is what they wanted. But in fact they are not getting what they think they are getting.

13

A case study in nutritional support

D.A. Bolton

The object of this chapter is to demonstrate the effective role pharmacists can play in nutritional support.

Parenteral and enteral nutrition have undergone considerable changes in the last 5 years, and the sophistication involved in providing this type of support has now altered the subject almost beyond recognition. The advent of the 3 litre bag approximately 3 years ago allowed pharmacists for the first time to become involved in this particular speciality, and at present in a number of hospitals the pharmacist has now become a key member of the nutritional team.

In Bangour General Hospital, most nutritional support is organized from the Pharmacy Department where staff are involved in assessing the patient, formulating the regime, preparing the regime and, in addition, monitoring the patient's progress.

CASE STUDY

The patient, Mrs W.G., a 56-year-old female, was seen as an emergency admission and was diagnosed as having spontaneous acute pancreatitis and an upper gastrointestinal haemorrhage. This lady had a history of gall bladder problems and ultrasound and radiological examination indicated the presence of gall stones. Consequently, surgery was performed to remove the common bile duct and the stones.

The following day a request was received in the Pharmacy to commence this lady on nutritional support. A T-tube had been placed for bile drain-

age, and in addition the patient had developed an ileus of the gastro-intestinal tract. In these circumstances parenteral nutrition was indicated. The patient's height and weight were determined and blood was taken for a full biochemical assessment. A 24 hour urine collection was also commenced to obtain an estimation of the patient's urinary urea as a gauge of catabolism.

On examination, the patient was receiving 3 litres intravenous fluid daily, plus intravenous cimetidine via a separate peripheral line. In addition to the T-tube drainage from the common bile duct, the patient was on constant nasogastric aspiration.

Pending biochemical results etc., a standard regime comprising the following was established (Table 13.1).

Table 13.1 3000 ml Intravenous solution

Nitrogen	7.1 g
Calories	1000
Sodium	150 mmol
Potassium	70 mmol
Magnesium	10mmol
Calcium	10 mmol
Zinc	50 μmol
Cimetidine	800 mg

Mrs W.G. Q4
Bag 1 Expiry 17/10/81
811017 Rate – 125 ml/h

Medical staff were experiencing problems in the continued availability of peripheral sites to infuse cimetidine. The pharmacy investigated the stability of cimetidine in the commonly used solutions for nutritional support. The manufacturers (Smith, Kline and French) were contacted about this and could indicate no compatibility problems concerning the individual components of the TPN, and, furthermore, work by Moore *et al.* (1981) indicated that continuous i.v. infusion in a TPN solution was acceptable. Consequently, cimetidine was added to the 3 litre infusate.

Over a period of 3 days the amounts of nitrogen and carbohydrate were increased to meet the catabolic needs of the patient and, where required, electrolyte supplements were added, again to meet the patient's needs. This patient also required insulin which was added to the 3 litre bag.

She progressed well until the intravenous feeding line blocked and then fractured underneath the skin tunnel. This was not detected immediately, and as a result a severe cellulitis developed on both sides of the patient's chest wall and also bilaterally on the neck. Total parenteral nutrition was stopped and at that time the anaesthetists were extremely reluctant to

attempt replacement of the central fading catheter, either via the infraclavicular or internal jugular routes.

It was considered that the patient might be fed parenterally using a peripheral line, either attempting to administer around 2000 calories daily by this route, or, as the patient was obviously overweight, to utilize her own fat resources as a source of energy and to supply peripheral isotonic amino acids with all relevant electrolytes etc. The latter method was chosen. Peripheral infusions of the commercially available product, Perifusin, were commenced, giving the patient approximately 3 litres per day. Additional electrolytes were added as appropriate. After 2 days the patient's potassium began to rise, as did her urea, due possibly to:

(1) renal failure, or
(2) breakdown of blood and blood products within the patient's gastrointestinal tract causing a release of intracellular potassium and also a high content of blood nitrogen.

It was obviously essential to remove potassium from the regime, and since Perifusin contains potassium it was decided to formulate our own isotonic amino-acid solutions. This was achieved by adjusting the tonicity of a hypertonic solution, Freamine, with water for injection. (Table 13.2). Freamine is an electrolyte-free amino-acid solution.

Table 13.2 Pharmacy prepared isotonic amino acids. 3100 ml peripheral nutrition solution

Nitrogen	10 g
Sodium	180 mmol
Chloride	180 mmol
Potassium	20 mmol
Magnesium	10 mmol
Calcium	5 mmol
Solvito	1 vial
Zinc	70 μmol
Osmolarity	320 mosmol/l

Several days later, the patient's gastointestinal tract began to function, but unfortunately the abdominal drain had not healed well and lower abdominal fistulae had developed. The following day, however, intravenous nutrition was reduced and oral fluids were commenced. In addition, a biochemical assessment of the fistula exudate was determined. Three days later the patient was still not drinking an adequate fluid volume and it was decided in these circumstances, since volume and electrolyte replacement was imperative, that the patient should be fed enterally. The patient was losing approximately 120 mmol sodium per day, plus 40–50 mmol potassium per day in the biliary drainage fluid. This was in

addition to urinary losses, and accordingly, appropriate electrolyte replacement was required.

It is normal practice in this hospital for the dieticians to prepare enteral feeds, but in these circumstances, since strict electrolyte control was essential and physicochemical compatabilties were involved, the preparation was taken over by the pharmacy department.

Electrolyte requirements were calculated and added to solutions which were administered nasogastrically using a small peristaltic pump. The enteral feed used was Clinifeed Iso, and like Cairns (1982) we did not experience 'creaming' problems. This regime continued for a further 7 days, at which time the fistula drainage was considerably reduced and healing was occurring. As a result of this, the sodium and potassium requirements were reduced. After a futher 5 days, deficiencies in serum phosphate and magnesium, were noted during routine biochemical assessment. The patient also showed clinical symptoms of hypophosphataemia. Accordingly, supplementary magnesium and phosphate were added to the nutritional intake. After a further 3 days, the patient, although improved, was extremely reluctant to abandon this form of nutrition and eat normally.

We overcome the by concentrating all electrolyte needs into an enteral feeding solution to be given only at night, thus permitting the patient to become fully ambulant during the day. In due course she adapted to a normal diet and her need for electrolyte supplement decreased. Approximately 1 week later she was discharged from the hospital.

There is no doubt that this patient's progress was influenced considerably by the nutritional support she received. The pharmacist, if inclined, can play an extremely active role, both in the preparation of feeding solutions and also as a member of the clinical team.

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Discussion

Dr Gibson: What was the albumin level at the point when the patient went home after 1 month of nutritional therapy?

Mr Bolton: It had just crept to over 30 g/l.

Dr Gibson: In relationship to this, did her renal status improve over a period of days or did it require a period of weeks?

Mr Bolton: Her improvement was very dramatic. A few days after this immediate problem, we were giving her potassium again. It was a very acute and rapidly withdrawing phenomenon which we have as yet not explained. It didn't seem to be the usual type of renal failure.

Dr Gibson: The point that I wanted to make was that, in relation to her protein needs which were considerable, I wondered if thought was given to high nitrogen tube feeding?

Mr Bolton: No, we felt that what we were giving here was adequate. We are reluctant to overfeed patients in our hospital and perhaps we do err slightly on the side of caution. We watch these individuals very closely and rather than increase the feed in the sense you are suggesting, we sometimes do give them albumin. It really depends on how clinically well they are, but if we start to see any sign of fluid leaking at the peripheral tissues, it is albumin that we would use rather than an increase in the amino acid load in the TPN.

Dr Gibson: The point I am making is that with the type of malnutrition she had, which was a protein type of malnutrition, in relationship to the disease which she had, her protein needs were much higher than that of an individual who had been in a hospital for other reasons. Therefore, the albumin in the case you are talking about would not be given for nutritional reasons. Giving a higher amount of protein in this type of individual is sometimes necessary, because their protein requirements per day are much higher.

Mr Bolton: Well, surely it is partly catabolic as well but I take your point. When I was in America, I noticed they used a different system. They would use a much higher input of nitrogen if they felt it was necessary, and renal function was satisfactory. In the UK, the approach is much more conservative.

Mr Purkiss: On the slides you showed, there were no phosphate levels. Was this because they were incorporated elsewhere of did you not measure phosphate levels?

Mr Bolton: Yes, we measured phosphate and what we found was really interesting. We were giving her around 40 mmols per day and it seemed to to be adequate. We don't do phosphates every day, maybe once a week or so. When she started on enteral feeding, her phosphate had gone down from about 1 to about 0.6 and we thought at the time that possibly that was why she was so depressed, because the two are very much connected. We did provide her orally with additional phosphates since she was on enteral feed, and her level was slightly above 1 when she left. She did pick up and whether it was the phosphates or whether it was just her overall clinical improvement, I don't know. Phosphate levels are something we look at and are aware of.

Mr Platt: With the amount of nitrogen you were putting into this patient, one would assume for her high catabolic state, she would have possibly been in quite a severe negative nitrogen balance. Did anyone measure the total nitrogen excretions?

Mr Bolton: I didn't actually say that, but right at the beginning we always do a day of urine collection which we look at for electrolytes and also urinary urea. I don't remember the figures exactly, but she was losing about 7 g of nitrogen per day in her urine and I guess insensible losses of 3 g or so, so we made the point of getting a marginal positive nitrogen balance.

Mr Platt: Did you make any further attempt to assess her nitrogen balance?

Mr Bolton: We did it once a week. We always held her in balance. You have to remember that apart from getting on to the enteral stage, she was being encouraged to eat as well.

Mr Nunn: Can I just make the point that we too have seen rises in potassium and urea in children, being the result of internal bleeds.

Mr Swallow: I was interested to know that the fistula started to develop when you changed over to enteral feeding. What was the fistual output in volume?

Mr Bolton: About 300–400 ml.

14

The introduction of a cytotoxic reconstitution and additive service in a regional chemotherapy centre

M. Earnshaw, C. Tate and H. Harris

Cookridge Hospital, a 154 bed unit, is the regional centre for radiotherapy in Yorkshire with approximately 55 000 out-patient attendances per year. The current trends of radiotherapy in combination with chemotherapy have led to a large increase in the use of cytotoxic agents, many of which require reconstitution prior to administration.

A pharmacy based additive and reconstitution service has been in operation at the Leeds General Infirmary for many years. Current district pharmaceutical policy is to develop such services in all pharmacy units wherever viable. Since most chemotherapy is administered between the hours of 9.00 a.m. and 5.00 p.m. on weekdays only, the installation of a centralized reconstitution service in Cookridge Pharmacy seemed a logical development to tackle. Furthermore, an under-utilized storeroom adjacent to the pharmacy was available for upgrading to provide an aseptic dispensing area.

At this stage initial investigations were carried out to determine the feasibility of a centralized service and it became apparent that several problems would need to be overcome in order to proceed.

It was originally planned to install a purpose built aseptic suite in the vacated storeroom incorporating a vertical flow laminar air flow hood. However, the high cost of this development, in excess of £20 000, ruled

out this option and a cheaper solution was sought.

Nursing staff appeared to be reluctant to give up their role of preparing cytotoxic agents for administration even though this required a considerable amount of their time. Medical staff were concerned about the inconvenience and possible delays in treatment that a centralized reconstitution service might produce.

Delays in obtaining haematological data were claimed to be important in determining the schedule of drug administrations and therefore the work flow to a centralized dispensing unit.

Most important of all, the Hospital Management Team (HMT) strongly indicated that no funds would be available for staffing such a development, although minor upgrading of the storeroom and installation of a laminar air flow hood was funded. Work commenced on the minor alterations to the storeroom in order to provide an acceptable clean room environment to house the laminar air flow hood measuring 3.3 m x 3.7 m. A vertical laminar air flow hood was installed and the environment evaluated by the quality controller.

Whilst installation work was proceeding a case was submitted to the HMT for funds to be provided for staffing the unit since it was clear that the pharmacist and technician providing the usual pharmaceutical services would be unable to handle all cytotoxic drugs requiring reconstitution. Five principal arguments were put forward in support of funding a pharmacy based reconstitution service.

(1) All reconstitutions and additions of cytotoxic drugs to intravenous fluids would be carried out in a controlled environment using strict aseptic techniques. Patients receiving immunosuppressants as part of their chemotherapy are particularly prone to developing infections. Good aseptic techniques operated under laminar air flow reduce the possibility of contamination during drug reconstitution.

(2) All reconstitutions and additions of cytotoxic drugs to infusion fluids would take place under the supervision of a pharmacist to ensure proper and accurate dilution. All products would be fully labelled with drug concentration, expiry date, storage conditions, batch number and patient's name. Incompatibilites between drug and diluent or drug and container material would be eliminated. Each dose would be unit packaged.

(3) Nurses would no longer have to spend considerable amounts of time assembling materials and reconstituting cytotoxic drugs. More time would therefore be available for more appropriate nursing duties.

(4) Nurses and medical staff handling cytotoxic agents on a regular basis without taking adequate precautions relating to protective clothing and techniques may be subjected to significant hazards from drug contact and drug absorption. Some cytotoxic agents cause dermato-

logical damage on skin contact, whilst many may produce mutagenic genes when absorbed. These hazards are significantly reduced by removing cytotoxic reconstitution from the open ward area to the controlled evironment in the pharmacy clean room.

(5) Significant financial savings resulting from reducing wastage and economy of purchase would be made. This would occur as a result of re-use of part-used vials in the pharmacy and economies of purchase resulting from the use of large-dose vials. To support this claim of financial savings a short survey was carried out to identify which products could be purchased in large-dose vials and an estimate of the likely savings was made based upon annual purchase figures of the drugs concerned. This potential saving, in excess of £6000 per year, persuaded the HMT to view the case carefully.

In due course approval was given for a 6 month pilot study to evaluate a pharmacy based cytotoxic service and funds were made available for technical support. It was then necessary to draw up an operational scheme and considerable time was spent liaising with medical, nursing and laboratory staff to iron out potential pitfalls prior to operating the service.

A more comprehensive investigation was carried out to identify the range and average number of cytotoxic preparations prescribed daily; the schedules involved and an estimate of the likely work load obtained. At the same time a pharmacy procedure was drawn up to provide guidelines on preparation of the work area, clothing, methods and procedures, packaging, records, labelling and transportation. (See Appendix.)

The service was initially provided to selected wards only in order to provide ample opportunity for pharmacy staff to overcome teething troubles. Delays in receiving prescriptions in the pharmacy were a problem but this improved following further liaison with the pathology laboratory handling haematological requests. In particular, the installation of an auto-analyser greatly improved the turn round time for blood counts.

Once medical and nursing staff realized that their active co-operation was essential if the pharmacy service was to be viable then an improved work flow resulted. Delivery and collection of drug charts and reconstituted drugs was time consuming for nursing staff and eventually a part-time pharmacy porter was funded for this duty.

After 1 month the service was extended to all wards and out-patients in the hospital. This produced approximately a 100% increase in the pharmacy work load, the department now handling an average 200 drug reconstitutions per week.

At the end of the 6 month pilot scheme the whole operation was reviewed. There was overwhelming support from all disciplines within the hospital to continue the service on a permanent basis. Initial reservations raised by medical and nursing staff had been overcome. Nursing staff

previously involved in preparing cytotoxic drugs for administration very quickly took on other nursing duties and both medical and nursing staff came to rely on pharmacy to provide unit doses of cytotoxic drugs for individual patients during normal working hours.

FINANCIAL SAVINGS

A further attempt was made to determine financial savings resulting from the reconstitution service and in the last month of the pilot study all prescriptions for cytotoxics were monitored and recorded. During this month each treatment prepared was costed. In addition a cost was determined as if the treatment had been prepared on the ward or in the out-patient clinic. Where patients on the same ward were receiving identical drugs at the same time this was taken into account. In this way it was possible to produce a fairly accurate estimate of the financial savings resulting from a pharmacy based reconstitution service. This analysis identified a potential annual saving on the cytotoxic drug budget in excess of £9500.

Every effort was made to reduce drug wastage to a minimum and unused drugs returned to pharmacy were re-issued wherever possible provided the expiry date had not been exceeded. Many cytotoxic drugs are stable for some days if refrigerated following reconstitution and advantage was taken of this in order to utilize drug vials completely.

SUMMARY

At the end of the pilot study the service was reviewed. The response of medical and nursing staff was encouraging and there was considerable support for a permanent reconstitution service. It was clear that such a service could be operated by the pharmacy department to include all wards and out-patients without producing delays in treatment administration. Furthermore, financial savings were sufficient to fund the necessary staff, materials and running costs and in due course the service was funded on a permanent basis.

APPENDIX

PHARMACY PROCEDURE

All reconstitutions take place under a vertical flow laminar air flow screen housed in a clean room.

A work bench is provided along one wall of the room and supports drug stocks, aseptic dispensing equipment, a typewriter and labels.

Protective clothing is worn by the technician carrying out the aseptic manipulations.

Cytotoxic drug treatments are written up on special cytotoxic drug treatment charts which are sent to pharmacy once satisfactory haematological results are obtained.

After checking the dose, route, method of administration and compatibility with the infusion fluid when necessary, details are entered in the record book and a batch number is assigned to the item concerned. The materials are assembled on stainless steel trays and a check is carried out by the pharmacist.

All drugs to be administerd by bolus injection are packed into an appropriate sized syringe and sealed with sterile blind hubs.

Each completed syringe or infusion container is examined by the pharmacist and labelled prior to placing in plastic delivery trays for transport to the ward.

In order to improve work flow during the busier parts of the day vials of the commonly used cytotoxics which are stable are reconstituted early in the morning. Vials of stable solutions remaining unused at the end of the day are refrigerated for use the following day.

Discussion

Ms Jennings: Could I ask how long the charts remain with you and if there is any problem of them not being available on the wards and how you arrange transport of charts to the pharmacy and drugs back to the wards?

Mr Earnshaw: The system is such that we have charts come down to the pharmacy and they are more or less done straight away, if they come down early in the day. It does sometimes pose a problem in terms of the nurses complaining about it, but in practice it has not posed a practical problem. We have had no complaints that charts have been away from the ward long enough to impair nursing treatment. Transport was a problem; nursing staff didn't have to spend the whole afternoon making up the cytotoxics, but had to spend all afternoon coming down to the pharmacy and this was a significant problem. So part of the savings were then used to appoint a pharmacy-based part-time porter just for the afternoon sessions. He goes around the wards and collects them after each ward has got its trays assembled; he takes them back to the ward ready for use. The nursing staff no longer have to do all the running around.

Dr Gibson: We set up a similar programme at the hospital that I was at and what we found was that to save the porters and nurses going back and forth, we found a central area within the clinic where we set up our reconstitution service. Is this a possibility?

Mr Earnshaw: I don't think it is very practical. Cookridge is not a very large hospital, with only 150 beds and I don't think we would save a great deal of time. We looked at other areas of trying to save time by pre-mixing some of the cytotoxics. We do get a list each morning of patients who are coming in for chemotherapy and that gives us some help, but I don't think having a satellite type pharmacy would be of use. It would pose problems in terms of staffing as we would have to have a second pharmacist.

Mr Williams: Had you given any thought to rotating staff through a unit like this? One wonders whether, even using good procedures, it is advisable to have any individual handling cytotoxic drugs for very long periods. Had you thought about that factor at all?

Mr Earnshaw: I think that from what we saw yesterday and the effectiveness of the various plans that are available, it is probably a significant hazard having a lot of staff rotating through rather than one person who is familiar with the system. We have appointed a senior technician for that post. Pharmacists rotate as part of their training and relief, but it is our intention that there will be a permanent based technician in that service who will be monitored at regular intervals for signs of any mutagenicity.

Mr Clarke: This raises another problem. Mr Williams has hinted that there may be some damage to staff caused by these cytotoxic agents. To what extent would your records reveal, say in 10 years time, that a particular pharmacist had done a particular spell of work, should he/she become damaged in some way and might seek compensation.

Mr Earnshaw: The records would be similar to the records in the Infirmary at Leeds. They are permanent records which are held in the pharmacy and will determine who prepared the material and who checked it, so there would only be two staff involved. I think we could certainly trace back.

SECTION FOUR

Drug Selection and Evaluation

Chairman:
Dean F. Fish

Chairman's introduction

F. Fish

Ladies and gentlemen, do we criticize or do we compliment the sponsors and organizers of this symposium for producing a very full 2 day programme on 'Hospital Pharmacy and the Patient', comprised of four sessions in the titles of which, at least, there is not a single mention of the term Clinical Pharmacy? Although definitions of this term differ as, perhaps, do expectations on the scale of implementation of the various aspects of clinical pharmacy practice, surely there can be no difference of opinion on the role of the pharmacist as described yesterday by Miss Helen Doery, namely 'to ensure that the patient receives the correct drug, in the correct dose, in the most suitable form for the chosen route of administration'. But to what extent are pharmacists involved in, or should they be involved in, the actual selection of the most appropriate drugs for the individual patient; in advising on the most sensible delivery system for that drug or combinations of drugs; and for monitoring (where necessary) drug levels in patients to check that the most effective dose is being given?

We have heard much of the need for the pharmacist to be appreciated as a significant member of the health-care team, but what is his or her special – perhaps unique – contribution, as a really *active* member of such a team, in the decision-making process regarding the choice and the management of drug therapy? To what extent does his or her degree course in pharmacy, and subsequently the pre-registration training, qualify our young graduate to deal with both the scientific and sociological demands, the interpersonal demands, of the real life situation when he or she is confronted with specific questions concerning drug choice and dosage regimens, and when expected to consider not only the quality of product

but also to contribute to the quality of patient care? As a graduate in the pharmaceutical sciences, when is the hospital pharmacist going to cease being a reluctant scientist and demonstrate by deeds and not by mere words of hope, his or her right to be regarded as an equal partner in the professional team which should be striving to provide the best possible health care to each and every patient?

We have heard of some welcome moves in some places but most of this session will deal with a particular aspect of clinical pharmacy practice in which, regrettably, I find the situation in Britain today not much changed, certainly not sufficiently changed, from that obtaining in mid-October, 1976. Then, in Glasgow, at a Guild of Hospital Pharmacists' Conference, I was invited to lecture on 'The analysis of drugs in body fluids – a role for the hospital pharmacist?' On that occasion I opened by saying 'having been asked to speak specifically about the analysis of drugs in body fluids in the hospital situation (as distinct from a forensic science context) I feel that we should look at things as they are, then at how they should be, and finally at how they might be if the right hospital pharmacists use the necessary initiative and persuade the appropriate authorities to make the right decisions'. I followed by saying that the answer to the question posed, 'is this a role for the hospital pharmacist?', could best be answered by asking a series of other questions pertinent to the problem and then seeing to what extent the pharmacists' training, knowledge and experience could contribute to providing answers. The questions to be answered were, as I saw them then:

(1) In what circumstances are such analyses required?
(2) For which drugs is analysis required?
(3) For which drugs is analysis routinely possible?
(4) To what extent is a service being provided?
(5) Who can best provide an adequate service?
(6) What are the problems in providing a service?
(7) What are the problems in the interpretation of results?
(8) Of what value are the data obtained?

So what are today's, or even tomorrow's, answers to yesterday's questions? To provide some, or all of these answers we have a variety of speakers with a variety of experience.

15

Hospital pharmacy and clinical pharmacokinetics – is academia in touch?

W.J. Tilstone

DEFINITION OF QUESTION

The remit given was to discuss whether pharmacists in hospital receive education in pharmacokinetics which is appropriate to their having an active role in patient care, but, in particular, to concentrate on the relative position of hospital pharmacists and clinical chemists in this area. This is a very complex and difficult remit but one undertaken cheerfully and hopefully with some degree of assurance given that my first degree was in pharmacy, I am based in a school of pharmacy, have a major research involvement in clinical pharmacokinetics, and spent 7 years as a clinical chemist in a teaching hospital. The question also requires certain further refinement in that it could relate to whether academia is in touch with developments in clinical pharmacokinetics and the hospital pharmacist and patient, or whether academia is in touch with the training of graduates to meet possible developments which will arise in the future.

CLINICAL PHARMACOKINETICS AND THE HOSPITAL PHARMACIST

In a very real sense clinical pharmacokinetics is a logical extension of the 'five Rs' of the pharmacist shown in Table 15.1. To these basic five require-

Table 15.1 The 'five Rs' of pharmacy

(1)	The Right drug
(2)	The Right dose
(3)	The Right formulation
(4)	The Right route of administration
(5)	The Right time

ments one could add the ability to deal with problems which arise when mistakes are made by giving the wrong drug, dose, formulation or route of administration. Much of this is covered by the basic undergraduate training in pharmacy given at every university and college offering pharmacy degrees in the United Kingdom. The parts which are missing in the present context are: (a) the necessary expertise in analytical chemistry, (b) the necessary expertise in dealing with medical men and patients, and (c) a physiological orientation to pharmacokinetic training which allows sensible decisions to be made at the bedside, rather than in the laboratory. This is not terribly surprising since, viewed as a whole, these would constitute a small fraction of what might be defined as appropriate training for the 'compleat pharmacist'. These omissions also fully explain the ease with which clinical chemists have successfully taken on the mantle of the expert in therapeutic drug monitoring.

When, some 15 years ago, it became generally known to medical men that drugs could be assayed in body fluids and that the results could be correlated with efficacy, toxicity, and compliance, then they sought expert help. The 'scientists' within the hospital setting who were known to clinicians by reputation and by personal contact were almost exclusively clinical chemists.

Hospital pharmacists at that time were totally unequipped to deal with this development despite their potential unique contribution as the hospital experts in drugs, including the preparation and manufacturing stages.

CLINICAL PHARMACOKINETICS AND THE CLINICAL CHEMIST

At about the same time as clinical pharmacokinetics was becoming a recognized discipline due to the joint interest in the schools of pharmacy, particularly in the United States, and in the schools of medicine, clinical chemistry had discovered the enormous potential of immunoassays for sensitive and accurate analyses of low molecular weight organic compounds – particularly in the endocrine area – and were ready to use this to offer a 'large number' therapeutic drug monitoring service, beginning of course with digoxin. These developments have continued and now there is a wide range of assay kits available using immunological procedures, particularly with the development of EMIT. This uses essentially the same

technology that is used in many other mass analysis areas of clinical chemistry and from an analytical point of view the chemist is well-trained and well-capable of performing this service.

The chemist of course is less well-trained than is the pharmacist to give a back-up interpretative service and has less inclination than many pharmacists to offer a proper, individual patient-orientated, clinical pharmacokinetics service. Analyses of large numbers of samples for a few drugs, often justified in terms of the limited range of the drugs used in hospitals which have a narrow therapeutic index (e.g. lithium, anticonvulsants, and cardiac glycosides), is a relatively low-level activity. The awareness that such analyses can be performed, however, has provided the stepping stone for a much better service in a number of areas which shall be outlined briefly below.

FUTURE DEVELOPMENTS IN CLINICAL PHARMACOKINETICS – OPPORTUNITY FOR THE PHARMACIST

The time is ripe for renewed interest in drug overdose. Since the early 1960s treatment of drug overdose has been almost exclusively on the basis of conservative therapy with a major involvement of clinical chemists playing their proper role as clinical chemists, helping to diagnose and maintain adequate renal, respiratory and general acid base control in the overdosed patient during intensive supportive therapy. Some interest has been shown in recent times in supporting more radical therapy such as haemodialysis and haemoperfusion but little or no assistance has been given by pharmacists. The position remains today that, although some 10% of hospital admissions are due to drug-induced disease, the fatality rate for poisonings is low – somewhere between 1 and 5% of overdose admissions. This still represents an unnecessarily high loss of life, and those who survive are a major drain on high-cost hospital resources.

A better knowledge of drug disposition in overdose would make prediction of outcome and guidance in active therapy considerably more successful and could surely be extended to more areas than the almost isolated example of paracetamol poisoning. The reluctance of clinical chemists to be involved in single-sample drug analysis and in unknown drug screening, together with their shortcomings in interpretation in these situations is a major inhibitory factor for advancement, but leaves this field clear for a major involvement by the pharmacist. As an example there was recently a death from salicylate poisoning in a Scottish hospital where acid base and fluid and electrolyte therapy, monitored and guided by clinical chemists, had proceeded apparently successfully and certainly along proven and accepted lines. Retrospective analyses of the limited salicylate plasma data available clearly showed the individual had taken a massive overdose, had saturated the two capacity-limited pathways of

elimination and required a much more active intervention for successful outcome.

Munchausen's syndrome continues to be a regular problem either directly of by proxy in children. Screening of blood or urine samples for suspected causitive agents, such as loop diuretics and anti-coagulants, not only will markedly facilitate differential diagnosis but could save lives. For example, take the case of a woman presenting with heavy periods, eventually given a hysterectomy and almost having a fatal bleeding episode at surgery. She was subsequently shown to be improperly consuming warfarin.

Clinical pharmacokinetics can also play a major role in unexplained therapeutic failures. A commonly cited example in this field is procainamide, which produces a very wide range of steady state plasma concentrations per unit dose. Almost a decade of intensive investigation has shown this variation to lie in the high clearance of the drug by a multiplicity of pathways, at least one of which shows genetically-determined polymorphism and may also be capacity-limited. More recent examples include the range of interactions with chronically administered drugs, such as cimetidine, and the possibility of population variability in response to oral hypoglycaemics.

The successful development of single-sample predictive computer programs has also revolutionized the very real and immediate assistance that the pharmacist specializing in clinical pharmacokinetics can give in helping with difficult therapeutic problems. For example, take the situation of a patient with septicaemia and worsening renal function being treated with aminoglycoside–penicillin combinations; and the wasted years in treatment of asthmatics because of the inability to cope with theophylline pharmacokinetics.

FUTURE DEVELOPMENTS IN TRAINING HOSPITAL PHARMACISTS IN CLINICAL PHARMACOKINETICS

At present, training of hospital pharmacists for patient contact roles is grossly inadequate at the undergraduate level and inadequate in most centres at postgraduate level. Schools of pharmacy tend to take the attitude that the subject should be taught as a mixture of basic sciences – which would lay the foundation for all subsequent areas of work – and of the uniquely professional aspects. In practice, pharmacy covers such a wide spectrum of activities that no one is achieving a proper education to equip them for the post in which they are placed. The answer to this is surely greater postgraduate training, particularly in-service training in the various fields of pharmacy, akin to the postgraduate training in the various branches of medicine.

A major limitation, however, is the current lack of properly trained

experts employed in hospitals. Surely the best training would be secondment of students at undergraduate or postgraduate instructional level to hospitals; there to spend significant periods *working* in patient contact areas, in contrast to observing or hearing of these roles.

There is also a lack of dialogue between the hospital pharmacist and university and all too frequently between hospital pharmacist and physician. I referred at the outset to my own experience and it is still notable that requests come from physicians, with whom I made contact as a clinical chemist, for assistance with drug-related problems; although fortunately the frequency of these has diminished as good quality, patient-orientated services from the hospital pharmacy have increased. Perhaps the best solution, and most urgently required development in training, would be joint appointments between universities and hospitals. This would allow establishment of education and research orientated pharmacists in the hospital environment and would allow students to receive this part of training there. Although a step in the right direction, the practice of bringing the hospital specialist to the university to give classes in isolation from the patient, nursing and medical staff is a poor substitute.

SUMMARY

Clinical pharmacokinetics is not simply a 'fashion' subject but is a logical extension of the purpose of pharmacy services in hospitals. The great opportunity for a meaningful active role in patient care can be seen by reference to the growth of clinical-chemistry based therapeutic drug monitoring services and the great inadequacies in these. Training of pharmacists, to take advantage of the opportunities offered in this field, requires recognition that patient involvement and involvement with other health-care professionals in the hospital setting is a difficult course to follow and would be assisted by joint university hospital appointments and by part of the pharmacist training being in the hospital at this critical interface.

There is also scope for review of what is taught, whether it be at undergraduate or postgraduate level, in university or in hospital. Clinical pharmacokinetics demands an expertise in drug analysis in body fluids – an immensely difficult and undervalued field. It also demands an ease in gaining a feeling for drug disposition in the patient and this in turn means moving from the physical chemistry, reaction order, model-based approach to the more physiological perfusion and clearance concept approach to pharmacokinetics.

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Theophylline therapy: the need for pharmacy involvement

R.A. Wolf

INTRODUCTION

Methylxanthines (theophylline, caffeine, theobromine) have been utilized in the treatment of asthma for nearly 50 years. For many years, it was thought that the pharmacological mechanism of action was inhibiting phosphodiesterase. Now, other basic cellular actions of the methylxanthines have received major attention in studies to explain their diverse effects. Listed in order of their increasing sensitivity to methylzanthines, they are: (1) those associated with the translocations of intracellular calcium; (2) those mediated by increasing accumulation of cyclic nucleotides, particularly cyclic-AMP; (3) those mediated by blockage of receptors for adenosine (Gilman *et al.*, 1980). Because the concentration of free theophylline in plasma rarely exceeds 50 μmol during therapy, this fact alone appears to limit severely the possible contribution of the other categories of action and leaves the blockage of receptors for adenosine as the leading candidate (Gilman *et al.*, 1980).

Other possible mechanisms that seem probable but need more investigation include potentiation of inhibitors of prostaglandin synthesis and the possibility that methylxanthines reduce uptake and/or metabolism of catecholamines in non-neural tissues (Gilman, Goodman, 1980).

Theophylline, in particular, has become a very important drug, relieving

the symptoms of asthma by relaxing bronchial smooth muscle. Bronchodilation effect of theophylline was shown to be related to its concentration in human serum in a study reported by Turner-Warwick (1957). Prevention of symptons of chronic asthma is impressive when therapeutic serum concentrations are maintained on a continuous around-the-clock basis at levels within the 10–20 mg/l range (Weinberger and Bronsky, 1974, 1975; Hambleton *et al.*, 1977). A drug's therapeutic range is defined as that range of the concentration associated with a high degree of efficacy and a low risk of dose-related toxicity. The therapeutic range is a statistical concept; it is the concentration range associated with therapeutic response in the majority of the patients.

Achievement of therapeutic drug concentrations is made more difficult by individual patient selection, cardiovascular and pulmonary status, age, presence of concurrent disease states, smoking history, diet, and use of other drugs (Powell *et al.*, 1977; Kappas *et al.*, 1976; Weinberger *et al.*, 1977; Cummins *et al.*, 1977; Gal *et al.*, 1978).

Progressive improvement in pulmonary function has been shown to occur in hospitalized asthmatics as serum theophylline concentrations increase from 5 to 20 mg/l, although the patients in this study were asymptomatic at the time of the study (Mitenko and Ogilvie, 1973).

In a double-blind, controlled evaluation where theophylline serum concentrations of 10–20 mg/l were achieved, much better control of asthma was observed than with a placebo of a fixed dose combination of ephedrine and theophylline giving serum theophylline concentrations under 10 mg/l (Weinberger, 1978). Serum concentrations above 10 mg/l effectively inhibit bronchoconstriction in prolonged inhibitory effect as serum concentrations above 15 mg/l (Bierman *et al.*, 1977). In the majority of instances, theophylline toxicity does not occur below a serum concentration of 13 mg/l (Jenne *et al.*, 1972; Jacobs *et al.*, 1976).

Adverse effects associated with serum concentrations above 20 mg/l are persistent and include nausea, vomiting, headache, diarrhoea, irritability, insomnia (Kordash *et al.*, 1977; Jacobs *et al.*, 1976; Hendeles *et al.*, 1977) and at higher levels, seizures, brain damage, cardiac arrhythmias, and death (Zwillich *et al.*, 1975; Jenne *et al.*, 1972). Jenne's work also revealed variations of 2.9–32.6 mg/l could result from a maintenance dose ranging from 200 to 300 mg every 6 hours, thus necessitating the need for serum-content determination (1972).

The purpose of this study was to determine whether appropriate doses of theophylline were being prescribed for chronic asthmatic patients as determined by drug monitoring. When drug monitoring revealed subtherapeutic serum levels of the drug, pharmacokinetic calculations were performed in an attempt to determine the appropriate dose for each patient. By performing this service, it was anticipated that patients would benefit from a more rational use of theophylline.

METHODOLOGY

All patients being followed in an adult chest clinic and in a general paediatric clinic that were currently being treated with theophylline or its derivatives, either singly or in combination with other medications, were included within the study.

An initial theophylline serum-content measurement was obtained on each patient utilizing the homogeneous enzymatic immunoassay (EMIT®). Also, the patient was asked to perform three consecutive exhalations into an electronic flow meter (Monoghan M403 Flowmeter®) which measures forced vital capacity (FVC), forced expiratory volume in one second (FEV_1), and peak flow rate (PFR) with each exhalation.

If the patient was identified as being in the designated therapeutic range, the patient was followed at regular intervals with further serum content measurements and medical examination. Where the patient was identified as being sub-therapeutic, the drug, dose, route of administration, and pharmacokinetic calculations were reviewed in order to bring the patient within the therapeutic range in a reasonable period of time. Once drug, dose, or route were changed, and a sufficient period of time had passed, subsequent serum-content measurements and dosage changes were made until a therapeutic concentration was reached. Serial lung function tests (FVC, FEV_1, PFR) were performed to obtain objective data as to whether placing patients into a therapeutic concentration was helpful.

RESULTS

Theophylline has been shown to be an effective drug, but one with a potential for toxicity. Demonstration of a narrow therapeutic range and the strong correlation of serum concentration with effect on bronchodilation and toxicity make the use of assays for theophylline in serum an important management tool (Bredon, 1982).

Of the 80 patients included within the study (Table 16.1), 53 (66.24%) had serum concentration levels of less than 10.0 mg/l. Some 22 of 53 (41.5%) of the patients had levels between 5.1 and 10.0 mg/l, and 20 of 53 (37.75%) of the patients had levels of 2.6–5.0 mg/l. The number of patients with levels $\leq$2.5 mg/l were 11 (20.75%). If the therapeutic range of 10–20 mg/l is absolute, 25% of the study patients could be considered therapeutic with no dosage changes necessary. If the therapeutic range is broadened to include serum levels of 5–20 mg/l, 42 patients (52.5%) would be considered to be therapeutic. This still leaves 38 patients (47.5%) who would be considered sub-therapeutic (as far as theophylline benefit is concerned, they might as well have been rubbing it on their skin). The pharmacist made recommendations of one type or another (drug change, dose change, dosage interval change, starting and dicontinuation of the

Table 16.1 Range of serum theophylline concentrations

Serum concentration (mg/l)	*Patient population*					
	Adults		*Paediatrics*		*Total*	
	Number	*%*	*Number*	*%*	*Number*	*%*
≤ 2.5	6	7.5	5	6.25	11	13.75
2.6–5.0	17	21.25	3	3.75	20	25.00
5.1–10.0	17	21.25	5	6.25	22	27.50
10.1–20.0	11	13.75	9	11.25	20	25.00
> 20	0	0	0	0	0	0
No level	3	3.75	4	5.0	7	8.75
Total	54	67.5	26	32.5	80	100.0

drug) in 66 of the 80 patients (82.5%) during the course of the study (Tables 16.2 and 16.3).

Objective criteria for the patient were judged by observing improvement in lung function tests. Where subsequent visits were made and peak flow measurement obtained, on all occasions dosage changes which raised the patient's status from the sub-therapeutic range to the therapeutic range, showed a concomitant increase in peak flow rate.

Table 16.2 Dosage changes in response to theophylline serum concentrations below 10 mg/l

Physician specialty	*Dose changed*	*Dose not changed*	*Total*
Adult	45	7	52
Paediatrics	16	6	22
Total	61	13	74

Table 16.3 Direction of dose changes in response to theophylline serum concentration

Theophylline serum concentration (mg/l)	*Response*		
	Dose increased	*Dose decreased*	*Maintain*
≤ 2.5	14	0	0
2.6–5.0	20	0	0
5.1–10.0	20	0	1
10.1–20.0	3	3	13
> 20	0	0	0

Of the drugs utilized within the study, the majority of the patients were on oral slow release aminophylline or oral slow release theophylline. Other products were being utilized initially when the patient entered into the study (choline theophyllinate, aminophylline suppositories) but because of

difficulty in maintaining therapeutic levels, all patients were switched to either oral aminophylline or theophylline.

DISCUSSION

The utilization and effectiveness of a pharmacist in drug therapy monitoring has been proven within the context of this study. Not only were drug levels monitored, but detailed drug histories were obtained, diaries kept on all paediatric patients, and in many instances, personal contact with the patient was made by the pharmacist either by verbal or written communication. Also, the pharmacist in many instances was seeing the patient in lieu of the physician, and it was the pharmacist who in these instances was doing the actual prescribing. The pharmacist was a very influential and important member of the health-care team.

In attempting to assess the impact of an in-patient pharmacokinetic service upon the use of serum theophylline assays, Bearce *et al.* (1979) found assays to be more appropriately used in an institution where a formalized pharmacokinetic service had already been established. The investigators judged that costs could be reduced by using this service to prevent unnecessary or erroneous orders and that care of the patient could be improved by maintaining more patients within the therapeutic range.

This study shows that patient care can be made more satisfactory by the utilization of a pharmacist within the out-patient department. Also, a reasonable conclusion is that properly ordered, documented and interpreted theophylline assays which provide accurate, usable results can have the direct result of improving the patient's clinical state.

CONCLUSION

The utilization of drug level monitoring within an out-patient clinic has proven to be beneficial for patient care. The pharmacist has participated as an active member of the health-care team and has been very influential in the decision-making process of drug, dose and evaluation of drug therapy. There is a definite role for the pharmacist in a hospital out-patient setting.

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17

Pharmacokinetics in the hospital pharmacy

R.T. Calvert

Although the origins of pharmacokinetics can be traced back to the papers published by Teorell, 1937, the potentional applications of the principles outlined in these papers were not realized until publication of a review on drug absorption and disposition by Nelson in 1961.

Today, there is an impressive literature on pharmacokinetics and its applications at both research and practice levels. It is taught in every school of pharmacy and is now finding a place in the curricula of schools of medicine. There are research groups in many universities involved in pharmacokinetics and each drug company is committed to major expenditure in this area. The pharmacokinetics of every new drug is now investigated before it is given a product licence and, therefore, details of its absorption, metabolism and elimination are available to users of the product. This is in contrast with the sometimes sketchy information available to users on older drugs. The published data on drug dispostion has been collated and published in several compilations (Bocher *et al.*, 1978 ; Evans *et al.*, 1980 ; Pagliaro and Benet, 1975). There is, therefore, a large body of knowledge available to the pharmacist about individual drugs. What should hospital pharmacists do with it?

Information concerning the pharmacokinetics of a drug can be used as a means of describing data, to enable pharmacists to make predictions about the outcome of dose changes, as a tool of research or as an educational tool.

The disposition of a drug in man can be described using generally accepted abbreviations which can convey what type of a drug we are deal-

ing with; alternatively, the disposition can be described in terms of a mathematical equation which allows us to graph out the plasma concentration time curve in an average person.

If we can describe the time course, it follows that, because the kinetics of most drugs obey linear principles at the concentration used, we can predict the result of changes in dose regimen of future blood concentrations. With the development of physiological models of drug disposition, we can predict the effect of changes in physiological functions, such as changes in blood flow or changes in liver enzymes on the concentration time profile of a drug in a particular patient.

The area of greatest application is currently in the research laboratories, where investigation of drug kinetics has proven rewarding in the design of new drug delivery systems and in our understanding of drug interactions.

Pharmacists have been involved in the education role of pharmacokinetics as undergraduates. However, involvement postgraduation does lead to the development of a better understanding of drug handling and an intuitive feeling for what happens to drugs in the body and the effect of disease states on the concentrations achieved.

There is a wide base of knowledge and considerable experience in the application of drug kinetics. However, we still find study days on 'Introduction of Pharmacokinetics' in every region. To date, there are few centres where pharmacists are involved in the application of pharmacokinetic principles to the treatment of individual patients, i.e. the measurement and interpretation of drug concentrations in patients. Most hospital pharmacists see it as an area which they are unwilling to master and reluctant to be seen applying in the ward situation. Involvement by hospital pharmacists in the interpretation of plasma concentration measurements can be worthwhile and rewarding and we should expect all large departments to be involved in these areas. I would, therefore, like to look at what the potentional involvement is, put forward suggestions as to why we have not been very committed to this area and offer some suggestions as to how the situation could be improved.

The area that we usually associate with pharmacokinetics is measurement of drug concentrations in individual patients and the use of this information to give an optimum drug regimen for the patient. This approach cannot be applied to all drugs. A list of criteria for selection of drugs for monitoring can be drawn up and is given in Table 17.1 and, based on these criteria, a list of candidates for monitoring can be selected. These are given in Table 17.2

This is a very small group of drugs compared to the number of drugs in use. The promotion of a rapid assay technique based on antibody/antigen reactions had made possible the provisions of a same-day assay service for several of these drugs using just one piece of equipment, which does not require extensive operator training. Although it is possible to analyse all

Table 17.1 Criteria for selecting drugs for therapeutic drug monitoring

(1)	There is no other endpoint more closely related to the ulitimate therapeutic objective.
(2)	There is wide *inter* patient variability in the drugs disposition but less *intra* patient variability.
(3)	The drug has a small therapeutic index
(4)	Concentration of the drug in plasma should directly relate to the effects of the drug.
(5)	The drug should be used for sustained effect over a relatively long time.
(6)	It must be possible to analyse plasma for the drug accurately and quickly.

Table 17.2 Drugs for consideration for routine drug monitoring

Digoxin	Propranolol
Lignocaine	Quinidine
Lithium	Salicylate
Phenobarbitone	Theophylline
Phenytoin	Methotrexate
Procainamide	Aminoglycosides

of these drugs using other techniques, most departments setting up drug assay services have been drawn to EMIT or similar systems, because of the advantages of speed and ease of use. Implementation of an assay service involves decisions on several questions, which are listed in Table 17.3. As with most problems in hospital pharmacy each hospital developing a service will probably arrive at different answers to these questions and hence develop a unique service. At Leeds the service is currently provided based on the scheme shown in Figure 17.1.

Table 17.3 Question associated with developing a drug monitoring service

(1)	Who should request measurements?
(2)	Who should assay samples?
(3)	Who should fund the service?
(4)	How should results be reported?

At present, we provide an acute service for six drugs in one laboratory and use the results from microbiology for gentamicin and nuclear medicine for digoxin. The service provides interpretation along with the result. Examples of progress in therapy made, based on use of this service, are phenytoin treatment on intensive care, where ineffective prophylactic

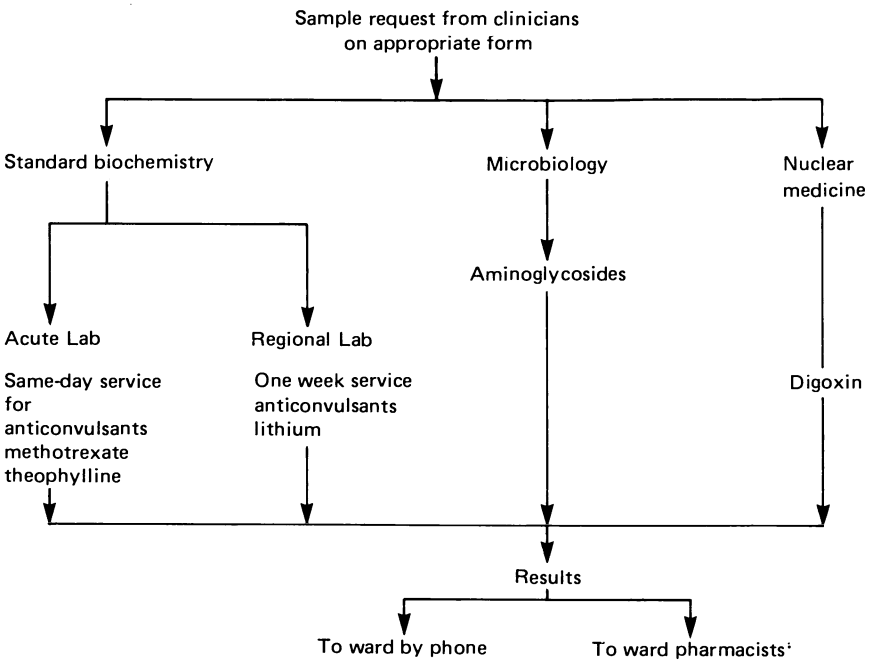

Figure 17.1 Flow diagram of current arrangements for drug monitoring at The General Infirmary at Leeds

treatment of head injuries has been identified and changed to effective therapy and with theophylline in neonates. In our experience this system has led to several problems and, as yet, we are not getting the best out of the service we provide. The major problems can be summarised as:

(1) Sample flow from the ward to the laboratory.
(2) Staff motivation; they find it difficult to contact medical staff and arrange for blood levels to be carried out.
(3) Clinical staff education; at present they have little concept of the contribution which drug monitoring can play in patient management.

A possible solution to some of these problems is the appointment of a person to be responsible for this area, who would accompany ward pharmacists on the follow-up of assay reports and be responsible for sample procurement and provision of the complete service. A second factor would be the ability of pharmacists to request that blood levels be determined for a patient, but we are a long way from this proposal being accepted. Drug monitoring is the major area of application of pharmacokinetics. It involves only a few drugs but in contrast to most pharmacy interventions it enables us to make a positive contribution to patient care.

A second area of application relies on an understanding of drug kinetics by the ward pharmacist and of the interaction of physiological function and drug disposition. Examples in this area would cover the effect of renal and liver function on drug dose regimens, effect of social habits on drug disposition and an understanding of drug interactions. This area relies on a knowledge of population average values for drug disposition parameters and the direction of change in these parameters produced by changes in physiological status. To be applied successfully, it requires pharmacists to have a detailed knowledge of drug kinetics, the effect of physiological changes on kinetics and the willingness to put forward their views.

A third area of application is in the evaluation of manufacturers' literature and the use of rational dose regimens, which can often be used to advocate cost savings. For example, the use of cephazolin 500 mg four times a day, compared to 1 g three times a day could save Leeds General Infirmary over £4000 per year.

There is, therefore, a case for the practical value of pharmacokinetics to be recognized by hospital pharmacists. It is an area where we can use our scientific background and play a positive role in improving patient care. To date, apart from two or three centres, we have been slow in putting this subject to practical use.

The reasons for this include the type of teaching courses used, which are research-based and concentrate on the descriptive aspects, whereas pharmacists in practice are involved more with interpretation and the predictive aspects of kinetics; the ignorance of many medical staff of this area; decentralized assay services; the reluctance of these services to pass results to the ward through pharmacy and finally the motivation of pharmacists to believe they can apply the principles of pharmacokinetics successfully.

A possible solution is the integration of teaching in this subject between schools of pharmacy and nearby hospitals. This I believe would promote a greater understanding by the schools of the requirements in hospital and would provide hospital pharmacy with centres of excellence to demonstrate the utility of these techniques to clinicians. We would obtain improved care for the patient and benefits for the pharmacist; its major disadvantage would be the hard work required to get involved.

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18

Practising drug evaluation

S. Hudson

The process of drug evaluation has importance nationally, in drug licensing, and importance locally in decisions about the treatment of individual patients. The evaluation of drug literature is one task within a range of activities directed at problem solving and decision making in patient care. Systems and services designed to evaluate drug literature must be tied in with systems and services for monitoring drug use and its consequences. Evaluated drug data must be *used*, so that it helps to prevent or identify and solve drug problems.

THE SIZE OF THE TASK

The size and scope of the task of drug evaluation is potentially daunting. The Medicines Act presented the Committee on Safety (Review) of Medicines (CSM/CRM) in 1975 with the prospect of assessing over 4000 proprietary medicines which had been given licences of right in 1971 (Binns, 1980). The Committee must complete its systematic evaluation of the products, by the end of this decade. The result of this exercise, which is visible to the practising pharmacist, is a revised data sheet which no longer includes indications for which there is no evidence of efficacy but which does include a more reliable list of possible adverse effects. The depth of the evaluation of a drug by the CRM is necessarily limited and does not extend to assessment of efficacy or toxicity relative to alternative treatments. The efficiency and safety of a drug tend to be assessed independently. The licensing authorities clearly do not set out to aid therapeutic decision-making.

In the choice of a non-steriodal anti-inflammatory agent, for example,

the range has increased fourfold to 28 different products since the implementation of the Medicines Act, and this emphasizes the need for evaluated comparative drug data.

The national evaluation of drug toxicity relies very much on voluntary (CSM yellow card) reporting during post-marketing experience. Assessments of a drug's toxicity change continuously as new published and unpublished reports appear. The process of the CSM responding to information on toxicity is slow because of the very nature of the system, which requires the accumulation of a quantity of individually unevaluated reports before suspicions formally become aroused (Inman, 1980).

A further indication of the size of the problem of evaluating drug literature is the quantity of literature involved. There are now said to be over 20 000 biomedical journals worldwide (Lock, 1982), even though only 3 200 are indexed in a readily available format (Index Medicus). A large proportion of these journals might be expected to contain relevant information on drugs. A selection of a mere 150 of those regularly productive of drug data manages to generate 15 000 new articles on drugs each year (Iowa Drug Information Service). Even more daunting is the exponential growth of biomedical literature which is doubling in volume every 10–15 years, i.e. 2–3 times faster than the world's population (Lock, 1982). The growth in the number of journals is a product of the changing character of the scientific and medical literature, with creation of new fields of research, increasing specialization and the merging of traditional disciplines (Ziman, 1980). The evaluation of the scientific literature on drugs increasingly demands a multidisciplinary approach.

THE PROBLEM IN PRACTICE

The need for drug evaluation is felt at individual hospital level and the pharmaceutical response can be seen both in organizational terms and in terms of individual patient care. In daily practice the availability of data on drugs is necessary for making rational therapeutic decisions. The demand for evaluated information on drugs is reflected in the types of questions raised by physicians and pharmacists. These questions involve controversies about the merits of different classes of drug in a certain disease; the relative merits of drugs from the same class; the selection of dose and mode of administration, perhaps for unlicensed indications; and the identification and assessment of risk of adverse effects. Most importantly, the practical context in which such questions arise often demands a prompt response. Frequently, reasonable decisions must be made in the absence of completely authoritative guidance. Such decisions clearly need to be made from an informed basis and with such expertise as is available at the time.

In the hospital setting drug-related problems are commonplace and pharmacists are regularly involved in three locations, on the ward, in the

drug information centre and in committee. In each location pharmacists perform distinct functions in helping drug selection. These three functions are inter-related and their mutual dependence demands that they be well orchestrated by the pharmacy manager.

On the ward

Pharmacists making daily visits to the patient's bedside and being in regular contact with prescribers and nurses are ideally placed to monitor drug treatment and associated events. In this situation, pharmacists make interventions in therapy and the character of these interventions has been studied. A recent large survey in the United States (Burkle *et al.*, 1982) has indicated that 24% of pharmacists' interventions related to the choice of drug, about 7% to adverse effects and 3% to drug interactions. We have recently completed a large-scale survey (unpublished) amongst five hospitals in the UK which shows very similar findings of 21%, 8% and 4% respectively (Table 18.1). A second smaller study from the USA has provided relative frequencies of 27%, 13% and 3% for the above categories of interventions (Lipman *et al.*, 1982). In a further recent American study about 19% of questions asked by medical staff related to drug choice, about 10% to adverse reactions and 1–2% related to drug interactions (Sweigert *et al.*, 1981). However, these broad categories conceal a range of types of according to the pharmacist's individual skill and training.

Monitoring drug treatment involves skills in the detection and investigation of potential problems when faced, at first perhaps, with only the medication record for information on a patient. Effective communication and good relations with physicians and nurses ensures a greater opportunity to identify problems. Once identified, a problem needs to be analysed in terms of its nature and effect on the patient and assessed in terms of how quickly it needs to be solved. Interpretation of diagnostic and pathological data may be necessary and the pharmacist can easily be drawn out of his (her) field of competence.

Good communication with other disciplines, particularly with medical staff, is very important. Only once a clear understanding of the patient's problem has been gained should much time and effort be spent analysing drug literature. The responsibility for evaluating the evidence obtained from the literature must be shared by the ward pharmacist and the drug information centre. Similarly the form of the report back to the prescriber (verbal or written) can be agreed between the pharmacists concerned. At this stage, evaluated information often needs thorough discussion with the prescriber, so that it may be applied to the problem in hand. Where a written drug information report is the means of response, follow-up and further discussion by the ward pharmacist can greatly add to the impact of the service and ensure a satisfactory outcome.

The extent to which this process of exchange of information is successful depends in practice on a number of complex variables. Foremost amongst these are the temperaments and personalities involved, the skill and training of the pharmacists and the extent to which the pharmacy service manages to provide pharmacists with suitable opportunities. Individuals differ in their abilities to create opportunities for themselves. The interventions in Table 18.1 can be separated (Table 18.2) into those which are solicited (information requests) and those which are unsolicited (problems identified by the pharmacist). In our survey from five hospitals in the UK, pharmacists showed the initiative as often as the prescriber, on matters of drug choice. In the USA survey, pharmacists might be thought to be more aggressive, since they made the approach three times more often than the prescriber. In both the USA and the UK surveys, matters involving adverse effects of drugs most often led to the physician/surgeon approaching the pharmacist. Limited individual patient contact by pharmacists during ward visits may explain why they rarely seem able to take the initiative on matters relating to adverse effects.

Table 18.1 Interventions by ward pharmacists

	*USA**	*UK*
Drug choice	24%	21%
Adverse reaction	7%	8%
Drug interaction	3%	4%
Dose	34%	33%
Number of interventions	3242	1544

*From Burkle, 1982

Table 18.2 Problem identification and information provision by ward pharmacists

	*USA**		*UK*	
	Problems	*Information*	*Problems*	*Information*
Drug choice	35%	11%	23%	20%
Adverse reaction	4%	8%	3%	13%
Drug interaction	3%	4%	3%	5%
Dose	34%	38%	43%	21%
Number of interventions	1408	1335	808	736

*From Burkle, 1982

In the drug information centre

Standard sources of evaluated information on drugs either rapidly go out of date (e.g. reference books) or often tend to be specialized (e.g. review articles) and so address themselves to drug effectiveness or drug toxicity

independently. Many sources (such as the British National Formulary) are not useful for unlicensed indications of drugs and secondary literature sources are concerned with the objective of making generalizations. Drug information services are often called upon to help apply drug data to particular circumstances around individual patients. The drug information pharmacist's first concern is to extract as much relevant data from the literature as possible in the time available. The second concern is to analyse and present the information in a logical form with some indication of its validity related to the problem in hand. Skill in communication is as important as skill in retrieving and analysing information. The enquirer's problem has to be appreciated at the outset in order that the information service is applied appropriately. The most efficient way of disseminating evaluated information on drugs is probably by word of mouth through a network of ward pharmacists. A good working relationship with mutual appreciation between ward and drug information pharmacists is very important.

The problem of the size of the drug literature is coming under control. The co-operation between drug information centres is producing a national network and some consensus on data handling methods, such that computer technology promises to revolutionize the storage and retrieval of drug information.

More important to the evaluation of drug literature is the question of its quality. First, particular research which needs doing may never get done. It may not be possible to solve practical problems simply because data are unavailable. Most clinical research on a drug inevitably occurs after marketing. Clinical trials tend to reflect the interests of researchers and drug manufacturers, neither of which may be the same as those of the consumers (doctors/pharmacists/patients). Therefore trials that need doing may never get done. The commonest examples are the essential comparative trials of drugs, which may get performed only years after a drug has been in general use, if at all. Early in the life of a new drug comparative assessment with established treatments from the literature is frequently therefore not possible.

The general quality of scientific literature is regularly criticized. Much of the volume of literature is of marginal use either because it is so academic that it is inapplicable, because it demonstrates incompetent techniques or because it produces trivial results. As many as half of all articles never get cited even once by other authors. Only about one paper in eight provides what is said to be important, new, useful information (Lock, 1982). One editor of a reputable journal publishes only 15% of manuscripts he receives (Relman, 1979); the rest are likely to be published elsewhere. Editorial review may simply be determining where, rather than whether, many papers are eventually published.

The evidence in the literature therefore requires careful analysis and

assessment according to scientific criteria. The clinical literature on a drug comprises review articles, hypotheses and opinions expressed in correspondence columns, short-term experimental procedures on volunteers or patients, case reports and clinical trials in groups of patients. Clinical trials carried out prospectively represent the most productive source of reliable data; that is assuming that they are well designed and adequately reported. In a survey of 155 articles from three major medical weeklies in 1976, almost 50% of clinical trials had no control (e.g. placebo) group. In over 50% of the trials that were controlled patients were allocated in non-random fashion ((Fletcher and Fletcher, 1979). A simple check-list, such as is presented in Table 18.3, can help in the analysis of clinical trials. When such a check-list is used it becomes evident that even apparently well-designed trials are not always well-reported, due to omissions. Another recent survey of four general medical journals claimed that 40% of papers omitted important information on whether assessment was 'blind', and 33% omitted information on whether the patient was 'blind'. Such information is important for eliminating the possibility of bias (Der Simonian *et al.*, 1982). 33% failed to clarify any adverse effects of their treatment and 73% failed to describe adequately the types of patients in the trial. The latter omission makes it difficult to decide whether the results of the trial can be applied to the general population suffering from the particular condition. On the question of statistical analysis, two surveys confirm that errors may be present in about 50% of articles from even highly regarded medical journals (Gore *et al.*, 1977; Glantz, 1980). Most of these errors are simple and do not require specialized statistical knowledge, merely practice and some familiarity with standard techniques (Glantz, 1980). Another recent, more fashionable criticism of clinical trials relates to those with 'negative' findings. In a study of 71 such trials, as many as 50% could really have shown a 50% improvement but the sample size was too small (Freiman, 1978). Articles appearing in less respected journals are likely to be even more readily criticized.

Analysing and evaluating drug literature is a task for which an undergraduate training provides poor preparation. Many drug information pharmacists tend to be self-taught in this respect and this raises the importance of recognizing one's own limitations. Clinical trial data can be readily analysed and reported, but interpretation and evaluation may require knowledge beyond the field of pharmacy. In particular, familiarity with the natural history of a disease process may be essential to identify all possible sources of bias. Two groups of patients in a trial may not be diagnostically or pathologically comparable, Similarly, diagnostic skills are necessary to distinguish adverse drug effects from underlying symptoms of disease. The pharmacists must concentrate on providing a descriptive report of an analysis of the literature, whilst evaluating the data as far as he feels comfortably able. It is important to recognize that complete interpretation

Table 18.3 Clinical trial check-list

(1) Types of patients	Entry criteria Confirmed diagnosis Exclusions Selected before randomized In-patient/out-patient?
(2) Design overall	Adequate controls Comparability of groups Minimization of bias Cross-over? Uniform if multicentre
(3) Allocation of patients	Randomization Blind Matching placebo
(4) Defined treatment regimen	Timing Route Compliance checks Fixed dose/variable dose Length of treatment
(5) Assessment	Blind Methods (objective/subjective) Criteria Different assessors? Measurement techniques Carry-over from cross-over?
(6) Adverse effects	Method of detection Symptoms recorded Check-lists?
(7) Patients withdrawn	Lost to follow-up Adverse effects Introduction of bias Types of patients Modify original sample?
(8) Statistical analysis	Specified methods Conventional techniques Adequate sample size
(9) Comparison with other trials	Discussed by author(s)?
(10) Validity of author(s) conclusions	Logical conclusions Opinion Speculation

may need to be left to discussion with the clinician concerned or with a specialist colleague. The application of drug information should be resolved during final discussion with the medical enquirer. The importance of this final discussion in the process underlines the need for good communications between pharmacists and medical staff.

In Committee

A reflection of the activity of the pharmacy service in therapeutics is the popularity of Drug and Therapeutics Committees, which grew from less than 70 in England in 1973 (Brown *et al.*, 1975) to 197 in the UK in 1981 (Hands, 1981). Closer involvement of pharmacists directly in patient care has been coupled with demands on pharmacists to assume a major share of the responsibility for the way drugs are used. This trend, heightened by the need for economies in the health service, has presented the pharmacy service with a central role in locally organizing comparative assessments of drug effectiveness, toxicity and cost. The output from these committees has included agreed drug policies and procedures, drug bulletins, antibiotic guides and drug formularies. A total of 46 prescribing guides/drug formularies have been prepared throughout the UK (Hands, 1981). Drug and Therapeutics Committees present an ideal opportunity for a multidisciplinary approach and, by consensus, can produce well-evaluated information. This information can be readily transformed into guidance which gains wide acceptance. Such committees need to be sensitive and address themselves to real, practical problems. Pharmacy representatives on committee should exploit the fact that ward pharmacists are in a position to help identify drug problems needing policy decisions and can monitor the effects of such policies. Two-way communication between pharmacists on committees and those visiting wards is essential.

LOCAL EVALUATION OF ADVERSE DRUG REACTIONS

The Committee on Safety of Medicines (CSM) receives over 10 000 adverse drug reaction (yellow card) reports annually. The estimate that these probably represent much less than 10% of all identified reactions which deserve documentation (Inman, 1972) is an indication of the potential that exists for improving the quantity of reporting.

Regionally co-ordinated adverse reaction monitoring by pharmacists and clinical pharmacologists has been in operation in the West Midlands since 1973 (Beeley and Talbot, 1980) and has recently been introduced in the Northern Region. Apart from a few such exceptions, the concept of local monitoring of adverse drug reactions 'has been greeted with masterly inactivity' (Editorial, *Br. Med. J.*, 1981). A postal survey of hospitals in 1979 indicated that although many pharmacy departments handle the supply of

yellow cards and express an interest in improving the CSM scheme, there is little control over the eventual fate of yellow cards issued (Talbot and Veitch, 1980).

Just as necessary as improvements in the quantity of adverse reaction reporting are improvements in the quality of reports. Both of these aspects are amenable to influence through local efforts. The drug information centre is most suitable for the co-ordination of any local scheme. A network of ward pharmacists is a potential motivating force as well as an attractive means of surveillance, of facilitating communications and a means of providing feedback. The drug and therapeutics committee might provide a forum for multidisciplinary involvement in detection and evaluation of suspected adverse drug reactions, as well as an instrument for gaining general acceptance of any pharmacy-based scheme.

In the Leicester Hospitals, we have sought to exploit the potential for local adverse drug reaction monitoring by, first, centralizing the issue of yellow cards from the drug information centre via dispensaries and ward pharmacists. The attachment of internal mail self-addressed envelopes has enabled the drug information centre to respond to each yellow card with an acknowledgement and brief literature report. Since 1977 the scheme has handled 192 adverse reaction reports and we have observed a greater than twofold increase in the annual number of reports forwarded to the CSM from hospitals in Leicester. Each yellow card has been scrutinized for completeness and acknowledged with a brief review of the literature. The drug information report has indicated wherever possible the estimated incidence and the nature and outcome of similar reactions described in the literature. An explanation of the likely toxic mechanism has been alluded to, where known, and reference made to case reports and other CSM reports on file. Until recently no attempt has been made to evaluate each report.

Since January 1982, the scheme has been developed (Figure 18.1) to include a medical input, which has enabled classification of selected adverse reaction reports on the basis of likely causal relationship to drug administration. This development has necessitated the referral of the yellow card to a panel of three local clinicians, two of whom are clinical pharmacologists. The clinician is asked to classify the suspected reaction as either probable, possible or unlikely to be due to the drug implicated according to specific operational criteria previously described (Karch and Lasagna, 1975). Should additional clinical or drug information be required, the clinician is free to request it. Requests for further clinical details are relayed back to the reporting doctor via the drug information centre, wherever possible involving the ward pharmacist.

The role of the ward pharmacist is central to maximizing the output from this kind of local adverse drug reaction scheme. First, as a *motivator* the ward pharmacist is in a position to encourage the putting of pen to paper. Ward pharmacists were involved in 80% of reports received from one

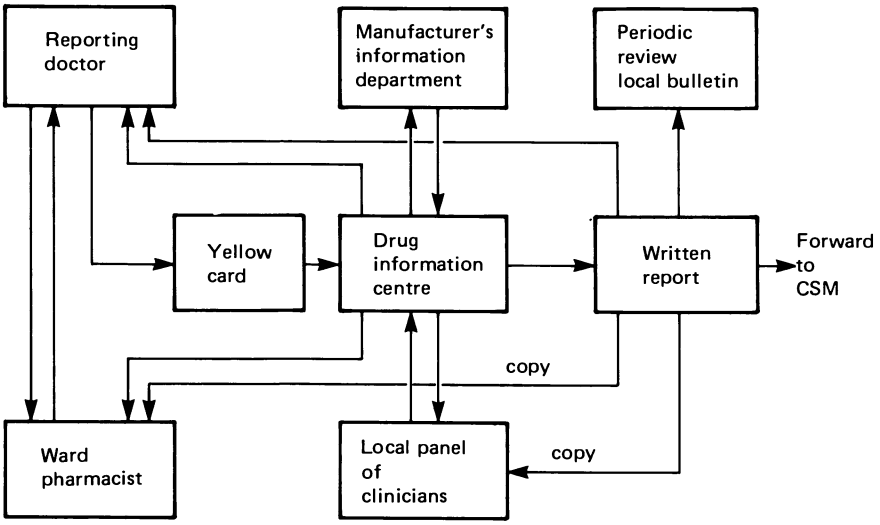

Figure 18.1 Local monitoring and evaluation of adverse reaction reports

group of hospitals in the West Midlands (Beeley and Talbot, 1980). Furthermore, a pharmacist made the initial documentation in 24% of reactions. The presence of a pharmacist on a ward round may be sufficient to raise the level of suspicion, amongst medical and nursing staff, about possible drug effects. Second, as an *educator*, the pharmacist can provide information about how well a reaction is already documented in the literature and advice on whether reporting is appropriate. If the decision to report is made, then the pharmacist may emphasize that certain details need to be recorded. Third, as an *investigator*, the pharmacist is well-placed to help obtain further historical details of a reported reaction, if these are necessary for clarification.

The successful interaction between doctors, pharmacists, drug information centre and clinical pharmacologists can also lead to a greater tendency for authors of yellow card reports to publish important cases in the medical literature, which itself is an important part of the adverse reaction 'early warning system'. In this way, pharmacists can play their part in both applying and contributing to the scientific literature on drugs.

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Discussion

Mr Sharkey: Could I ask Dr Wolf whether he was able to assess the degree of compliance in his patients before the end of the study and if that compliance resulted from such counselling during the study.

Dr Wolf: Compliance is certainly a major part of a study like this. We did not do any formalised process of identifying compliance or non-compliance except that when we knew patients were on a higher dose than that which they were previously on and still had levels that were either non-detectable or within a very low range. We suspected that there was non-compliance associated with each patient, but certainly compliance is a very important factor that one must consider in any type of study such as this.

Mr Purkiss: Professor Tilstone, the only qualification you didn't give us a cryptic message for was the M.Sc. Can I suggest one to you: M.Sc.= mistakes subsequentially corrected! The trouble is that hospital pharmacists have got around to meeting the patient now and really it is up to the academics to have a patient at the end of their teaching and I wonder if you would like to comment on that.

Professor Tilstone: What you say about hospital pharmacists getting around to meeting patients, yes! I accepted that in my presentation. I think, however, in the particular field that I was asked to speak about in clinical pharmacokinetics, really there is still in the United Kingdom a huge gap between what could be done by the pharmacist in direct patient and clinician contact in that area. I think this is an area which is still very much lacking in good quality and good quantity pharmacist-patient contact. Now I am frantically trying to think of a suitable acronym for the MSc. and not succeeding. It is only in the past few years that we have been able to find good quality pharmacists practising clinical pharmacokinetics locally that we can send the students to for in-field training. The practice just didn't exist as recently as five years ago.

Dr Veitch: Can I address my question to Bob Calvert? Along with many of the other speakers in this conference and other hospital pharmacy conferences which I have attended, there has been continuous reference to

how academic staff are not in line with what is going on in hospitals and how hospital staff are not benefiting from the experience which they gain from their undergraduate courses and in their pre-registration experience. The particular point I want to make is that you mentioned today that when Pharmacists are taught academic pharmacokinetics, they can't apply it in the clinical setting. What I want to ask you is when did you discover this? When you were an academic or when you moved over into the hospital scene?

Dr Calvert: It was when I left the research lab that I actually saw patients and realised that complicated computer programs are not the be all and end all of pharmacokinetics and that applications are much more intuitive than they are mathematical.

Dr J. Harris: I must be one of these peculiar academic pharmacists who actually sees patients. I would like to address a comment to Ray Wolf. That is, we have just completed about a 50 patient survey on theophylline and our results very much bear out what you found and that is about 50% of the patients are underdosed and that clinicians were extremely surprised to find this. Unlike you, we found that about 15% of patients were over-dosed and this is the sort of figure that Scott Bryson and his group working in Glasgow reported some months ago. What sort of maximum dose were your patients getting? The patients we saw seemed to come in from the community and they were either getting 1 bd theophylline preparation or 2 bd and those who were getting 2 bd were nearly always over-dosed.

Dr Wolf: In almost all the instances in the adult population, the patients were receiving "Phyllocontin" 225mg, 1 bd in the majority of cases, initially. Even when this was increased to 2 bd, in no instance did we have any patient's serum concentration go over 20 mg per litre.

Mr Harrison: I would like to ask the panel if they agree with Steve Hudson's assertion that we should be generalists not specialists.

Professor Tilstone: I must say that I do not agree and I think the ideal solution is a school of pharmacy which is producing a battery of individuals with a range of specialist expertise where they are truly expert in each of the different areas that a hospital pharmacy would have to cover. From that battery, of course, all the other members would pick up some knowledge and a little expertise in what his fellow pharmacists were doing. There is a greater requirement for a greater number of specialists in different areas.

Dr Wolf: Having come from America and being the rebels we are called occasionally, I would have to agree with Professor Tilstone. I think specialties are the thing of the future for the fact that each specialty is so diverse and medications and treatments within those specialties are so diverse that you need a pharmacist to be in control of the knowledge that is used for treating within those specialties.

Dr Calvert: I think specialists are needed, but only after an adequate training programme. To see people specialising almost after their pre-registration year is not appropriate. I think the idea of specialist areas after two or three years as a grade 1 pharmacist is the only way to go forward in the future.

Mr Hudson: I think the best way a pharmacist can offer his services to a specialist physician is to offer information and advice on matters outside his specialty so you have to know everything else. I'd plump for a generalist.

CHAIRMAN'S SUMMARY

You have been infused at a fairly steady rate with a pre-calculated dose, hopefully not an overdose, of science – suitably diluted – and I expect that we have all reached a steady state. Let us hope that this dose of science will have a very long half-life and that you will feel the benefit for a very long time – at least until the next Travenol Symposium.

Closing Address

T.J. Bradley

In his welcoming address, Mr Clarke predicted a number of events and most of these have appeared and evolved. Just let me look at one or two of them in detail. The first one is that Travenol have brought together the right ingredients for a symposium. The second one was mentioned of Alcuin, the old master, and I should like to turn back the clock and show you one or two characters and base my closing address and vote of thanks on these.

The first is ℞, the Travenol symbol for a successful conference. We have had sessions with good-quality speakers and also a session for the presentation of a number of short papers by authors. It has been this combination that has proved successful. The allocation of time, starting at 8.00 a.m. each day and going on to midnight, a period of 16 hours, has been divided equally between sessions circulation and following inclinations. I would like to thank Travenol very much for the symposium who have done a marvellous job over the arrangements here at York University.

The theme of the conference has been 'Hospital Pharmacy and the Patient'. The design of the sessions has been to use them as probes, to learn more about aspects of hospital pharmacy practice and how these become related to the patient.

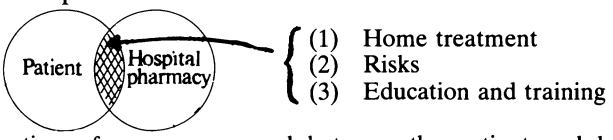

Figure 1 Exploration of common ground between the patient and hospital pharmacy

Session One concentrated on aspects of home treatment and the need to encourage the drift towards the self-reliant patient in the areas of home parenteral nutrition, cytotoxic medicines and new insulin delivery systems. (see Figure 1)

The second session focussed on risks of a health and safety nature to staff in handling cytotoxic medicines and microbiological hazards arising from a source that has not been fully investigated here to fore – the home environment.

The appearance on the hospital scene of ubiquitous micro-organisms that have developed antibiotic and antimicrobial resistance such as *Staphylococcus epidermis, Mycobacterium tuberculosis*, *Acinetobacter* and *Pseudomonas aeruginosa* requires the supply of more data to alert practitioners to self-inflicted cross-infection.

The third probe is education and training – for both practitioners and patients, essential for the understanding needed to yield the self-reliant patient. Suzanne Wood and Helen Doery presented the evidence for understanding that 'common core' of knowledge that permeates the training of all health-care professionals and developing the gaps by team work, discussion and interest.

This theme has recently been advocated in the House of Lords by Baroness MacFarlane when she proposed that Health-Care Facilities be established in British Universities to promote an interchange of knowledge at undergraduate level on health education, behavioural science, communication skills, environmental health, biomedical sciences, nursing, etc. Aston University in Birmingham has introduced combined postgraduate courses on the above lines and it will be interesting to watch how the Schools of Pharmacy respond.

Indeed in the last session, 'Who was in touch' in the current debate, Schools of Pharmacy vs. Profession, seemed to generate the feedback from hospital pharmacists on agreement for shared responsibility for 'Clinical Pharmacy' courses at both undergraduate and postgraduate level between academics and practitioners. The Schools of Pharmacy must consider relaxing their divine beliefs that they are the sole arbitrators of course contents, standards of assessment, etc., and enter in to joint responsibility contracts with practitioners, whereby all aspects of clinical pharmacy courses are shared with professional practitioners on an equally independent basis through the medium of Regional Pharmacy Education and Training Committees.

The theme of the symposium has been 'Hospital Pharmacy and the Patient'; the aim was to consider some aspects of hospital pharmacy practice and learn about the patient. My last character

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will sum up the information that has been presented to 220 hospital pharm-

acy pratitioners, equivalent to a 10% sample, hopefully to consolidate and raise the base line of our branch of pharmacy practice.
Consider Figure 2.

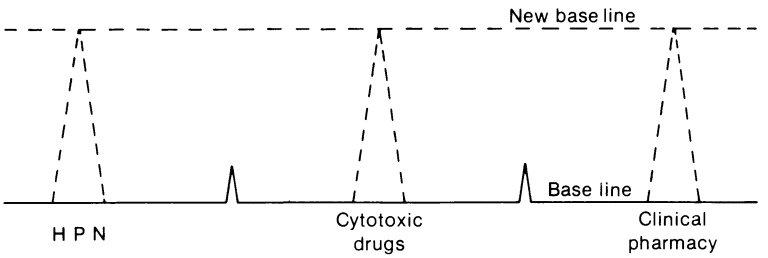

Figure 2 Aim to elevate base line of hospital pharmacy practice

Over the past 2 days we have listened to authors describing developments they have made in their branch of practice, e.g. Dr Anderson and his cytotoxic drugs handling policy, continuous insulin infusion and perhaps the wider implications of changeover to 100 unit insulin, home parenteral nutrition and involvements for both hospital and community pharmacists and the series of papers on a variety of topics from drug information, stability of steriod creams, and pharmacokinetics to monitoring of prescribing in hospitals. As we prepare to return, it is to consider the material presented here in York over the months ahead and by taking action on relevant items we can indeed raise the level of professional practice. Let us now show our appreciation to all in the traditional manner for a successful conference.

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