MACDOPE

A Simulation of Pharmacokinetics

Would-be doctors, pharmacists, nurses and many other health care workers need to know what happens to drugs and their metabolites inside their patients. *MacDope* will help them to understand the time courses of a range of drug types, their fates and dispositions in human subjects. By using *MacDope*, students learn both the characteristics of the patients which determine the intensity of drug action and the properties of the drugs responsible for different patterns of pharmacokinetic behaviour. *MacDope* can handle simultaneously up to four drugs taken from its range of 20 familiar drugs. It will not only teach students the kinetic features of a drug, but also the dependence of these features on the drug's properties. The precision *MacDope* demands will teach users how to write prescriptions correctly too.

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THE MAC SERIES OF MEDICAL AND PHYSIOLOGICAL SIMULATIONS

MACDOPE

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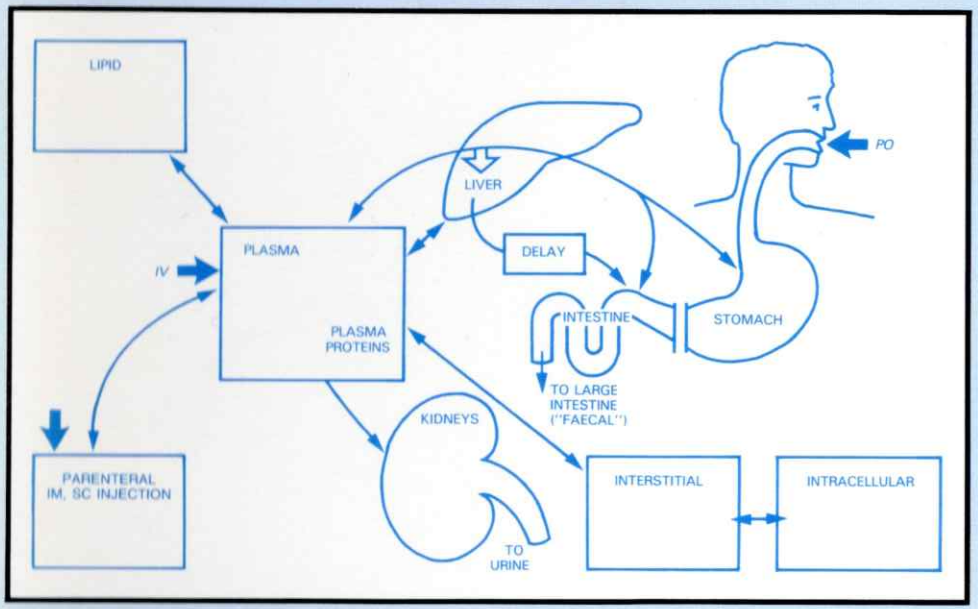

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LIMITATION OF LIABILITY

Mathematical models cannot be expected to provide completely accurate descriptions of the systems under consideration; our aim is to make these models relevant and helpful to someone learning about the behaviour of the system. To this end, they have been revised and developed through many versions over a seventeen year period and have been in continuous use at many centres during that time.

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1. The model

1.1 Introduction to *MacDope*

Many patients who visit a physician come away with a prescription which is dispensed, and most patients begin with good intentions of complying with the prescribed drug regime. A physician practising medicine intelligently needs to know what happens to the drug after the patient has taken the medicament. This knowledge is important also to all the health care workers who are involved in the treatment, particularly pharmacists and nurses. *MacDope* is a computer simulation which can help in the understanding of the time course of drugs and of their fate, including disposition, in human subjects.

Cardiac glycosides, anti-arrhythmic agents, anti-convulsants, anti-depressants, certain hypotensive agents, beta-blocking agents, theophylline and many antimicrobials are only effective if used at the correct dose-level. Physicians, pharmacists and nurses need to know the use of these agents and their possible adverse effects from overdose. One aim of the *MacDope* program is to help you acquire this knowledge by modelling and printing out detailed information on the interaction of the subject with the drug. Pharmacokinetics is the branch of medical science which is concerned with the quantitative study of the absorption, distribution, metabolism and elimination of drugs, and *MacDope* is a simulation of human pharmacokinetics.

There are a number of objectives which you can expect to achieve by working with *MacDope*.

1. You will certainly learn how to write a prescription. (The program is quite pernickety and simply won't execute instructions which are not phrased in the required fashion!)
2. You will learn the properties of drugs responsible for different patterns of pharmacokinetic behaviour.
3. You will also learn which characteristics of patients are important determinants of the intensity of drug action.

1.2 Brief technical description

MacDope differs from most computer-based simulations of pharmacokinetics in that properties of drugs and properties of patients are kept quite separate. This is not the case in a simulation which could, for example, demonstrate changes of digoxin level as a function of time if programmed with the half-life of this drug. *MacDope* is not programmed with data such as volume of distribution and half-life of drugs. Instead, those physiological variables, the subject factors, which determine the disposition of drugs in the body, are generated in one part of the program and are allowed to interact with drug factors which describe the drug's behaviour in the patient. From these somewhat complex processes, volumes of distribution and half-lives emerge. You can do experiments to determine the apparent volume of distribution and it is also possible to see how this volume depends on factors such as lipid solubility or the pK_a of the drug. Many types of drug can be simulated.

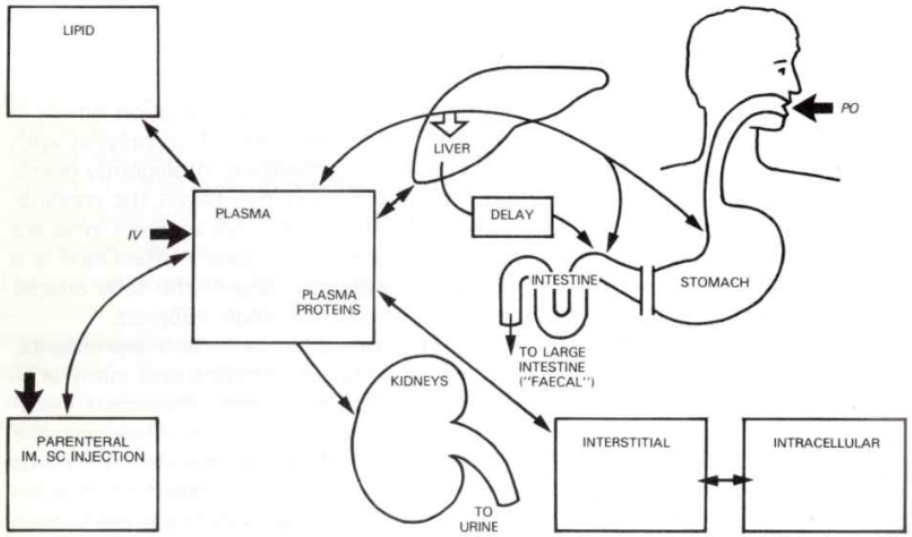


Figure 1. Structure of the model. The eight compartments and their interconnnections are illustrated. Drugs may be administered orally, by intravenous bolus or drip and intramuscularly.

Figure 1 shows the main compartments in the model; arrows indicate movement of drug between compartments. There are eight compartments. Three are required for entry of drug other than by the intravenous route; these are the gastric, intestinal and intramuscular volumes. Distribution involves four compartments: plasma, lipid, interstitial and intracellular fluid. The eighth compartment is the liver. Elimination may be by non-absorption of drug from the intestinal tract, by metabolism or by renal excretion. Hepatic metabolism and renal tubular transport processes may be modelled as linear or non-linear processes using Michaelis – Menten kinetics.

Binding of the drug to plasma protein is simulated and, as in metabolism and renal tubular elimination, this process is saturable. Additional features such as destruction of drug in the gastric compartment, metabolism of drug in the intestinal and plasma compartments, back diffusion of non-ionized drug from urine and induction of hepatic enzymes are dealt with as simple first-order processes. Of course, all drugs do not require that all these features be used in a realistic simulation, but they are provided in order to accommodate a wide range of drugs. Drugs taken orally as tablets take some time to be released; this effect is modelled as a combination of two first-order processes.

1.3 How is the model used and what can it do?

The use of the model does not require any computer expertise. If you can type (however slowly), you can converse with *MacDope*. Basically, the model can tell you how drugs are distributed in the body as a function of time following administration. The printout tells you the levels of drug in the blood, the amount

bound to tissue protein, the amount in the gastro-intestinal tract, the amounts distributed outside the plasma and the concentration excreted in the urine. The first type of information you can obtain comprises concentrations of drugs achieved following a prescription. Already this allows you to perform a range of experiments: you can, for example, administer a single dose of a drug by various routes and observe the effect of route of administration on blood and other levels achieved. You can then compare levels from single dose with those obtained with multiple dosing. The single-dose results may be used to predict multiple-dose levels and comparison between predicted and observed levels permits characterization of the overall drug kinetics as first order, saturable or subject to enzyme induction.

The second type of information you can get concerns the effect on plasma levels of changing either drug properties or subject properties. You can, for example, ask yourself whether it matters if a patient is fat or thin, or whether the elimination of drug is altered by changing the urine pH. You can determine whether altered renal function has an effect on blood levels or on the rate of drug elimination; you will find that renal tubular function and glomerular filtration rate can be changed independently. If you say to yourself: 'I am going to give a patient phenytoin for the treatment of epilepsy. Does it matter whether renal function is normal?', you can answer this question by administering the drug under different conditions of renal function and watching the sorts of response you get. If you exceed toxic or lethal concentration limits set for a drug, through bad or inaccurate prescribing, a message will be displayed.

Similar studies may be made by altering hepatic function. It is of interest then to study the effect of impaired liver function on the pattern of metabolism of the drug as determined by urinary excretion studies (see Section 4.2). A limited number of preset subjects, including a healthy male volunteer, is available, and you can create your own subjects by specifying age, sex, weight and height. Similarly, you can choose to work with a normal subject or with a patient with impaired functions by specifying abnormal values for some subject factors (see Appendix 4).

Information generated by the program may be presented graphically with the horizontal axis representing time (after dose), and the vertical axis the logarithm of the concentration of the drug. If so requested, the program gives a logarithmic plot of total drug concentration in the blood but this can be varied to plot free drug instead of total drug, i.e. excluding the protein-bound fraction. Graphs of urine levels of drug and metabolites may also be obtained. For quantitative studies, the display required is the numerical table of results with columns of figures, for drug and for metabolites. You can then observe simultaenously the total drug in the plasma, the percentage that is protein-bound, the amounts in the gastro-intestinal tract and in the distribution compartments outside the plasma, at specified intervals; urine concentrations are also given and these results are mean values over the preceding time interval (see Section 4.2).

The program is not limited to handling one drug at a time; up to four drugs can be administered simultaneously from a list of over 20 familiar drugs that have been programmed into *MacDope*. At most, however, your experiments

are likely to involve two drugs being prescribed simultaneously for a patient. The program allows you to write up to six simultaneous prescriptions. One great advantage in using *MacDope* in pharmacokinetics coursework is that you are able to design your own experiments and to modify the design if it proves to be unsatisfactory. The effect of patient dysfunctions on the results may also be studied. This type of experimental work would only be possible in real life for a few students. The computer simulation makes such experiments accessible, without causing any but simulated damage to the subjects involved.

1.4 Implementation

MacDope is written in Fortran 77 and makes use of high-level graphics programming approaches. It is best arranged such that the user works at a VDU to enter commands and interact with the program, but can also obtain a printed copy of the prescriptions entered, parameters of the model altered and simulations generated. If a local printer is available, this will be ideal. However, an optional facility of the program is the ability to generate a disc file with the output from the current user's session selectively written into it. This can be printed at the end of the session as a record of the work done, if necessary on a shared printer on a network, or one attached to another computer. The file is where possible given the name 'user.log' but this may vary between versions for different computers. The procedure for printing it is described in the text file 'read.me' included on the disc (see Section 2.1). On some microcomputer versions, a printed 'screen dump' can be obtained at any time.

2. Operating the program – an introduction

2.1 Getting started and writing your first prescription

The program may be run by booting the computer in the usual way, then placing the disc in drive A: and typing 'Macdope' and then ENTER from the DOS 'A>' prompt. Two title pages will be displayed, each of which will clear after a key is pressed.

A text file called 'read.me' included on the disc gives more information about the operation of the software and lists any updates to the manual. Please read this file (for example by typing 'type read.me' from the DOS prompt) before using *MacDope*.

The program opens with a title banner followed optionally by a short introduction for new users and instructions for choice of simulated subject as follows:

```
To proceed, type 1 then press <ENTER>.
For a brief introduction and instructions, type 2
Type your name, for reference later when signing prescriptions
```

If an instruction is not clear, type 'Q' (Query) and, where possible, a brief explanation will be given. To return to the main menu of options at any point, type '*'. Terminate all commands by pressing the ENTER key.

```
Do you want . . 1. Normal young adult male volunteer,
2. Preset subjects, 3. To specify your own patients or subjects.
```

In order to run the program you need to choose your subject. We would suggest that at first you should use the young adult male volunteer. Then try prescribing a stat oral dose of cimetidine, as in the example below.

Example 1. Cimetidine, to show the graphical display and continuation of a run. Responses entered in the dialogue (the questions are explained in detail in Section 2.4)

```
To proceed type 1, then press <ENTER>
For a brief introduction and instructions type 2
1
Type your name, for reference later when signing prescription
GILES
If an instruction is not clear, type Q (Query) and, where possible, a short explanation will
be given.
To return to the main menu of options at any point type *.
Terminate all commands by pressing the <ENTER> key.
Do you want . . 1. Normal young adult male volunteer,
2. Preset subjects, 3. To specify your own patients or subjects
1
- - -NEW SUBJECT- - -
Enter the prescriptions. End with signature GILES
(Queries? type Q; for druglist type QQ)
Prescription A - >
CIMETIDINE 300MG PO STAT
Prescription B - >
GILES
Do you want to 1. Change, 2. Continue, 3. Restart, 4. Inspect, 5. Stop
1
1. Prescn, 2. Type of run, 3. Store/Bktr, 4. Patient Factors, 5. Drug Factors
2
Type length of run in hours (currently = 24.0)
2
Do you want 1. Graphs of total plasma drug concn., 2. Free drug concn., 3. Urine concn.,
4. Numerical display of all
1
Do you want to plot output every . . 1) 15, 2) 30, 3) 60, 4) 120 mins, 0) Every iteration,
5) At time interval specified (hr)
1
Type 1 for display output only, 2 To store copy for printing
2
Choose display scale from 1) 2hr, 2) 4hr, 3) 8hr, 4) 12hr, 5) 24hr, 6) 48hr, 7) 96hr, 8)144hr,
9) 288hr
1
Do you want to 1. Change, 2. Continue, 3. Restart, 4. Inspect, 5. Stop
2
```

At the end of the run, choose to continue

```
Do you want to 1. Change, 2. Continue, 3. Restart, 4. Inspect, 5. Stop
2
```

At the end of the continued run,

```
Do you want to 1. Change, 2. Continue, 3. Restart, 4. Inspect, 5. Stop
5
Please type your name to be used in labelling output
GILES
```

The program may then be terminated and the stored results printed using the appropriate command to the operating system (see Section 1.4). Figure 2 shows the results as a semilog graph of plasma concentration in mg/l against time in hours. Figure 3 shows the continuation of the run for a further 2-hr period.

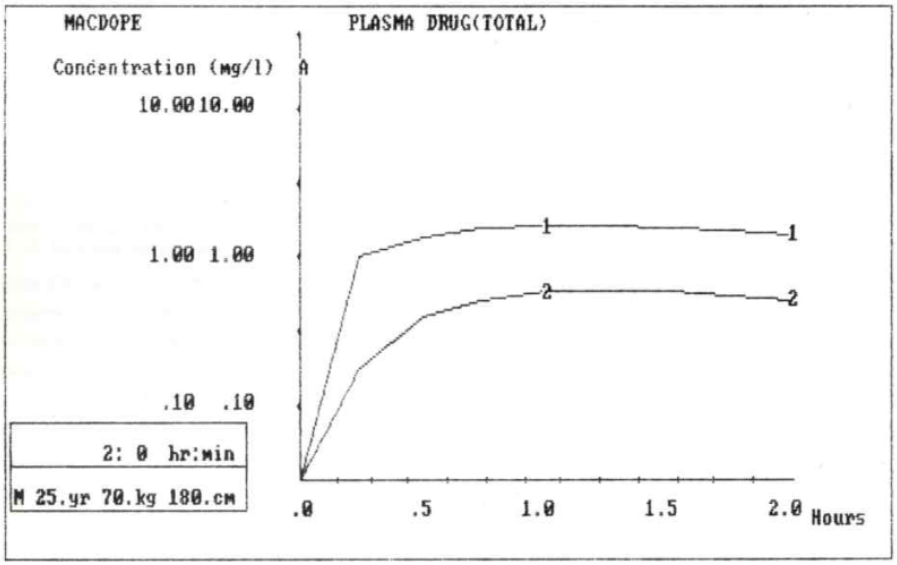


Figure 2.

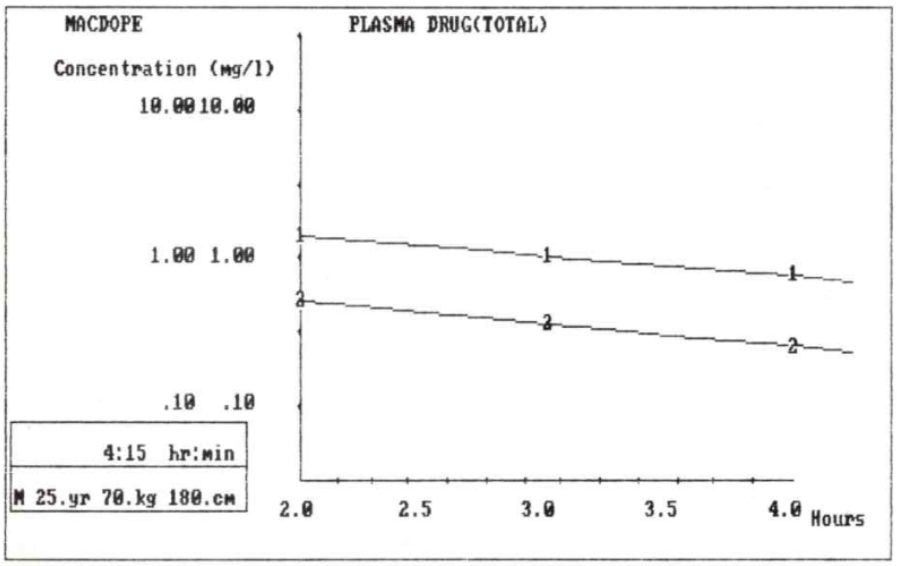


Figure 3.

All prompts requesting a response appear in the same region, towards the bottom of the screen. If an erroneous entry is detected, a corrective message will appear and you will be asked to enter a revised response. 'Help messages' appear, on request, in a single region of the screen, below the graphical display area. Should a graphical display have to be erased (e.g. to clear space for information requested on drug factor values) and the simulation then be continued, the display will be regenerated automatically. Should the simulation run be extended beyond the specified time range, the time axis will automatically be translated forward.

In these plots, the vertical axis units are given separately for the drug (symbol 1) and for the metabolite (symbol 2). Each scale is placed above the start of the name of the substance involved, shown underneath the plot.

The upper box on the left-hand side of the plot gives the time after dose, which changes during the run as each point on the graph is calculated. The lower box gives the four defining characteristics of the subject: sex, age, body mass and height.

The time at which the dose is administered is indicated by the letter A (for prescription A) at the top of the vertical axis indicating that the dose is given at zero time.

The prescription is displayed to the right, below the plot. Full details of prescribing procedures in the program are given in the next section.

2.2 Prescription writing — the full story

This section appears complicated because prescription writing is complex. Many jargon terms derive from archaic practices and, to be realistic, the simulation accepts these. There is also the sort of subtle distinction that exists between taking a drug 'three times a day (TID)' and 'every eight hours (Q8H)'. Often, too, you would want to start at one dose level to obtain an initial effect or to prime the patient and then cut back to a lower maintenance level. This is described under 'Serial treatment' in this Section.

Basically, a prescription consists of drug name, amount, route and frequency of administration. In addition, you can (but don't have to) limit the number of doses.

Here is an example:

```
INDOMETHACIN    25      MG      PO      Q8H     X3
                :       :       :       :       :
                :       :       :       :       (vi) Limit on doses
                :       :       :       :
                :       :       :       (v) Timing, every eight hours
                :       :       :
                :       :       (iv) Route (PO, IM, IV, IVDRIP etc.)
                :       :
                :       (iii) Units - g, mg, mmg (micrograms), mg per hour,
                :             etc. for IVDRIP
                :
                (ii) Quantity in each dose
                :
(i) Drug name — spelt correctly!
```

The following paragraphs explain in detail how to handle features (i) – (vi)

and the terms which are acceptable. The program will insist on (i) to (v) being specified; (vi) is optional.

In the example, a dose of 25 mg of indomethacin is given every 8 hours, with a total of 3 doses.

Example 2. Indomethacin, to show a multiple dose run with a limited number of doses.
Normal subject

```
Do you want . . 1. Normal young adult male volunteer, 2. Preset subjects,
3. To specify your own patients or subjects
1
- - -NEW SUBJECT- - -
Enter the prescriptions. End with signature GILES
  (Queries? type Q; for druglist type QQ)
Prescription A - >
INDOMETHACIN 25MG PO Q 8H x3
Prescription B - >
GILES
Do you want to 1. Change, 2. Continue, 3. Restart, 4. Inspect, 5. Stop
1
1. Prescn, 2. Type of run, 3. Store/Bktr, 4. Patient Factors, 5. Drug Factors
2
Type length of run in hours (currently = 12.0)
48
Do you want 1. Graphs of total plasma drug concn., 2. Free drug concn., 3. Urine concn.,
4. Numerical display of all
1
Do you want to plot output every . . 1) 15, 2) 30, 3) 60, 4) 120 mins, 0) Every iteration,
5) At time interval specified (hr)
4
Type 1 for display output only, 2 To store copy for printing
1
Choose display scale from 1) 2hr, 2) 4hr, 3) 8hr, 4) 12hr, 5) 24hr, 6) 48hr, 7) 96hr, 8) 144hr,
9) 288hr
6
Do you want to 1. Change, 2. Continue, 3. Restart, 4. Inspect, 5. Stop
2
```

The letters A at the top of the plot (Figure 4) show the times at which the three doses of prescription A are given. The peaks in plasma concentration increase successively towards a steady state value. After the third and last dose, the semilog plot becomes effectively linear.

(i) Drug name

Entry of QQ in response to the prompt for prescriptions causes the screen to be cleared and a paginated list to be displayed of the names of the drugs available and their metabolites. The drug names must be spelt out exacly as in this list, but the metabolites do not need to be prescribed; the relevant ones are automatically supplied by the program. The drug names are conventional except for benzyl penicillin, which is BENZPENICILLIN, and for fentanyl citrate

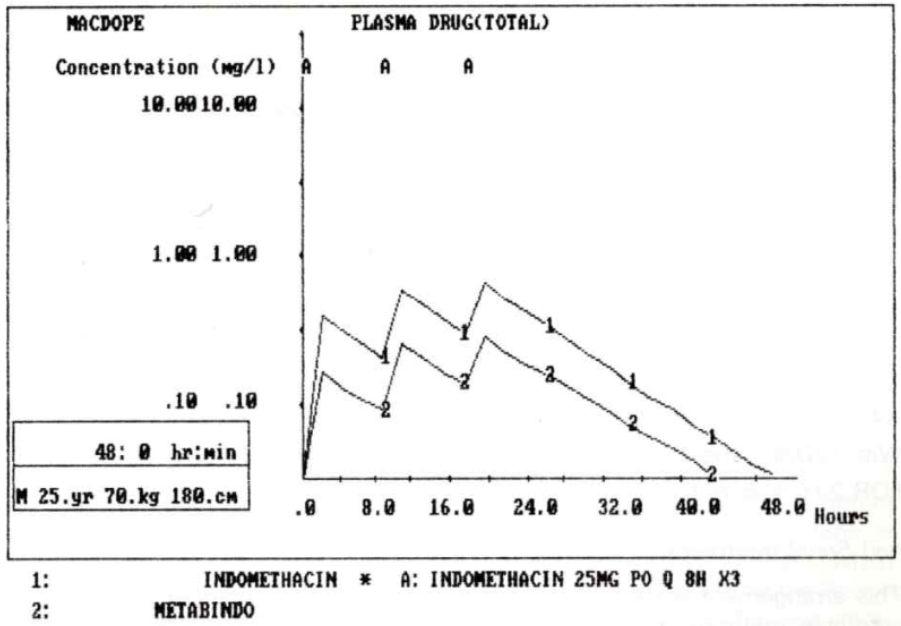


Figure 4.

which is FENTANYLCIT. The current drug list is shown in Appendix 3. Appendix 6 contains instructions on the requirements and procedures for entering a new drug into the drug data file.

(ii) Amount of dose

Any number, whole number or decimal, is accepted. A warning is given if the dose exceeds a maximum recommended for your subject.

(iii) Units

Units may be grammes (G), milligrammes (MG) or microgrammes (MMG).

(iv) Route of administration

PO	=	per os (by mouth).
IM	=	intramuscular: this route may in some cases cause computational difficulties which may be minimised by using the research mode (see Section 4.1) for all IM prescriptions, with the precision factor set to 1.0.
IV	=	intravenous.
IVDRIP	=	continuous intravenous drip.

(v) Timing

STAT = statim, immediately.
Q6H = every 6 hours.
QID = four times daily (0800, 1200, 1600, 2000).
TID = three times daily (0800, 1400, 2000).
BID = twice daily (0800, 2000).

Note that for QID, TID and BID, zero time is taken to be 8 a.m.

For IVDRIP, PER MIN or PER H defines the rate at which the amount under (ii) is given.

(vi) Limit on dosing — Use of 'X'

A fixed number of doses can be specified. Thus:

X4 = limit to four successive doses.

With IVDRIP, the drip can be cut off after a specified period. Thus:

FOR 2 H = limit the drip to 2 hours duration.

(vii) Serial treatment — Use of 'THEN'

This arrangement is particularly useful for drugs like phenytoin which show saturable metabolism. The first prescription gives relatively high doses to establish an effective plasma level; the second prescription, starting with THEN, gives lower maintenance doses which avoid the progressive rise in plasma levels caused by the saturation.

Example 3. Phenytoin, serial prescription for a drug using 'THEN'. Dialogue for the simulation run.

```
Do you want . . 1. Normal young adult male volunteer, 2. preset subjects,
3. To specify your own patients or subjects
1
- - -NEW SUBJECT- - -
Enter the prescriptions. End with signature GILES
  (Queries? type Q; for druglist type QQ)
Prescription A - >
PHENYTOIN 120MG PO Q8H x3
Prescription B - >
THEN PHENYTOIN 60MG PO Q8H
Prescription C - >
GILES
Do you want to 1. Change, 2. Continue, 3. Restart, 4. Inspect, 5. Stop
1
1. Prescn, 2. Type of run, 3. Store/Bktr, 4. Patient Factors, 5. Drug Factors
2
Type length of run in hours (currently = 24.0)
96
Do you want 1. Graphs of total plasma drug concn., 2. Free drug concn., 3. Urine concn.,
4. Numerical display of all
1
```



```
Do you want to plot output every . . 1) 15, 2) 30, 3) 60, 4) 120 mins, 0) Every iteration,
5) At time interval specified (hr)
4
Type 1 for display output only, 2 To store copy for printing
1
Choose display scale from 1) 2hr, 2) 4hr, 3) 8hr, 4) 12hr, 5) 24hr, 6) 48hr, 7) 96hr, 8) 144hr,
9) 288hr
7
Do you want to 1. Change, 2. Continue, 3. Restart, 4. Inspect, 5. Stop
2
```

The three letters A at the top of the plot (Figure 5) indicate the timings of the doses in prescriptions A; the letters B similarly indicate timings for prescription B.

The first three doses produce the required plasma concentration of phenytoin; the subsequent smaller doses maintain this concentration, avoiding drug accumulation caused by the limited capacity metabolism of phenytoin.

Cancelling prescriptions

After the program has accepted your prescription, you can cancel it (before signing your name) by typing 'CANCEL'. Prescriptions for which no time or dose limit is specified will continue to be given indefinitely. However, when the run is complete you can enter '1' (for Change) followed by '1' for the Prescn option, which cancels all previous prescriptions and then calls for new ones.

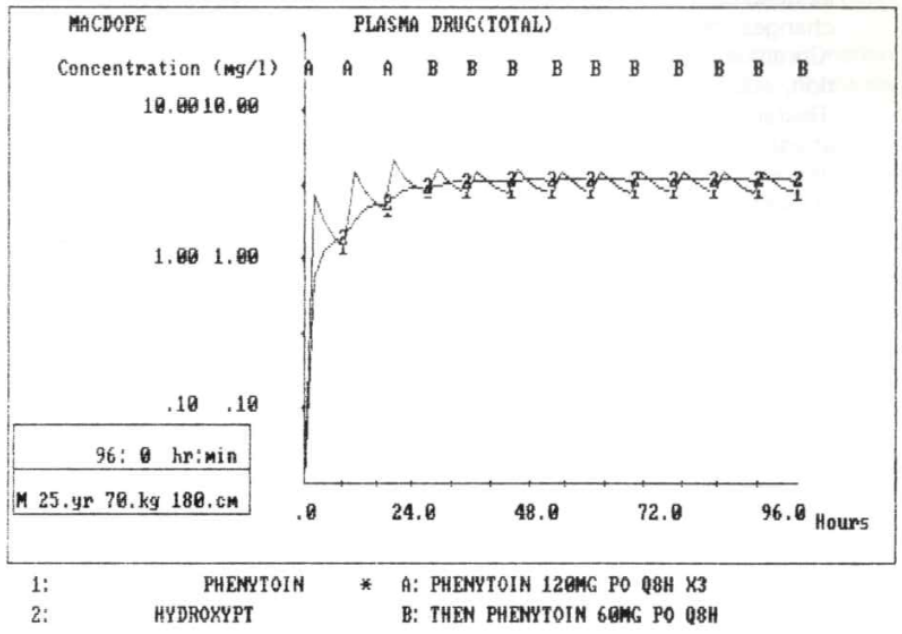


Figure 5.

Substances already present due to previous prescriptions, will, of course, continue to be present unless the simulation is restarted afresh.

Errors

A prescription which is acceptable will be followed by the prompt for the next prescription. The program may tell you that a prescription is incomplete or cannot be executed. If it is incomplete, merely re-enter the complete prescription. Errors are usually due to wrong spelling of drug names (type 'QQ' to see the correct spelling of all drugs available), the use of impermissible symbols or abbreviations, punctuation errors or forgetting to enter the route. You must terminate the set of prescriptions with your name or initials as originally given when you started the program.

2.3 The main menu of options

After the last prescription has been entered and at the end of any run, the program returns to offer the main choice of options as follows:

```
Do you want to 1. Change, 2. Continue, 3. Restart, 4. Inspect, 5. Stop
```

'Change' gives you access to many possibilities for altering prescriptions (you can use this option before a run if you see you have made an error), subjects, drugs and other details of the simulation and output required, as described in the following sections. After you have made the desired changes, the program returns to the main options menu.

'Continue' starts the computation with the current values for prescription, subject, type of run and drug and subject parameters.

'Restart' removes both prescriptions and subjects and allows you to start afresh.

'Inspect' gives a summary of drug distribution in the body, as described in Section 2.5.

'Stop' terminates the work with *MacDope*. You are asked for a label to identify the file of output from simulations which you have prepared and the program ends. These results may then be listed on a printer, as required.

2.4 How to set up a simulation run

The run may be set up by selecting '1. Change' from the main options menu. Following entry and the signing of the last prescription, an answer of 'Q' to the next question gives a description of the replies available; '2' gives a change of run. The subsequent questions call for a definition of the new run.

```
Do you want to 1. Change, 2. Continue, 3. Restart, 4. Inspect, 5. Stop
1
1. Prescn., 2. Type of run, 3. Store/Bktr, 4. Patient Factors, 5. Drug factors
```

On pressing 'Q' in answer to the second question, the following description

of the alternative options, including 6 and 7 which are not otherwise displayed, is obtained.

1. allows you to give or add prescriptions of the same or other drugs,
2. allows changes in length of run and type of display,
3. allows the present state to be stored, and recreated later,
4. and 5. allow inspection and changes in Patient and Drug Factors,
6. lists Subject Parameters,
7. lists Drug Factors.

Choice of option 2 enables a change of simulation run to be made. The following questions then appear.

```
Type length of run in hours (currently = 12.0)
Do you want 1. Graphs of total plasma drug concn., 2. Free drug concn., 3. Urine concn.,
4. Numerical display of all
Do you want to plot output every . . 1) 15, 2) 30, 3) 60, 4) 120 mins, 0) Every iteration,
5) At time interval specified (hr)
Type 1 for display output only, 2 To store copy for printing
```

These questions allow the user to define the length of the run in hours (maximum 120 — pressing ENTER alone leaves the current value unchanged), the type of output required and the interval between output results. The user is then asked about storing copy for printing. A request for stored copy causes succeeding results, but not the dialogue, to be written to a disc file, named as described in Section 1.4, which may then be printed out on leaving the program. The printed file will contain all the output for which a copy has been requested.

The 'Help message' obtained by entering 'Q' in response to the question concerning type of graphical or numeric display gives details of the otherwise unadvertised PDZ option (see Section 4.7).

The types of display available are:

1. Graphical display of total concentrations.
2. Graphical display of free plasma concentrations (i.e. unbound by protein).
3. Graphical display of urine concentrations (the urine concentrations are mean values over the preceding time interval).
4. Numerical display of all the results (described in Section 3.1).
5. Numerical display, including the PDZ option.

The graphical displays show concentrations on a logarithmic scale. The results are plotted with marker '1' for unchanged drug, '2' etc. for metabolites. The time scale may be set interactively, as described below. If no setting is given, the scale is set, by default, using a stored drug parameter. The vertical scale is governed by drug parameter 18 (dp18). To move the scale up one decade, this factor is changed from the current value to ten times that value.

You are next asked to specify the intervals at which results are to be displayed. These are coded as:

0 (zero) gives results at each computational iteration. This option will only be required under special circumstances such as rapid anaesthesia with thio-

pentone with the research mode (see Section 4.1).

1,2,3 or 4 for 15 min, 30 min, 1 hr or 2 hr.

5 permits the choice of any, usually longer, time interval. For example, with a slow-moving drug such as phenobarbitone (Example 4) or with a long run with repeated dosing, or particularly with urinary excretion studies (Section 4.2), intervals of 4, 8 or 12 hours may be appropriate. For this option you are asked to specify the interval in hours.

Finally you are asked to specify the time scale for the plot in hours coded as:

1 for 2hr 2, 5hr 3, 8hr 4, 12hr 5, 24hr 6, 48hr 7, 96hr 8, 144hr 9, 288hr

If no run details are entered, a default mode of display, length of simulation and frequency of output are selected, which are appropriate for the drug being used (based on certain drug factors, see Appendix 5).

2.5 The Inspect option

This feature of *MacDope* is used at the end of a graphical presentation to display numerical details of the concentrations. It is invoked as option 4 in the main menu of options. In Example 4, the values at the end of the preceding run are displayed. This particular table was requested at the end of the run in which phenobarbitone was given orally. Note that results are printed for drugs 1 and 2. Drug 1 is the parent drug and 2 is its metabolite.

Abbreviations used in the Inspect table are as follows:

INTERSTITIAL; INTRACELLular fluid; URINE CONCentration, all in mg/litre. (Multiply by urine flow rate, a subject factor — Appendix 4 — to obtain urinary excretion rate.)

2.6 How to avoid repetitive dialogue

When you are very familiar with the interactive dialogue, it may become tedious to wait for the computer to type the next prompting message. Therefore, if you know what is coming, you can enter several responses in one line, separated by slashes ('/'), and when all the responses are entered, press the ENTER key. The succeeding questions will be suppressed and the instructions will be executed in sequence by the computer without interruption. Note, however, that you can't use slashes to terminate prescriptions, nor in places where options are not predetermined. This method is used in the next and all subsequent examples. It is best to start each set of slashes with a selection from the main menu of options and to give the request for stored results separately.

Example 4. Phenobarbitone, to show extended intervals for results with a slow drug and the Inspect option, and also the use of the slash separator in the dialogue.

Instructions after entry of the prescription which is shown below the graph (Figure 6) are:

```
Do you want to 1. Change, 2. Continue, 3. Restart, 4. Inspect, 5.Stop
1/2/96/1/5/8
```

1/2/96/1/5/8 gives a 96-hour run with total plasma concentration graphs and results at 8-hourly intervals.

```
Type 1 for display output only, 2 To store copy for printing
1
Choose display scale from 1) 2hr, 2) 4hr, 3) 8hr, 4) 12hr, 5) 24hr, 6) 48hr, 7) 96hr, 8) 144hr,
9) 288hr
7
Do you want to 1. Change, 2. Continue, 3. Restart, 4. Inspect, 5. Stop
2
```

At the end of the run

```
Do you want to 1. Change, 2. Continue, 3. Restart, 4. Inspect, 5. Stop
4
```

After inspection,

```
Do you want to 1. Change, 2. Continue, 3. Restart, 4. Inspect, 5. Stop
5
```

The graphical results are shown in figure 6 and the 'Inspect' option values are given in figure 7. The Inspect option gives the results at the end of the final iteration, which is a time somewhat later than the 96 hours.

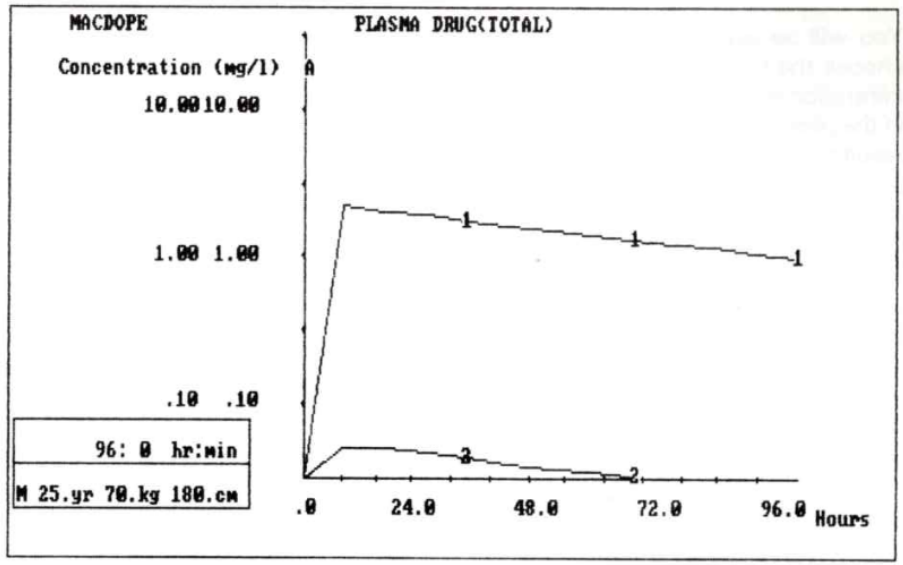


Figure 6.

Results at 96:37 (all drug concns. in mg/l)

DRUG NO.	TOTAL PLASMA	PROTEIN BOUND(:)	STOMACH	INTES-TINE	INTER-STITIAL	INTRA-CELL.	URINE CONC.
1	1.0128	39.0	.1167	.2490	.6263	.6384	2.2180
2	.0246	31.3	.0015	.0024	.0176	.0036	1.9570

Undissolved drug (mg) in -STOMACH	-INTESTINE	drug entering LARGE INTESTINE (mg/hr)
.000	.000	.062
.000	.000	.001

Figure 7.

3. Operating the program — further details

3.1 Setting up a run with numerical output of results

Select the Change option in the main menu of options and select option 2 to change the type of run.

```
Do you want to 1. Change, 2. Continue, 3. Restart, 4. Inspect, 5. Stop
1
1. Prescn, 2. Type of run, 3. Store/Bktr, 4. Patient factors, 5. Drug factors
2
```

You will be asked first to specify the length for the run (hours) and then to choose the type of display. Here the options are (1) graphs of total drug concentration in plasma on a logarithmic scale, (2) graphs of free concentrations in the plasma, (3) graphs of urinary concentrations and (4) the table of numerical results.

```
Type length of run in hours (currently = 2.0)
Do you want 1. Graphs of total plasma drug concn., 2. Free drug concn., 3. Urine concn.,
4. Numerical display of all
```

The 'help message' for this question gives information about selecting the otherwise unadvertised PDZ option; details are given in Section 4.7. This option (5) requires two further drug parameters to be set.

Finally you are invited to select output at 15-, 30-, 60- or 120-minute intervals, at every computational iteration (see Section 2.5) or at intervals specified by the user. This last option is useful for slowly changing drugs and for studies of urinary excretion. The intervals between results should not be made shorter than is necessary, otherwise an extensive output may result.

In the table of results, column 1 displays the time after the first dose, column 2 gives total plasma concentration in mg/litre, the standard concentration unit in *MacDope*, column 3 gives the percentage of the drug in the plasma which is bound to protein and column 4 give the amount in the gastro-intestinal tract in mg. The fifth column gives the amount in mg distributed outside the plasma, i.e. the sum of amounts in the interstitial and in the intracellular fluids

and in the lipid, and the sixth column gives urinary concentration in mg/litre as a mean value over the preceding time interval, corresponding to the experimental technique of pooling urine samples for analysis. This arrangement permits use of extended time intervals in urinary recovery studies, without loss of accuracy. The final column is for the PDZ option; if this is not chosen, it contains zeros.

Example 5. Paracetamol, to show the table of results.

The standard subject is selected and a prescription of paracetamol 500 mg PO STAT is given. The subsequent dialogue is as follows:

```
Do you want to 1. Change, 2. Continue, 3. Restart, 4. Inspect, 5. Stop
1/2/8/4/3
```

(2 for run, 8 for 8-hr run, 4 for table of results, 3 for results every hour)

```
Type 1 for display output only, 2 To store copy for printing
2
```

PARACETAMOL *

CONJUGATE		PL.CONC.	BD.	GI AMNT.	EX.VASC.AMNT	URINE	PDZ
A	0: 0	.0000	.0	.00	.000	.000	.000
A	0: 0	.0000	.0	.00	.000	.000	.000
	1: 0	4.4564	24.5	1.13	193.571	83.513	.000
	1: 0	2.7575	.0	.00	64.512	2878.884	.000
	2: 0	2.9894	25.8	.64	135.159	25.661	.000
	2: 0	1.2097	.0	.00	38.335	1459.243	.000
	3: 0	2.0867	26.6	.44	93.891	17.586	.000
	3: 0	.6992	.0	.00	22.050	947.985	.000
	4: 0	1.4488	27.2	.30	64.940	12.127	.000
	4: 0	.4258	.0	.00	12.826	624.855	.000
	5: 0	.9899	27.6	.20	44.246	8.296	.000
	5: 0	.2655	.0	.00	7.522	411.223	.000
	6: 0	.6819	27.9	.14	30.422	5.659	.000
	6: 0	.1723	.0	.00	4.614	272.367	.000
	7: 0	.4764	28.1	.10	21.225	3.910	.000
	7: 0	.1158	.0	.00	2.963	184.373	.000
	8: 0	.3227	28.3	.07	14.362	2.685	.000
	8: 0	.0762	.0	.00	1.879	124.819	.000

The table gives results in pairs of rows, the upper row being the drug and the lower row the metabolite. The letters A to the left of the table indicate the times at which the dose is given; the first main column shows time after dose in hours and minutes, the second column gives plasma concentrations in mg/litre. The results indicate that paracetamol is rapidly absorbed and the plasma levels of both drug and metabolite decline from the first hour. Column 3 gives the percentage of paracetamol in the plasma which is bound to plasma proteins, as 24.5 increasing to 28.3 as the concentration decreases. The column 4 figures (in mg) confirm the rapid absorption, with very little paracetamol left in the gastro-intestinal tract after 1 hour. The fifth column (in mg) shows quite extensive extravascular distribution of the drug and the sixth column shows mean urine concentrations over the preceding time interval. These mean con-

centrations in mg/litre multiplied by the urine flow rate in litre/hr and by the length of the interval in hr, give the amounts of drug and metabolite excreted in the interval, in mg. For example, the 4th urine concentration of metabolite is ~625 mg/litre, the urine flow rate is 0.066 litre/hr and the time interval is 1hr; therefore the amount of metabolite excreted between 3 and 4 hours is $625 \times 0.066 \times 1 = 41.3$ mg.

3.2 The Store/Backtrack option

You may wish to do a number of different things with a subject set up in exactly the right state at the end of a series of manoeuvres (such as loading with a cumulative drug, or altering renal or hepatic function), or you may wish to return to your starting point in order to study changes of drug or subject parameters. It is then tedious to recreate these same conditions each time and much easier to be able to backtrack to where you were before. This option is also useful when you are about to do something which may prove to be lethal!

At any stage you can select the main option Change and then store the current state of the model or backtrack to the last stored state. The model state is stored at the outset automatically.

```
Do you want to 1. Change, 2. Continue, 3. Restart, 4. Inspect, 5. Stop
1
1. Prescn, 2. Type of run, 3. Store/Bktr, 4. Patient factors, 5. Drug factors
3
Do you want to 1. Store present state, 2. Backtrack to last stored state, 3. Store drug on disc file
1
Stored at this point ***********
```

The third option in the last question is used for the permanent alteration of drug parameters and for setting up new drugs (see Appendix 6).

In Example 6, the operator wishes to compare intravenous and intramuscular dosage with kanamycin. The intravenous run is set up and before running the simulation, the present state of the system is stored. At the end of the run, a backtrack is made to the stored state and the prescription is then changed to give the IM dose. In this way the same new subject and type of run are preserved and the starting time goes back to zero.

Example 6. Kanamycin, showing the use of Store/Backtrack to compare routes of administration.
Normal subject
Prescription: KANAMYCIN 250 MG IV STAT

```
Do you want to 1. Change, 2. Continue, 3. Restart, 4. Inspect, 5. Stop
1/2/8/1/2
```

(sets up an 8-hr run with a graph of plasma concentration at half-hourly intervals)

```
Type 1 for display output only, 2 To store copy for message
1
Choose display scale from 1) 2hr, 2) 4hr, 3) 8hr, 4) 12hr, 5) 24hr, 6) 48hr, 7) 96hr, 8) 144hr,
9) 288hr
3
```



```
Do you want to 1. Change, 2. Continue, 3. Restart, 4. Inspect, 5. Stop
1/3/1
Stored at this point ***********
Do you want to 1. Change, 2. Continue, 3. Restart, 4. Inspect, 5. Stop
2
```

At the end of the run

```
Do you want to 1. Change, 2. Continue, 3. Restart, 4. Inspect, 5. Stop
1/3/2
*********** Backtrack to last store
Do you want to 1. Change, 2. Continue, 3. Restart, 4. Inspect, 5. Stop
1/1
*** Current prescription(s) cancelled
Enter the prescriptions. End with signature GILES
  (Queries? type Q; for druglist type QQ)
Prescription A - >
KANAMYCIN 250 MG IM STAT
Prescription B - >
GILES
Do you want to 1. Change, 2. Continue, 3. Restart, 4. Inspect, 5. Stop
2
```

The IV bolus dose gives initially high concentrations, declining quite rapidly to give a linear plot after about 1 hr. Kanamycin is not significantly metabolised and so there is no second graph for a metabolite.

The IM dose gives a graph showing a maximum with more sustained high plasma levels. After 4 hours the plot is again linear.

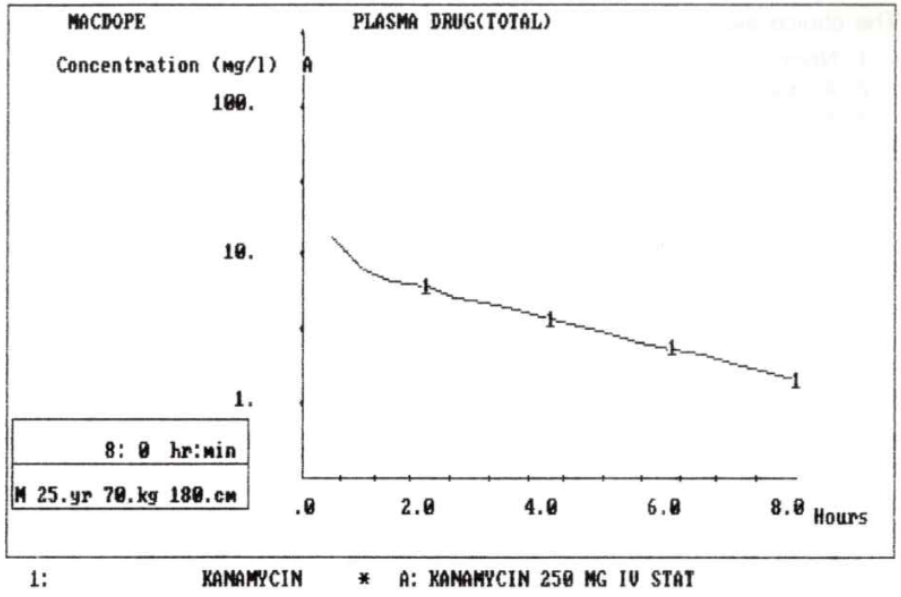


Figure 8.

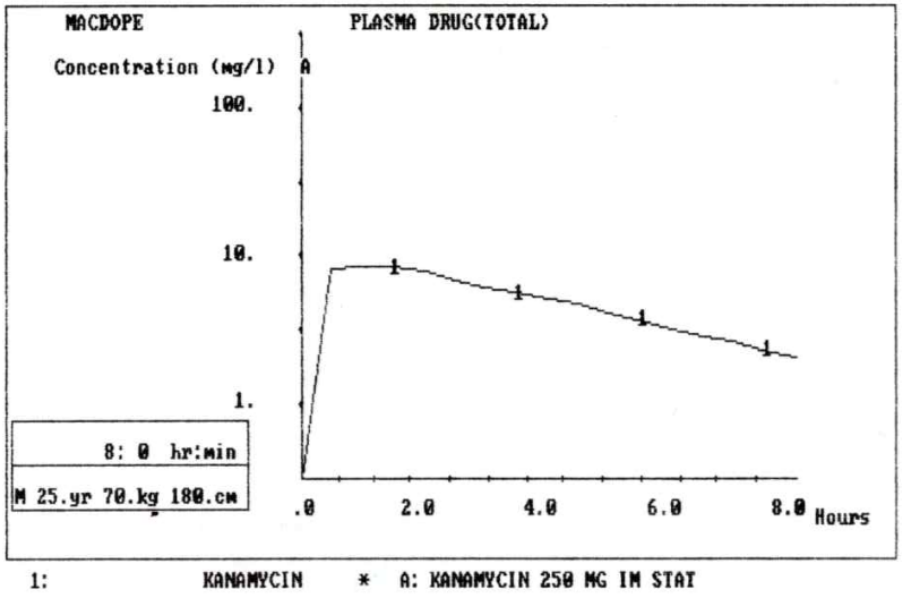


Figure 9.

3.3 Choosing your simulated subject.

The choice available for the simulated subject is:

1. Normal 70kg adult male.
2. A selection of 6 preset subjects.
3. A subject specified by sex, height, weight and age.

A complete printout of the subject factors is obtained by choosing '1' for Change from the main menu followed by '6' for Subject Factors. The 23 factors are given in a table running consecutively in rows from left to right. The meaning of each of these factors is given in Appendix 4.

The dialogue for choosing a preset subject is:

```
Do you want . . 1. Normal young adult male volunteer, 2. Preset subjects,
3. To specify your own patients or subjects
2
Select one of the following subjects by number
1. One month old infant,      2. Little girl (3 years)
3. Young female (25 yrs),     4. Athletic male (25 yrs)
5. Octagenarian with severe wasting
6. Fifty year old female in renal failure
```

The questions asked in setting up a new subject are:

```
Do you want . . . 1. Normal young adult male volunteer, 2. Preset subjects,
3. To specify your own patients or subjects
3
Please specify . . . 1. Male, 2. Female
```



```
Give me the height in cm (183 cm = 6 ft)
Now weight in kg
and age in years
```

Example 7. Theophylline, to show the effects of a change in subject from adult to child without changing the prescription.
Standard subject
Prescription: THEOPHYLLINE 180 MG PO Q6H

```
Do you want to 1. Change, 2. Continue, 3. Restart, 4. Inspect, 5. Stop
1/2/24/1/4/1
```

(for 24-hour plasma concentration graph with results every 2 hr)

```
Type 1 for display scale from 1) 2hr, 2) 4hr, 3) 8hr, 4) 12hr, 5) 24hr, 6) 48hr, 7) 96hr, 8) 144hr,
9) 288hr
5
Do you want to 1. Change, 2. Continue, 3. Restart, 4. Inspect, 5. Stop
2
```

At the end of the run,

```
Do you want to 1. Change, 2. Continue, 3. Restart, 4. Inspect, 5. Stop
3
Do you want . . . 1. Normal young adult male volunteer, 2. preset subjects, 3. To specify
your own patients or subjects
2
Select one of the following subjects by number
1. One month old infant,      2. Little girl (3 yrs)
3. Young female (25 yrs),     4. Athletic male (25 yrs)
5. Octagenarian with severe wasting
6. Fifty year old female in renal failure
2

- - -NEW SUBJECT- - -
Enter the prescriptions. End with signature GILES
  (Queries? type Q; for druglist type QQ)
Prescription A - >
THEOPHYLLINE 180 MG PO Q6H
Prescription B - >
GILES
Do you want to 1. Change, 2. Continue, 3. Restart, 4. Inspect, 5. Stop
1/2/24/1/4
Type 1 for display output only, 2 To store copy for printing
1
Choose display scale from 1) 2hr, 2) 4hr, 3) 8hr, 4) 12hr, 5) 24hr, 6) 48hr, 7) 96hr, 8) 144hr,
9) 288hr
5
Do you want to 1. Change, 2. Continue, 3. Restart, 4. Inspect, 5. Stop
2
```

The second plot (Figure 11) shows considerably higher plasma concentrations of theophylline than does Figure 10; in fact they are beyond the range of the concentration scale. Drug factor number 18 sets a suitable range for therapeutic plasma levels. When the concentrations are above the range, the scale on the vertical axis may be shifted up by a decade by changing factor 18 to ten times its previous value. In order to maintain the relative positions of the two curves, this change is also made for the metabolite.

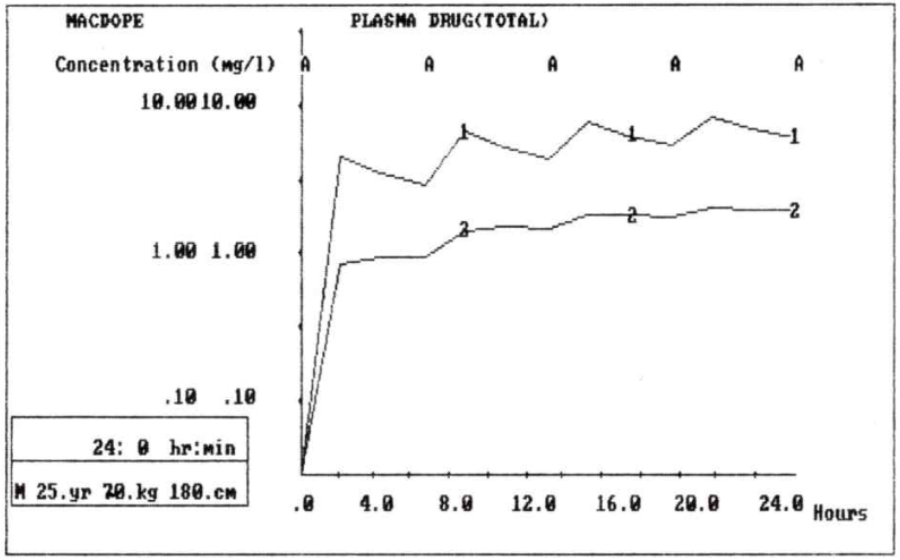


Figure 10.

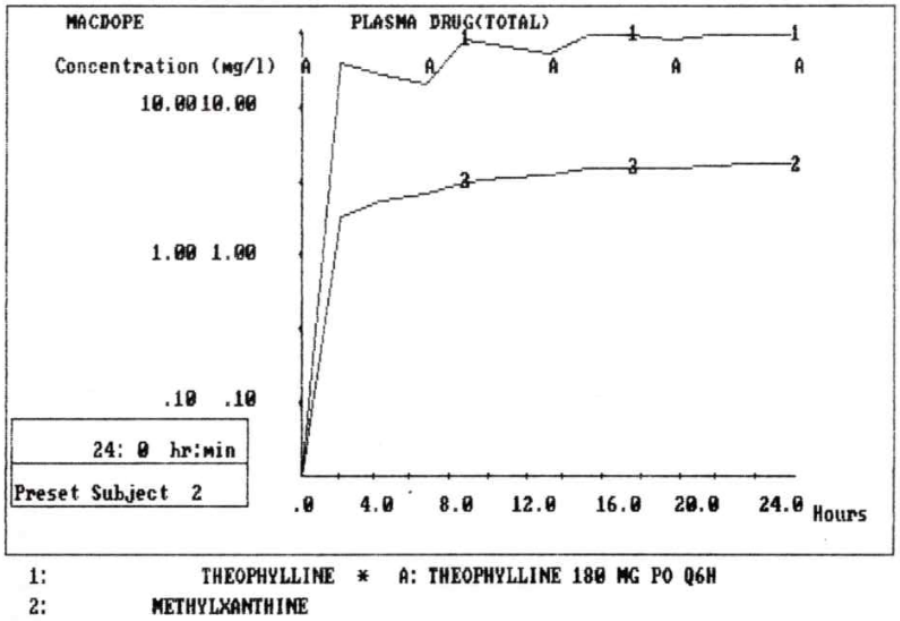


Figure 11.

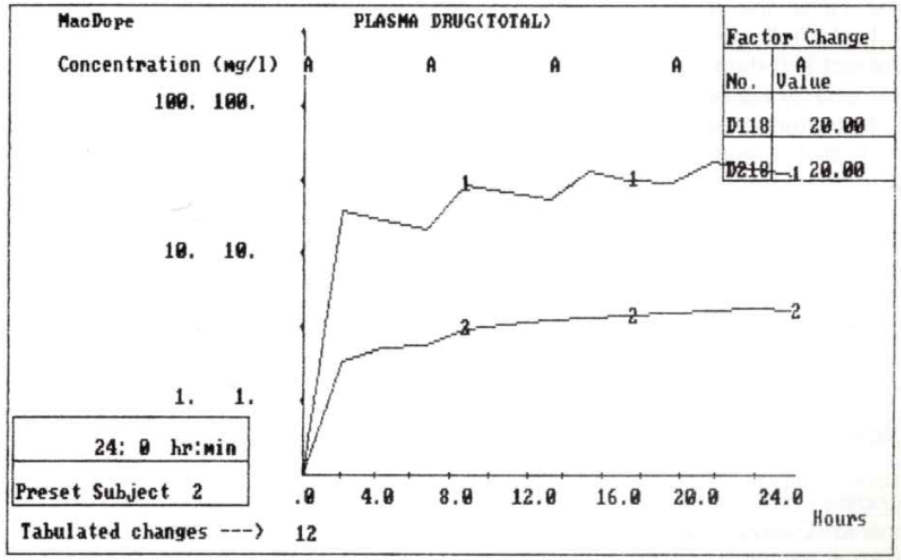


Figure 12.

Changes to drug factors are discussed in section 3.6. The instructions required — in abbreviated form — are '1/5/1/18'; '1' for change, '5' for drug factor, '1' for drug number (theophylline), '18' for factor 18.

The present stored value of this factor is given as 2 mg/litre and so a new value of 20 is entered. The same change is made for the metabolite (drug number 2 on the list below the graph scales): '1/5/2/18'. The stored value is again 2 and is changed to 20.

The run with subject 2 is then made with the result shown in Figure 12. The shift of a decade in the vertical scale means that the highest values of plasma concentrations are well below the top of the scale.

The drug factor changes are shown in boxes at the top right hand corner of the display. D118 means drug 1 parameter 18; the new value is then shown. The times at which changes are made is shown below the graph along the line labelled 'Tabulated changes --->'.

3.4 Changing subject factors

On selecting the Change option from the main menu, followed by '4. Change Subject Factors', a short list of subject factors is displayed and you are asked which factor you wish to change. After responding with a valid factor number (throughout the program, invalid entries detected are signalled below the prompt/response region, asking for a correction), the current value of the factor is given and you enter the new value. Any of the factors in addition to

the 12 on the short list may be modified (for full list see Appendix 4).

In the following example, the user has prescribed valproate with a normal subject and then with a subject with an abnormally high urine pH. The change is made by altering the subject factor 10, from its normal value of 5.5 to 7.5.

Note that when the main option 'Restart' is used, a new subject is selected with all the normal subject factors; in order to preserve altered factors the Store/Backtrack facility is used (Section 3.2).

Example 8. Valproate, showing change of a subject factor.
Standard subject
Prescription: VALPROATE 200 MG PO STAT

```
Do you want to 1. Change, 2. Continue, 3. Restart, 4. Inspect, 5. Stop
1/2/8/4/4
```

(for an 8-hour run with a table of results every 2 hours)

```
Type 1 for display output only, 2 To restore copy for printing
1
Do you want to 1. Change, 2. Continue, 3. Restart, 4. Inspect, 5. Stop
1/3/1
Stored at this point ***********
Do you want to 1. Change, 2. Continue, 3. Restart, 4. Inspect, 5. Stop
2
```

VALPROATE OXOVPA	*	PL.CONC.	BD.	GI AMNT.	EX.VASC.AMNT	URINE	PDZ
A	0: 0	.0000	.0	.00	.000	.000	.000
A	0: 0	.0000	.0	.00	.000	.000	.000
	2: 0	25.7726	89.3	24.41	35.324	2.049	.000
	2: 0	1.0281	67.7	.00	2.190	18.918	.000
	4: 0	19.9360	89.7	2.13	57.628	2.515	.000
	4: 0	1.3076	68.5	.00	6.110	44.816	.000
	6: 0	15.7708	90.0	.23	59.724	1.854	.000
	6: 0	1.2877	69.1	.00	8.486	46.207	.000
	8: 0	12.9677	90.1	.03	55.841	1.469	.000
	8: 0	1.2324	69.6	.00	9.952	43.857	.000

```
Do you want to 1. Change, 2. Continue, 3. Restart, 4. Inspect, 5. Stop
1/3/2
********** Backtrack to last store
Do you want to 1. Change, 2. Continue, 3. Restart, 4. Inspect, 5. Stop
1/4/10
Factor 10 (currently = 5.500), specify new value
7.5
Factor 10 = 7.500 (previously = 5.500)
Do you want to 1. Change, 2. Continue, 3. Restart, 4. Inspect, 5. Stop
2
```

VALPROATE OXOVPA	*	PL.CONC.	BD.	GI AMNT.	EX.VASC.AMNT	URINE	PDZ
A	0: 0	.0000	.0	.00	.000	.000	.000
A	0: 0	.0000	.0	.00	.000	.000	.000
	2: 0	23.7099	89.5	22.93	34.310	88.723	.000
	2: 0	1.0083	68.0	.00	2.230	18.794	.000
	4: 0	16.8873	89.9	2.29	50.978	98.788	.000
	4: 0	1.1968	68.9	.00	5.622	41.557	.000
	6: 0	12.2040	90.2	.23	50.135	66.373	.000
	6: 0	1.1172	69.7	.00	7.619	40.395	.000

	PL.CONC.	BD.	GI AMNT.	EX.VASC.AMNT	URINE	PDZ
8: 0	9.2694	90.4	.02	44.201	48.237	.000
8: 0	1.0130	70.1	.00	8.596	36.281	.000

The figures in the table show that the increase of urine pH from 5.5 to 7.5 causes a sharp increase in the valproate concentrations in the urine with a consequential reduction in plasma concentrations.

3.5 Changing drug factors

On selecting option '1. Change' from the main options menu and then entering 'Q', the help message indicates that all the drug factors can be listed, using the unadvertised option 7. When the drug has metabolites, it is necessary to specify further if the factors required are for the unchanged drug (numbered 1), or for a metabolite (2,3 etc.). The table displays the factors running consecutively in rows from left to right; the meaning of each factor is given in Appendix 5. One particularly useful drug factor modification is that for giving sustained release, discussed more fully in Section 4.6.

You can change drug factors by entering option 5 (Change Drug Factors), followed by the number of the drug on the list (1 for parent drug, 2 for first metabolite etc., if a single drug has been prescribed). You then get a short list of 7 drug factors. This list (like that for subject factors) is incomplete and there is a rather daunting list of 52 factors in all (given in full in Appendix 5) which may be needed to specify each drug fully. Any other factor, in addition to those on the short list, can be changed. The dialogue is as follows.

```
Do you want to 1. Change, 2. Continue, 3. Restart, 4. Inspect, 5. Stop
1
1. Prescn, 2. Type of run, 3. Store/Bktr, 4. Patient factors, 5. Drug factors
5
Specify drug number as given in output headings
1
ASPIRIN *
1. PK = 3.5                          2. R.C.PARENT.ABSRPN = 0.33
3. LIPID/WATER PARTN = 0.0           4. R.C.PLASMA TO LIPID = 0.00
5. CONC.RATIO I/C:PLASMA = 0.50      6. R.C.PLASMA TO I/C = 0.50
7. R.C.INTEST.ABSRPN = 20.00
Type the numbers of factors to be changed — 0 if none
```

The full list of parameters for a drug is obtained by entering '1/7' at the main options menu, followed by the drug number on the prescription list (1 for parent drug, 2 for first metabolite, etc.).

```
AMPICILLIN *
```

2.5000	0.9000	0.0000	0.0000	0.0000
0.0000	40.0000	1.0000	0.0000	0.2200
0.0300	0.0000	6000.0000	1.0000	1.0000
1.3000	1.0000	2.5000	300.0000	0.0000
3.5000	60.0000	0.0000	0.0000	1.3000
400.0000	0.0250	0.0000	0.0000	0.0000
0.0000	0.0000	0.0000	0.0000	1.0000
0.0000	−316.0000	1.0000	1.0000	1.0000
1.0000	0.0000	2.0000	349.0000	0.0000
0.0000	0.0000	0.0000	1.0000	0.9000
16.0000	−347.0000			

All the factors may be changed to create an entirely new drug. This is how new drugs are tested and added to the library (see Appendix 6).

When you select the main menu option '3. Restart', the current drug factor changes are lost. To preserve these changes see Section 4.1, describing the use of the model in 'research mode'.

Example 9. Ampicillin, to show change of a drug factor.
Standard subject
Prescription: AMPICILLIN 1G PO STAT

```
Do you want to 1. Change, 2. Continue, 3. Restart, 4. Inspect, 5. Stop
1/2/4/1/1
```

(four-hour run, graph of plasma concentration, results every 15 minutes)

```
Type 1 for display output only, 2 To store copy for printing
1
Choose display scale from 1) 2hr, 2) 4hr, 3) 8hr, 4) 12hr, 5) 24hr, 6) 48hr, 7) 96hr, 8) 144hr,
9) 288hr
2
Do you want to 1. Change, 2. Continue, 3. Restart, 4. Inspect, 5. Stop
1/3/1
Stored at this point ***********
Do you want to 1. Change, 2. Continue, 3. Restart, 4. Inspect, 5. Stop
2
```

At the end of the run

```
Do you want to 1. Change, 2. Continue, 3. Restart, 4. Inspect, 5. Stop
1/3/2
********** Backtrack to last store
Do you want to 1. Change, 2. Continue, 3. Restart, 4. Inspect, 5. Stop
1/5/1/1/10
```

[to change factor 1 (pK_a) of drug no. 1 (the parent drug) to 10]

```
Factor 1 = 10.000 (previously = 2.5000)
Do you want to 1. Change, 2. Continue, 3. Restart, 4. Inspect, 5. Stop
```

(to store again with the drug factor change for replotting)

```
1/3/1
```

The change of pK_a from the stored value of 2.8 to 10.0 gives ampicillin the acid/base properties of one of its esters, such as pivampicillin (see Figures 13 and 14). The absorption from the gastro-intestinal tract is increased, giving a marked increase in the early plasma levels, which in fact go off the scale of the graph.

The second plot may be brought onto the scale, as with theophylline in Example 7, by multiplying drug factor 18 (normal value, 2.5) by ten. This change is made for both drug and metabolite and the results are shown in Figure 15.

4. Operating the program — for more advanced users

4.1 The 'Research' mode

Very experienced users will want to get at the model quickly; they may be irritated by having to sign their prescriptions; they may want to alter the

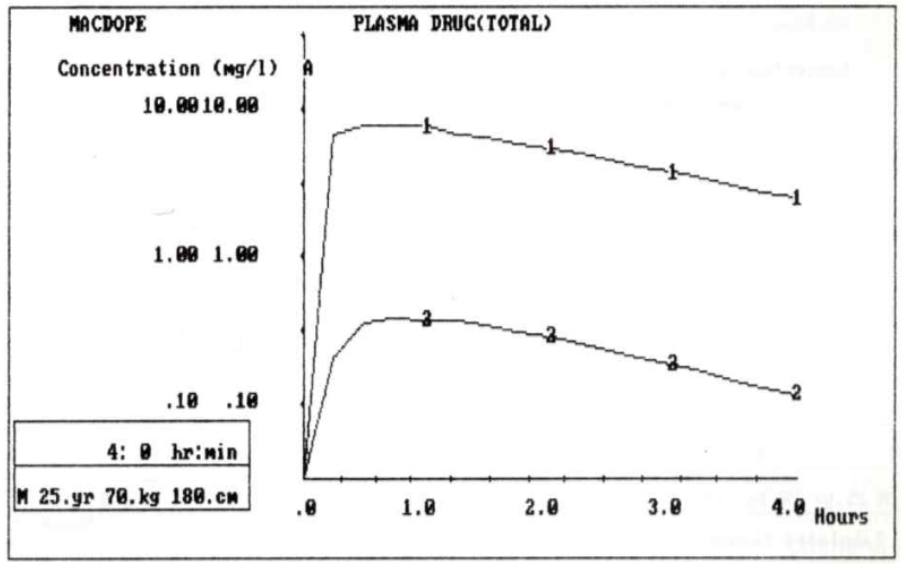


Figure 13.

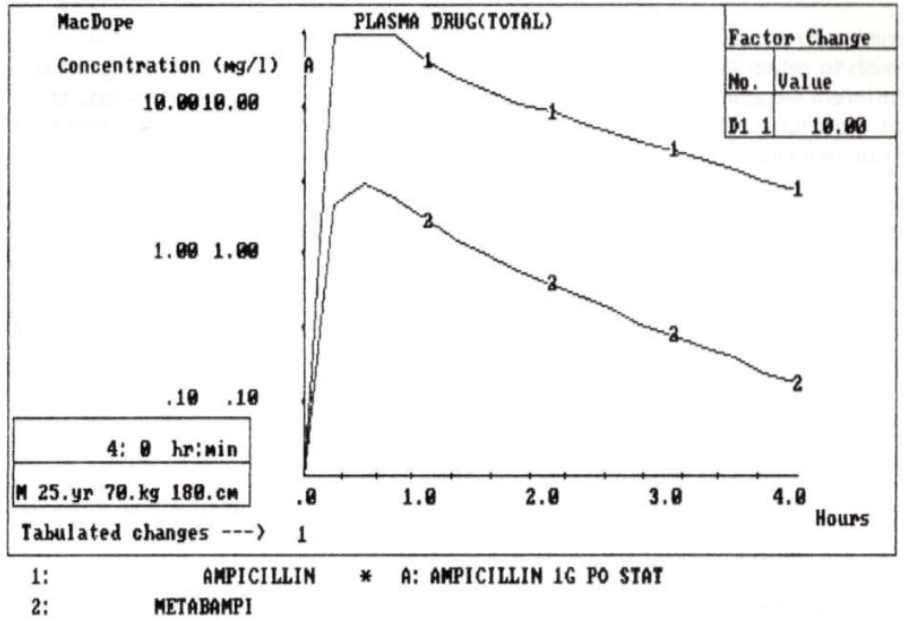


Figure 14.

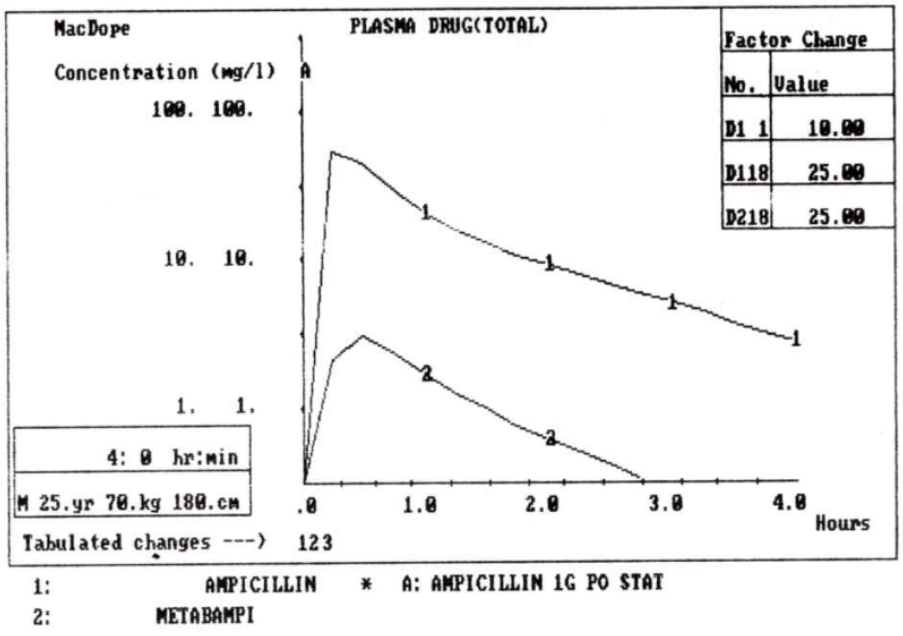


Figure 15.

minimum iteration interval (the interval for the numerical integration); they may wish to retain their own changes to drug parameters while performing several different experiments, and, conceivably, they might want to examine the state of the model at each iteration interval. All these options become available if your response to the first prompt, on entry to the program,

To proceed, type 1 then press <ENTER>.
For a brief introduction and instructions type 2.

is '0' (zero) instead of '1' or '2' (this option is not mentioned in the dialogue). The differences from the 'normal' mode of use of the program are as follows.

1. No signature is required in the final prescription, simply press the ENTER key.
2. In setting up a run, values for the iteration interval and for the precision factor governing the numerical integration process must be specified, and so may be varied.
3. On restarting the program by choosing option 3 in the main menu of options, a facility is provided to enable the user to preserve any changes in drug parameters which have been made; this facility is particularly useful in developing new drug representations.

The iteration interval in *MacDope* is variable, ranging from a normal minimum value of 3.5 minutes (changeable) to a maximum value equal to 4 times the minimum. When prescriptions are activated or other changes are made, the

drug level may vary rapidly and the iteration interval keeps at the minimum value. As things begin to stabilize, the iteration interval increases gradually; note that a very small value for the iteration interval may improve accuracy but it may result in slow simulation runs due to increased consumption of computer processing time.

The precision factor may be varied between a maximum value of 50 and a minimum of 1. Fifty is generally used. With some drugs, calculation difficulties may arise, particularly with IM prescriptions, causing irregular results, a warning message, or in some cases just causing the calculation to stop. Should any of these events occur, the cure is often to reduce the precision factor to 10 or 1.

A standard value of the precision factor for each drug is determined by drug parameter 49. A value of zero for this parameter is interpreted as a default value of 50.

In the research mode, the iteration interval and the precision factor are requested whenever the details of the simulation 'run' are re-specified (see Section 2.3).

One drug for which the research mode has to be used is lignocaine. This substance is metabolised very rapidly and correct plasma concentrations are only obtained by using a short iteration interval — 0.1 minutes is recommended — and a precision factor of 1.

Example 10. Thiopentone, to show use of the research mode with results every iteration.
Research mode chosen
Standard subject
Prescription: THIOPENTONE 125 MG IV STAT

Do you want to 1. Change, 2. Continue, 3. Restart, 4. Inspect, 5. Stop
1/2/2/1/0

(for a run of 2 hours, plasma level graphs, results every iteration)

Type 1 for display output only, 2 To store copy for printing
1
Choose display scale from 1) 2hr, 2) 4hr, 3) 8hr, 4) 12hr, 5) 24hr, 6) 48hr, 7) 96hr, 8) 144hr, 9) 288hr
1
Min. iteration time (currently 3.5 min)
1
Precision factor (currently 50.0) Try 10
1
Do you want to 1. Change, 2. Continue, 3. Restart, 4. Inspect, 5. Stop
2

Thiopentone by the IV route is used as a short acting anaesthetic. The action occurs during the few minutes after dose, when the plasma levels are high above the stable values reached at about 20 minutes after dose (see Figure 16).

The use of the research mode enables you to obtain plasma concentrations at the end of each iteration period and, by setting the iteration interval to 1 minute, the early results are obtained at 1-minute intervals. Later the iteration interval opens out.

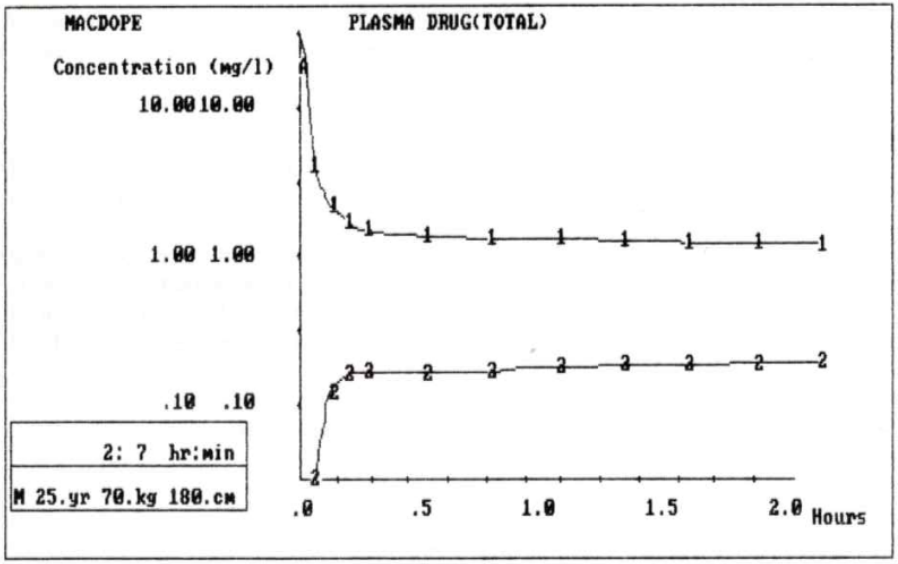


Figure 16.

4.2 Drug metabolism. Complete urinary excretion studies

When a drug has more than one metabolite, the complete set of metabolites (maximum 3) is obtained by adding M to the name of the drug in the prescription. The M is added directly on to the drug name without a space in between; the drugs which require the M are indicated in the list in Appendix 3. Use of the M suffix results in a more elaborate printout in the table of results; it is therefore only used when necessary. One situation where the full range of metabolites is required is in total urinary recovery studies. For example, on prescribing ASPIRIN, only the metabolite SALICYLATE is displayed. This metabolite provides only a minor excretion route for the drug. In order to study the full excretion, it is necessary to specify ASPIRINM and it is then seen that the main urinary excretion route is SALICYLURATE. The number of metabolites in *MacDope* is at present limited to three per drug in order to avoid over elaborate calculations, possibly leading to numerical instability. As a result, with a drug like aspirin, where the number of metabolites is at least five, some of them are grouped together.

The site of metabolism is governed by drug parameter 46. A value of 0 (zero) gives general metabolism, as with the hydrolysis of aspirin to salicylate, 1 gives metabolism in the liver and −1 specifies metabolism in the intestine, as with sulphasalazine. Liver metabolism may be either by a first-order kinetic mechanism or by saturable Michaelis–Menten kinetics. In the latter case, the possibility of competitive inhibition by other drugs exists in the model. With

ASPIRINM, there is first the general hydrolysis to SALICYLATEM and then the metabolites of salicylate formed with Michaelis–Menten kinetics (salicylurate and salicyl phenolic glucuronide) are grouped as SALICYLURATE, while those formed by first-order processes (salicylacylglucoronide and gentisic acid) are grouped as SALACGLUC. Owing to the procedure adopted for coding of drug and metabolite names in the model, it has been found necessary to give some abbreviated or unusual names to some metabolites in order to avoid duplication of codes automatically generated by the program.

In a complete urinary recovery study, accurate results are obtained when long time intervals are used, such as the 12 hours in the example shown. The urine concentrations are mean values over the preceding time interval corresponding to the experimental technique of pooling urine samples over intervals in this type of recovery study.

The amount of each substance excreted in milligrams is found by adding together all the mean urine concentrations of this substance and multiplying by the time interval and by the urine flow rate (0.066 litre/hr for the normal subject). For the example with the 400 mg dose, 48-hour recoveries are: aspirin 5.1 mg; salicylate 12.6 mg; salacgluc 9.5 mg; salicylurate 341.2 mg; total 368.4 mg.

Example 11. AspirinM to show 48-hour urinary excretion results with a full range of metabolites, with two shorter runs to work out clearances at two dose levels.
Standard subject
Prescription: ASPIRINM 400 MG PO STAT

```
Do you want to 1. Change, 2. Continue, 3. Restart, 4. Inspect, 5. Stop
1/2/48/4/5/12
```

(for a 48-hour table of results every 12 hours)

```
Type 1 for display output only, 2 To store copy for printing
1
Do you want to 1. Change, 2. Continue, 3. Restart, 4. Inspect, 5. Stop
1/3/1
Stored at this point ***********
Do you want to 1. Change, 2. Continue, 3. Restart, 4. Inspect, 5. Stop
2
ASPIRINM *
SALICYLATEM *
SALACGLUC
SALICYLURATE
```

		PL.CONC	BD.	GI AMNT.	EX.VASC.AMNT	URINE	PDZ
A	0: 0	.0000	.0	.00	.000	.000	.000
A	0: 0	.0000	.0	.00	.000	.000	.000
A	0: 0	.0000	.0	.00	.000	.000	.000
A	0: 0	.0000	.0	.00	.000	.000	.000
	12: 0	.0443	66.6	.31	4.193	6.315	.000
	12: 0	.8015	71.4	.00	30.397	15.211	.000
	12: 0	.0033	.0	.00	.181	11.320	.000
	12: 0	.3608	.0	.00	.000	382.021	.000
	24: 0	.0047	66.7	.00	.484	.066	.000
	24: 0	.1057	71.4	.00	4.447	.604	.000

	PL.CONC	BD.	GI AMNT.	EX.VASC.AMNT	URINE	PDZ
24: 0	.0005	.0	.00	.029	.610	.000
24: 0	.0497	.0	.00	.000	42.066	.000
36: 0	.0005	66.7	.00	.056	.007	.000
36: 0	.0151	71.4	.00	.655	.083	.000
36: 0	.0001	.0	.00	.004	.088	.000
36: 0	.0071	.0	.00	.000	5.933	.000
48: 0	.0001	66.7	.00	.006	.001	.000
48: 0	.0021	71.4	.00	.094	.012	.000
48: 0	.0000	.0	.00	.001	.013	.000
48: 0	.0010	.0	.00	.000	.848	.000

Do you want to 1. Change, 2. Continue, 3. Restart, 4. Inspect, 5. Stop
1/3/2

********** Backtrack to last store
Do you want to 1. Change, 2. Continue, 3. Restart, 4. Inspect, 5. Stop
1/2/10/4/4

(for a 10-hour table, with results every two hours)

Type 1 for display output only, 2 To store copy for printing
1
Do you want to 1. Change, 2. Continue, 3. Restart, 4. Inspect, 5. Stop
1/3/1

Stored at this point **********
Do you want to 1. Change, 2. Continue, 3. Restart, 4. Inspect, 5. Stop
2
ASPIRINM *
SALICYLATEM *
SALACGLUC
SALICYLURATE

		PL.CONC	BD.	GI AMNT.	EX.VASC.AMNT	URINE	PDZ
A	0: 0	.0000	.0	.00	.000	.000	.000
A	0: 0	.0000	.0	.00	.000	.000	.000
A	0: 0	.0000	.0	.00	.000	.000	.000
A	0: 0	.0000	.0	.00	.000	.000	.000
	2: 0	.8227	65.5	27.28	25.156	33.600	.000
	2: 0	22.6004	70.4	.00	108.199	53.283	.000
	2: 0	.0976	.0	.00	.428	33.343	.000
	2: 0	3.5970	.0	.00	.000	657.885	.000
	4: 0	.2976	66.4	11.09	17.163	1.771	.000
	4: 0	6.0161	71.2	.00	104.086	22.192	.000
	4: 0	.0250	.0	.00	.522	20.120	.000
	4: 0	2.1236	.0	.00	.000	726.374	.000
	6: 0	.1683	66.5	4.56	12.114	.850	.000
	6: 0	2.6863	71.3	.00	78.142	6.985	.000
	6: 0	.0108	.0	.00	.422	6.421	.000
	6: 0	1.1025	.0	.00	.000	393.651	.000
	8: 0	.1034	66.6	1.86	8.525	.501	.000
	8: 0	1.6931	71.4	.00	57.216	3.793	.000
	8: 0	.0069	.0	.00	.322	3.545	.000
	8: 0	.7229	.0	.00	.000	234.739	.000
	10: 0	.0666	66.6	.76	5.981	.315	.000
	10: 0	1.1501	71.4	.00	41.718	2.496	.000
	10: 0	.0047	.0	.00	.242	2.390	.000
	10: 0	.5067	.0	.00	.000	161.703	.000

Do you want to 1. Change, 2. Continue, 3. Restart, 4. Inspect, 5. Stop
1/3/2

********** Backtrack to last store

Do you want to 1. Change, 2. Continue, 3. Restart, 4. Inspect, 5. Stop
1/1

*** Current prescription(s) cancelled
Enter the prescriptions. End with signature GILES
(Queries? type Q; for druglist type QQ)
Prescription A – >
ASPIRINM 4000 MG PO STAT

Prescription B – >
GILES

Do you want to 1. Change, 2. Continue, 3. Restart, 4. Inspect, 5. Stop
2
ASPIRINM *
SALICYLATEM *
SALACGLUC
SALICYLURATE

		PL.CONC.	BD.	GI AMNT.	EX.VASC.AMNT	URINE	PDZ
A	0: 0	.0000	.0	.00	.000	.000	.000
A	0: 0	.0000	.0	.00	.000	.000	.000
A	0: 0	.0000	.0	.00	.000	.000	.000
A	0: 0	.0000	.0	.00	.000	.000	.000
	2: 0	9.1001	52.1	272.81	352.437	474.137	.000
	2: 0	257.4211	57.7	.08	1682.399	830.383	.000
	2: 0	1.2564	.0	.00	4.946	331.053	.000
	2: 0	4.9517	.0	.00	.000	808.082	.000
	4: 0	3.6405	57.0	112.49	243.653	27.582	.000
	4: 0	181.5347	62.3	.08	1971.511	516.447	.000
	4: 0	.8282	.0	.00	7.767	327.219	.000
	4: 0	4.7379	.0	.00	.000	1084.270	.000
	6: 0	2.1147	58.5	45.54	171.748	13.164	.000
	6: 0	156.3734	63.8	.08	1960.180	384.561	.000
	6: 0	.7089	.0	.00	8.716	259.682	.000
	6: 0	4.6509	.0	.00	.000	1071.029	.000
	8: 0	1.3445	59.3	18.55	121.330	7.794	.000
	8: 0	141.9557	64.6	.07	1872.694	332.264	.000
	8: 0	.6424	.0	.00	8.961	232.788	.000
	8: 0	4.6019	.0	.00	.000	1064.513	.000
	10: 0	.8935	60.0	7.64	85.798	4.992	.000
	10: 0	130.4244	65.2	.06	1759.607	298.167	.000
	10: 0	.5915	.0	.00	8.864	214.583	.000
	10: 0	4.5616	.0	.00	.000	1059.818	.000

For the 48-hr excretion study (the first table in the example), extended intervals for results are used without loss of accuracy because the urine concentrations are mean values over the preceding time interval. The clearance studies are made at two dose levels, 400 and 4000 mg; short runs are used with more closely spaced results so as to reduce error in assessing the mean plasma levels over an interval.

4.3 Urinary clearance

The urinary clearance of a drug is the hypothetical volume of plasma cleared of the drug via the urine in unit time. The calculated clearance from the table of results is:

$$\frac{\text{mg/hr excreted in urine over a time interval}}{\text{mean plasma concentration over the same interval in mg/litre}} \text{ (litre/hr)}$$

If a substance is not metabolized and is not secreted or re-absorbed in the kidney

tubules, the clearance is equal to the glomerular filtration rate (GFR, 7.5 litre/hr for the normal subject). This result is obtained with inulin which is used as a test substance to determine GFR.

When a drug is metabolised the total urinary clearance is the sum of the clearances as unchanged drug and as the metabolites. The clearance of drug as a metabolite is:

$$\frac{\text{mg/hr of metabolite excreted over a time interval}}{\text{mean plasma concentration of unchanged drug over the time interval}}$$

Clearances are usually less than the GFR owing to tubular re-absorption and protein binding. When re-absorption is extensive as with phenobarbitone and there is no rapidly excreted metabolite, the drug is very persistent and has a long plasma half-life. When excretion occurs at the GFR a short half-life results. Some drugs and many metabolites show specific secretion at the tubules resulting in rapid elimination with a clearance greater than GFR and a short half-life. Examples are ampicillin and benzpenicillin.

When metabolites are formed by first-order kinetics the clearances of drug as metabolites are independent of drug dose; when one metabolite is formed by saturable kinetics, the clearances are likely to vary with dose. At high doses the clearance of the saturable metabolite decreases markedly.

From the last two runs in the example with aspirinm, clearances of salicylate and the other metabolites have been calculated. Aspirin is effectively a transient pro-drug and is of limited interest in longer term considerations.

For the 400 mg dose, the mean plasma level of salicylate over the 8 to 10 hour interval is (1.69 + 1.15)/2 = 1.42 mg/litre. The amount of salicylate excreted is the urine concentration at 10 hr, which is the mean value over the 2-hr period, multiplied by 2 for the length of interval and by 0.066 litre/hr for the urine flow rate. The mean rate of excretion per hour over the interval is half this amount, that is (2.50 × 0.066 × 2)/2 = 0.165 mg/hr. The clearance of salicylate itself is then 0.165/1.42 = 0.116 litre/hr. Multiplying by 16.67 to give ml/min results in 1.93 ml/min.

The clearance of salicylate as salacgluc is the rate of excretion of salacgluc over the interval, divided by the mean plasma concentration of salicylate, (2.39 × 0.066)/1.42 = 0.11 litre/hr = 1.85 ml/min. The clearance of salicylate as salicylurate is (161.7 × 0.066)/1.42 = 7.5 litre/hr = 125 ml/min.

Similar calculations for the 4000 mg dose give clearances of salicylate as itself of 2.41 ml/min, as salacgluc of 1.74 ml/min and as salicylurate of 8.56 ml/min. The salicylate and salacgluc values are not greatly changed by increasing the dose and are well below the glomerular filtration rate of 125 ml/min indicating that these excretion routes are first order and may involve re-absorption of the substances at the kidney tubules. The very large decrease in the clearance of salicylate as salicylurate, from 125 to 8.6 ml/min, at the high dose, shows that this route involves a capacity-limited process. In fact, the saturation effect is in the liver, in the formation of the salicylurate.

4.4 The first pass effect and liver blood flow

The extent of metabolism of some drugs is often a function of the route of

administration. When given intravenously, the drug is distributed to tissues before reaching the usual site of metabolism in the liver; when given orally, the drug passes to the liver in the portal system before it is distributed. The drug therefore reaches the liver at a higher concentration when given orally than when given intravenously, and consequently is more extensively metabolized by the oral route. This effect is called the first pass effect since it is the first pass of the oral dose drug through the liver which produces the extra metabolism. With many drugs the effect is small but, particularly when a metabolite is the main excretion route of the drug, the first pass effect may cause plasma levels of unchanged drug to be very low when given orally when compared with levels following intravenous injection. In the case of lignocaine the levels following oral dose are too low for the oral route to be of use in systemic dosing.

The first pass effect is very much a function of liver blood flow. In *MacDope* there is no explicit circulation: transfers are between compartments. The equivalent of liver blood flow is the transfer kinetic coefficient of plasma to liver. By a calibration based on experimental results on the first pass effect with nortriptyline, a first-order transfer rate constant of 23.0 hr^{-1} has been evolved for the normal subject of *MacDope*. This subject factor (number 23) may be changed to simulate changes in blood flow.

Results with nortriptyline given in equal 50 mg doses by the IV and PO routes are shown in the following example. In order to make the plots more comparable, the IV dose is given as a drip over one hour. Although oral plasma levels are low, this drug is usually given by the oral route; there are no toxic metabolites produced as in the case of lignocaine.

Example 12. Nortriptyline, to show the first pass effect.
Standard subject
Prescription: NORTRIPTYLINE 50 MG PER H IVDRIP FOR 1 H

```
Do you want to 1. Change, 2. Continue, 3. Restart, 4. Inspect, 5. Stop
1/2/8/1/2
```

(for an 8-hr run with plasma graph, and results every half-hour)

```
Type 1 for display output only, 2 To store copy for printing
1
Choose display scale from 1) 2hr, 2) 4hr, 3) 8hr, 4) 12hr, 5) 24hr, 6) 48hr, 7) 96hr, 8) 144hr,
9) 288hr
3
Do you want to 1. Change, 2. Continue, 3. Restart, 4. Inspect, 5. Stop
1/3/1
Stored at this point **********
Do you want to 1. Change, 2. Continue, 3. Restart, 4. Inspect, 5. Stop
2
```

After this run is complete

```
Do you want to 1. Change, 2. Continue, 3. Restart, 4. Inspect, 5. Stop
1/3/2
********** Backtrack to last store
Do you want to 1. Change, 2. Continue, 3. Restart, 4. Inspect, 5. Stop
1/1
```

```
*** Current prescription(s) cancelled
Enter the prescriptions. End with signature GILES
  (Queries? type Q; for druglist type QQ)
Prescription A  - >
NORTRIPTYLINE 50 MG PO STAT
Prescription B  - >
GILES
Do you want to 1. Change, 2. Continue, 3. Restart, 4. Inspect, 5. Stop
2
```

The higher overall plasma levels for the IV route (see Figures 17 and 18), result in a greater area under the plasma level – time curve than for the oral route. The IV dose is given as IVDRIP over one hour in order to avoid high initial concentrations, which might cause toxic symptoms, and in order to obtain more reliable estimates for areas under the plasma concentration – time curve (AUC, see Section 4.5). In order to obtain estimates for the complete AUC values, the runs would have to be continued over a longer period, with extended intervals for results (see Example 13).

The complete areas under the IV and PO curves are 2.82 and 1.10 mg hr/litre, respectively; the fraction absorbed from the oral dose is 0.82, giving a liver extraction ratio of 0.48, so that about half the drug absorbed from the oral dose is metabolised by the first pass effect in the liver.

4.5 Changing intervals for results during a run. AUC

When the area under a plasma concentration – time curve is required, the usual

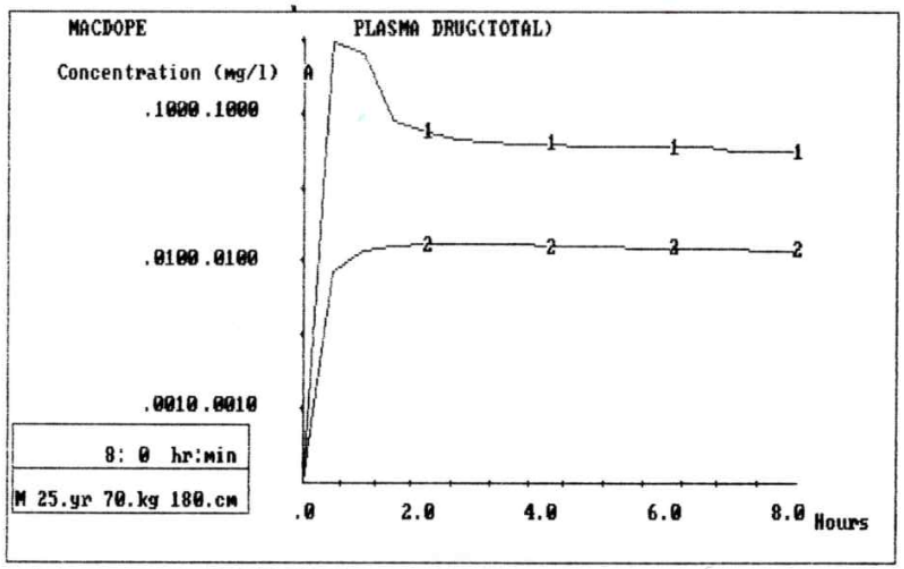


Figure 17.

experimental procedure is to obtain results at closely spaced intervals at the start of the run and then to extend the intervals as the run proceeds. This result is achieved in *MacDope* by setting the run in a series of sections, completing the first section before starting the next.

One characteristic of the program to be noted is that the first result in a new section will have the same interval as the preceding section. Planning is required to design a series of consecutive runs which will give a tidy overlap so that the final longer results do give values at round figure times. The time period for the last run is set one hour longer than the required 40 hr, in order to ensure that the last result, 48 hr after dose, is tabulated.

Example 13. Diazepam, to show changing intervals during a run.
Standard subject
Prescription: DIAZEPAM 10 MG PO STAT

```
Do you want to 1. Change, 2. Continue, 3. Restart, 4. Inspect, 5. Stop
1/2/1.75/4/1
```

(1.75 hour table with results every 15 minutes)

```
Type 1 for display output only, 2 To store copy for printing
1
Do you want to 1. Change, 2. Continue, 3. Restart, 4. Inspect, 5. Stop
2
```

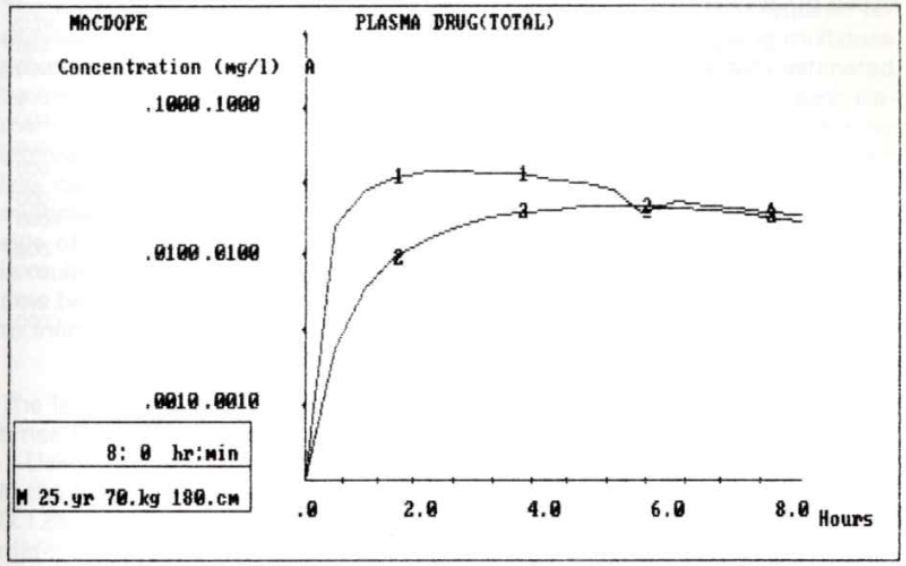


Figure 18.

DIAZEPAM *
DESMEDIAZEPAM

		PL.CONC.	BD.	GI AMNT.	EX.VASC.AMNT	URINE	PDZ
A	0: 0	.0000	.0	.00	.000	.000	.000
A	0: 0	.0000	.0	.00	.000	.000	.000
	0: 15	.0903	97.0	9.48	.015	.010	.000
	0: 15	.0032	95.9	.00	.000	.002	.000
	0: 30	.1730	96.7	8.94	.068	.037	.000
	0: 30	.0119	95.5	.00	.003	.017	.000
	0: 45	.2358	96.4	8.40	.155	.060	.000
	0: 45	0.233	95.0	.00	.010	.042	.000
	1: 0	.2898	96.0	7.72	.307	.084	.000
	1: 0	.0387	94.5	.00	.027	.080	.000
	1: 15	.3168	95.7	7.18	.456	.103	.000
	1: 15	.0504	94.1	.00	.047	.122	.000
	1: 30	.3322	95.5	6.67	.622	.116	.000
	1: 30	.0608	93.8	.00	.072	.159	.000
	1: 45	.3389	95.4	6.17	.797	.124	.000
	1: 45	.0697	93.6	.00	.102	.193	.000

Do you want to 1. Change, 2. Continue, 3. Restart, 4. Inspect, 5. Stop
1/2/5/4/3

(5 hour table, results every hour)

Type 1 for display output only, 2 To store copy for printing
1
Do you want to 1. Change, 2. Continue, 3. Restart, 4. Inspect, 5. Stop
2
DIAZEPAM *
DESMEDIAZEPAM

	PL.CONC.	BD.	GI AMNT.	EX.VASC.AMNT	URINE	PDZ
2: 0	.3385	95.3	5.58	1.021	.004	.000
2: 0	.0787	93.5	.00	.144	.007	.000
3: 0	.3044	95.2	3.95	1.678	.124	.000
3: 0	.0942	93.5	.00	.290	.268	.000
4: 0	.2556	95.5	2.69	2.182	.103	.000
4: 0	.0967	93.8	.00	.424	.282	.000
5: 0	.2141	95.8	1.82	2.500	.080	.000
5: 0	.0938	94.2	.00	.518	.260	.000
6: 0	.1791	96.1	1.22	2.698	.063	.000
6: 0	.0889	94.6	.00	.581	.234	.000
7: 0	.1454	96.3	.76	2.829	.049	.000
7: 0	.0820	94.9	.00	.624	.206	.000

Do you want to 1. Change, 2. Continue, 3. Restart, 4. Inspect, 5. Stop
1/2/41/4/5/4

(41 hour table, results every four hours)

Type 1 for display output only, 2 To store copy for printing
1
Do you want to 1. Change, 2. Continue, 3. Restart, 4. Inspect, 5. Stop
2
DIAZEPAM *
DESMEDIAZEPAM

	PL.CONC.	BD.	GI AMNT.	EX.VASC.AMNT	URINE	PDZ
8: 0	.1240	96.4	.51	2.879	.004	.000
8: 0	.0764	95.0	.00	.640	.017	.000
12: 0	.0699	96.8	.09	2.838	.025	.000

	PL.CONC.	BD.	GI AMNT.	EX.VASC.AMNT	URINE	PDZ
12: 0	.0555	95.5	.00	.609	.140	.000
16: 0	.0500	96.9	.02	2.670	.015	.000
16: 0	.0428	95.7	.00	.523	.097	.000
20: 0	.0416	97.0	.00	2.490	.011	.000
20: 0	.0350	95.8	.00	.439	.075	.000
24: 0	.0370	97.0	.00	2.321	.009	.000
24: 0	.0297	95.8	.00	.370	.062	.000
28: 0	.0339	97.0	.00	2.162	.008	.000
28: 0	.0260	95.9	.00	.314	.053	.000
32: 0	.0316	97.0	.00	2.006	.008	.000
32: 0	.0229	95.9	.00	.268	.046	.000
36: 0	.0291	97.1	.00	1.869	.007	.000
36: 0	.0206	95.9	.00	.233	.041	.000
40: 0	.0272	97.1	.00	1.741	.007	.000
40: 0	.0187	95.9	.00	.205	.037	.000
44: 0	.0253	97.1	.00	1.621	.006	.000
44: 0	.0171	96.0	.00	.182	.033	.000
48: 0	.0238	97.1	.00	1.510	.006	.000
48: 0	.0156	96.0	.00	.163	.030	.000

The time interval scheme in this example is suitable for a number of drugs. For very slow-moving drugs, such as phenobarbitone, it is necessary to add a further section with results every 8 or 12 hr. The area under the plasma concentration – time curve from these results is assessed in the next section.

4.5.1 Calculation of area under curve — rectangle method

The area under the plasma concentration – time curve (AUC) is required for assessing bio-availability and the first pass effect and for designing multidose schemes from single dose results (see Section 5). AUC is generally estimated by the trapezium rule which involves adding up the areas of trapezia, each element being the mean of two adjacent concentrations multipled by the time interval between them. An equivalent value for AUC may be obtained with less calculation by using a rectangle method. In this, each concentration is multiplied by the difference between the mid-times of the intervals on either side of that concentration time. The last concentration, if it is not negligible, is multiplied by the difference between the concentration time and the mid-time before it; an extrapolation term is then added to give the estimate of AUC to infinite time. This extrapolation term is equal to

(final concentration)/(late time elimination constant).

The late time elimination constant is found from the slope of the line at late times in the plot of log(concentration) against time.

Using the diazepam results in Example 13, the AUC is estimated as follows. In the first group of results, the intervals are all 0.25 hr and the mid-times are 0.125 hr on either side of the concentration times. The difference between mid-times is therefore 0.25 hr in each case and so all the plasma concentrations may be added together and multiplied by 0.25.

$$1.78 \times 0.25 = 0.444 \text{ mg hr/litre}$$

The first result of the second section has an interval mid-time before the result

of 0.125 hr and a mid-time for the interval after the result of 0.5 hr. The difference of mid-times is 0.625 hr and so the contribution to AUC for this results is

$$0.339 \times 0.625 = 0.212 \text{ mg hr/litre}$$

The other results in this second section all have mid-times 0.5 hr on either side of the results and so mid-time differences are 1.0 hr. The concentrations are therefore added together and multiplied by 1.0.

$$1.099 \times 1.0 = 1.099 \text{ mg hr/litre}$$

The first result of the third section has a mid-time before the result of 0.5 hr and a mid-time after of 2 hr and so a difference of 2.5 hr.

$$0.124 \times 2.5 = 0.310 \text{ mg hr/litre}$$

The remaining results of the third section, excluding the last one, are added together and multiplied by the difference of mid-times, 4.0 hr.

$$0.345 \times 4.0 = 1.380 \text{ mg hr/litre}$$

The last concentration is multiplied by the difference of mid-time before and the time of the result, i.e. 2.0 hr.

$$0.024 \times 2.0 = 0.048 \text{ mg hr/litre}$$

The late time elimination constant is 0.0167 hr^{-1} and so the extrapolation term is

$$0.023/0.0167 = 1.377 \text{ mg hr/litre}$$

Adding together all these contributions gives a value for the AUC, to infinite time, of 4.87 mg hr/litre.

A more accurate result would be obtained by extending the run for a further 48 hr so as to reduce the extrapolation term relative to the total area.

4.6 Sustained release preparations

Drugs which are rapidly eliminated are often given orally in a sustained release preparation from which the drug is released slowly during passage through the gastro-intestinal tract. Ideally, the release should be at a constant rate, i.e. with zero-order kinetics. In *MacDope*, this sustained release effect is controlled in the first place by drug parameter 34. The value of this parameter is normally zero but it may be set to a value in hours which gives the period over which a uniform release of drug is obtained. It is unrealistic to set this period at too high a value. With a drug like oxprenolol, which has a relatively short plasma half-life of around 2 hr, the simulation gives a sharp drop of plasma concentration at the end of the release period which is not observed experimentally. Consequently, a second zero-order release process has been introduced which is governed by drug parameters 47 and 48. Parameter 47 gives a second period in hours for zero-order dissolution while 48 gives the proportion of total dose going to this second dissolution process, which runs concurrently with the first. For example with 34 = 6, 47 = 16, 48 = 0.4, and a dose of 160 mg, 64 mg would go to process 2 giving 64/16 = 4 mg/hr for 16 hr, while 96 mg would go to process 1 giving 16 mg/hr for 6 hr. For the first six hours, both processes

are running together giving an overall release rate of 20 mg/hr dropping to 4 mg/hr for the final 10 hours.

Example 14. Oxprenolol, normal and sustained release.
Standard subject
Prescription: OXPRENOLOL 160 MG PO STAT

```
Do you want to 1. Change, 2. Continue, 3. Restart, 4. Inspect, 5. Stop
1/2/24/1/3
Type 1 for display output only, 2 To store copy for printing
1
Choose display scale from 1) 2hr, 2) 4hr, 3) 8hr, 4) 12hr, 5) 24hr, 6) 48hr, 7) 96hr, 8) 144hr,
9) 288hr
5
Do you want to 1. Change, 2. Continue, 3. Restart, 4. Inspect, 5. Stop
1/3/1
Stored at this point **********
Do you want to 1. Change, 2. Continue, 3. Restart, 4. Inspect, 5. Stop
2
```

At the end of the run,

```
Do you want to 1. Change, 2. Continue, 3. Restart, 4. Inspect, 5. Stop
1/3/2
********** Backtrack to last store
Do you want to 1. Change, 2. Continue, 3. Restart, 4. Inspect, 5. Stop
1/5/1/34/8
```

[to change drug parameter 34 (release period) to 8 hr]

```
Factor 34 = 8.000 (previously = 0.000)
Do you want to 1. Change, 2. Continue, 3. Restart, 4. Inspect, 5. Stop
2
```

After a further run,

```
Do you want to 1. Change, 2. Continue, 3. Restart, 4. Inspect, 5. Stop
1/3/2
********** Backtrack to last store
Do you want to 1. Change, 2. Continue, 3. Restart, 4. Inspect, 5. Stop
1/5/1/34 47 48/6/16/0.4
```

(gives values to the three release parameters)

```
Factor 34 = 6.000 (previously = 0.000)
Factor 47 = 16.000 (previously = 0.000)
Factor 48 = 0.400 (previously = 0.000)
Do you want to 1. Change, 2. Continue, 3. Restart, 4. Inspect, 5. Stop
2
```

The second run (Figure 20), with a single sustained release process gives more even release of drug over 8 hr than the conventional tablet (Figure 19). After 8 hr there is a sharp drop of plasma level, which is not observed experimentally. The third run (Figure 21), with the two release processes, gives increasing plasma concentrations up to 6 hr, the end of the first process. The concentrations then decline slowly until the end of the second process at 16 hr; subsequently they decline rapidly. The results with the two processes give a better representation of experimental results than does the single release process.

Note that in changing the three drug factors in one command, the numbers

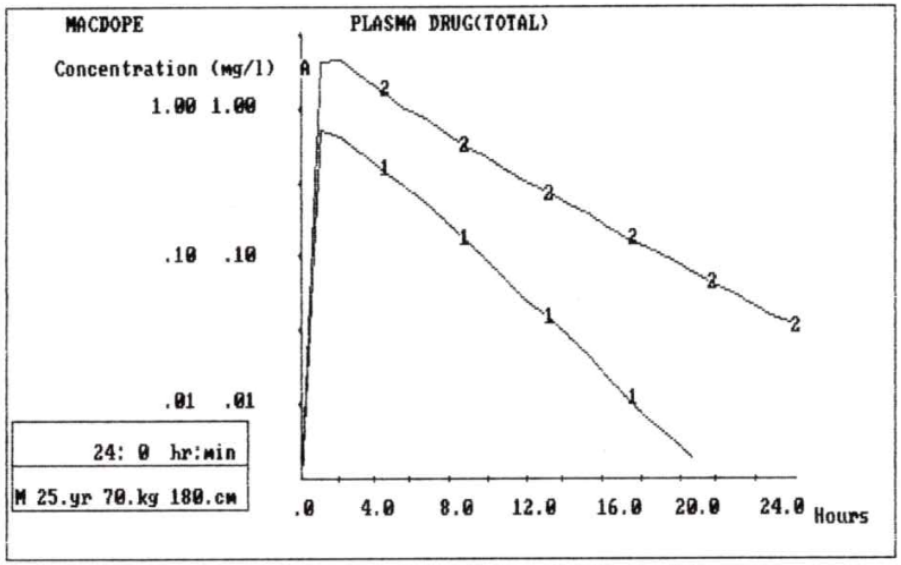


Figure 19.

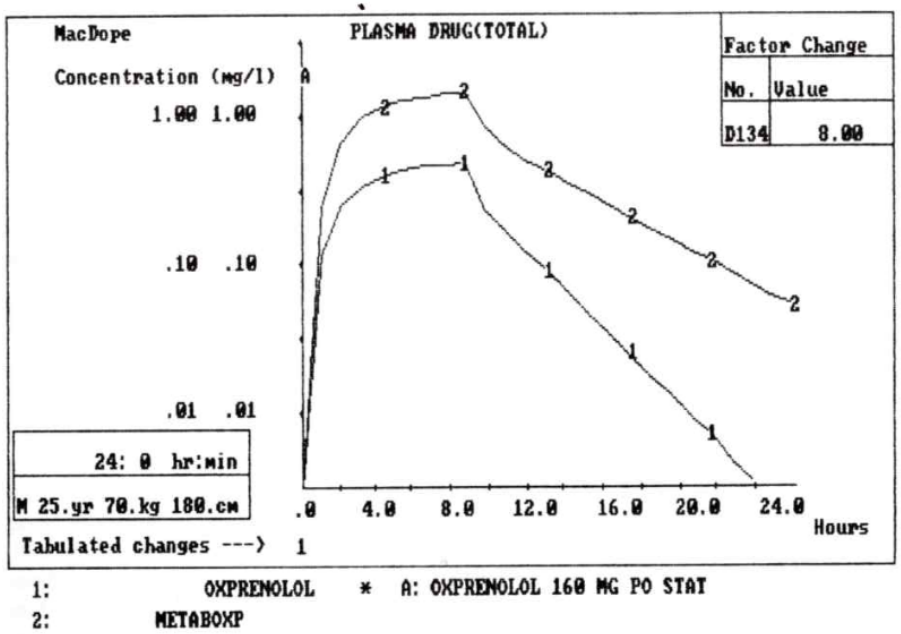


Figure 20.

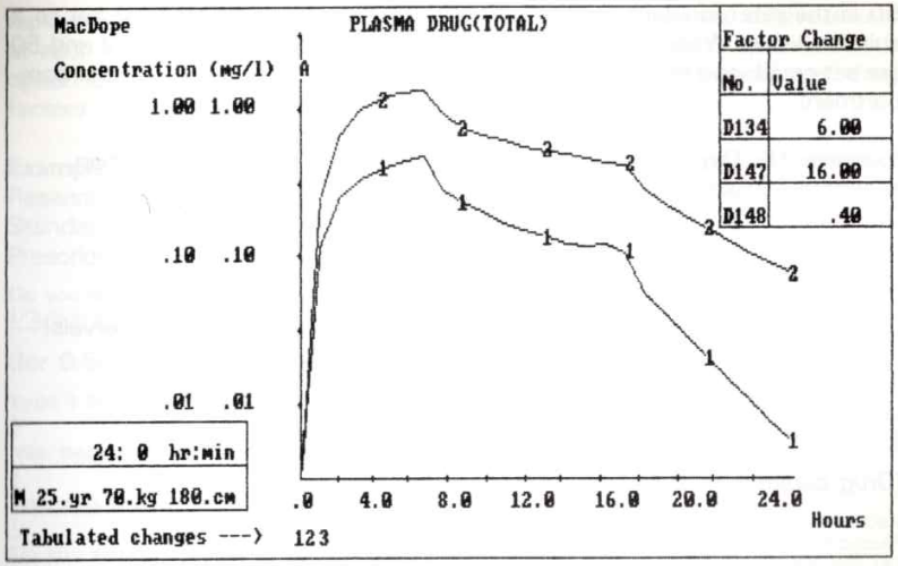


Figure 21.

of the factors are separated by spaces, while the new values to be entered are separated by slashes.

4.7 Pharmacodynamic action zone

The kinetics of the activity of a drug (pharmacodynamics) is in some cases markedly different from the kinetics of the plasma levels. This effect occurs when a drug exerts its action as a result of being strongly bound to receptor sites. When the plasma level falls, the drug is only released slowly and the activity persists. Oxprenolol is a good example of such a drug with a plasma half-life of around 2 hours but an action (pharmacodynamic) half-life of around 10 hr.

MacDope incorporates a pharmacodynamic action zone (PDZ). This zone is a compartment of small volume (0.01 litre), normally used as a depot for IM injections. The action zone cannot, therefore, be used with dosage by the IM route.

When setting the type of display in the Run Change dialogue (see Section 2.3), the choice of option 5 invokes the PDZ mechanism and the output is given as a table of results with a separate heading for PDZ. The figures under this heading are all zero unless the PDZ option is used. The action zone concentrations are in arbitrary units and are only intended for comparisons.

When the PDZ option is used, the drug transfer rate (parameter 2) from plasma to action zone has to be set to an appropriate value. Drug parameter

50 is the rate constant for the reverse transfer and also has to be set to a suitable value. When the PDZ option is not in use, drug parameters 2 and 50 are set equal, and represent transfer rates to and from the intramuscular compartment.

Example 15. Oxprenolol, to show the pharmacodynamic (PDZ) option.
Standard subject
Prescription: OXPRENOLOL 160 MG PO STAT

```
Do you want to 1. Change, 2. Continue, 3. Restart, 4. Inspect, 5. Stop
1/2/16/5/4
```

(16-hour table of results, with values, including PDZ, at 2-hour intervals)

```
Type 1 for display output only, 2 To store copy for printing
2
Do you want to 1. Change, 2. Continue, 3. Restart, 4. Inspect, 5. Stop
1/5/1/2 50/20/0.2
```

(Drug parameters 2 and 50 are set – essential for use of PDZ)

```
Factor 2 = 20.000 (previously = 3.000)
Factor 50 = 0.200 (previously = 3.000)
Do you want to 1. Change, 2. Continue, 3. Restart, 4. Inspect, 5. Stop
2
OXPRENOLOL *
METABOXP
```

		PL.CONC.	BD.	GI AMNT.	EX.VASC.AMNT	URINE	PDZ
A	0: 0	.0000	.0	.00	.000	.000	.000
A	0: 0	.0000	.0	.00	.000	.000	.000
	2: 0	.6657	79.4	75.42	13.329	13.784	382.942
	2: 0	2.1684	42.0	1.62	16.791	254.621	125.795
	4: 0	.3999	79.6	26.30	14.100	12.046	617.008
	4: 0	1.3696	42.3	1.50	26.880	268.527	85.175
	6: 0	.2334	79.8	9.46	9.775	7.239	620.245
	6: 0	.8751	42.5	1.08	25.901	172.226	54.012
	8: 0	.1342	79.9	3.54	6.053	4.096	534.594
	8: 0	.5872	42.7	7.3	21.807	113.133	36.089
	10: 0	.0731	79.9	1.31	3.503	2.273	424.148
	10: 0	.4027	42.7	.49	17.201	76.988	24.578
	12: 0	.0398	79.9	.48	1.942	1.235	318.966
	12: 0	.2779	42.8	.32	13.056	53.096	16.940
	14: 0	.0217	80.0	.18	1.082	.662	235.259
	14: 0	.1970	42.8	.22	9.825	37.073	11.981
	16: 0	.0112	80.0	.06	.572	.357	166.189
	16: 0	.1375	42.8	.15	7.157	26.244	8.341

The PDZ values are in arbitrary units and need to be calibrated against experimental results of studies of pharmacodynamic activity; it is in this calibration that the values of drug factors 2 and 50 are decided. The PDZ values for metabolites are ignored unless this substance is known to be active.

In the table for oxprenolol, the 2- and 10-hr PDZ values are similar, indicating the period of pharmacodynamic activity. The intermediate values match quantitative data on heart rate lowering by oxprenolol.

A second example to illustrate the use of the PDZ option is given with the

rapid acting analgesic, fentanyl citrate. The research mode is used to give results at each iteration interval of 3 minutes. The table of results is specified with option 5 so as to include PDZ values and the two PDZ rate constants, drug factors 2 and 50, have in this case, both been set to 3.0 h.

Example 16. Fentanyl citrate to show pharmacodynamic zone levels.
Research mode in use
Standard subject
Prescription: FENTANYLCIT 0.2 MG IV STAT

```
Do you want to 1. Change, 2. Continue, 3. Restart, 4. Inspect, 5. Stop
1/2/0.5/5/0
```

(for 0.5-hour run with results every iteration, PDZ table)

```
Type 1 for display output only, 2 To store copy for printing
2
Min. iteration time (currently 3.5 min)
3
Precision factor (currently 50.0) Try 10
1
Do you want to 1. Change, 2. Continue, 3. Restart, 4. Inspect, 5. Stop
2
FENTANYLCIT *
METABFENT
```

		PL.CONC.	BD.	GI AMNT.	EX.VASC.AMNT	URINE	PDZ
A	0: 0	.0000	.0	.00	.000	.000	.000
A	0: 0	.0000	.0	.00	.000	.000	.000
	0: 3	.0660	80.8	.00	.000	1.435	.000
	0: 3	.0000	41.2	.00	.000	.000	.000
	0: 6	.0416	80.8	.00	.026	.906	.136
	0: 6	.0000	41.2	.00	.000	.000	.000
	0: 9	.0251	80.8	.00	.043	.546	.207
	0: 9	.0043	41.2	.00	.015	.977	.002
	0: 12	.0161	80.8	.00	.052	.351	.230
	0: 12	.0030	41.2	.00	.043	.680	.005
	0: 15	.0098	80.8	.00	.058	.213	.234
	0: 15	.0037	41.2	.00	.061	.825	.008
	0: 18	.0065	80.8	.00	.061	.141	.221
	0: 18	.0024	41.2	.00	.076	.545	.011
	0: 21	.0040	80.8	.00	.063	.087	.205
	0: 21	.0025	41.2	.00	.084	.564	.012
	0: 24	.0028	80.8	.00	.064	.061	.185
	0: 24	.0018	41.2	.00	.091	.404	.014
	0: 27	.0018	80.8	.00	.064	.040	.166
	0: 27	.0018	41.2	.00	.094	.403	.016
	0: 30	.0014	80.8	.00	.064	.031	.146
	0: 30	.0014	41.2	.00	.097	.319	.017
	0: 33	.0010	80.8	.00	.064	.022	.129
	0: 33	.0014	41.2	.00	.098	.314	.018

In this case, a stored copy is requested for the table of results, which has the advantage of giving a continuous table rather than the paginated output from the printing of successive screenfuls of results. The subject, prescription and

drug list are given at the top of the table, together with details of any parameter changes.

The value of PDZ for fentanyl citrate at 30 minutes is similar to the first value, indicating the period of significant activity of the drug.

4.8 Calculation instability

Under some circumstances, particularly with highly bound drugs such as phenytoin and warfarin, and with the IM route for a number of drugs, calculation instability may occur in some concentration regions. The symptoms of instability are:

1. A message is printed out stating that 'the dose is too large, try altering the precision factor'. This factor can only be altered in the research mode. In some cases, with the IM route, the message is not printed but calculation stops completely.
2. A row of zeros appears in one of the rows of results in a table, probably meaning that a negative value was calculated.
3. An anomalous concentration result appears which differs markedly from those around it. Such a result is readily recognised by plotting a graph of the adjacent values.
4. The plasma concentrations start to oscillate.

The possible remedies are:

1. Terminate the program, list your stored output if required and then re-enter specifying the research mode of use (see Section 4.1). Reduce the precision factor to its minimum value of 1 and also shorten the iteration interval.

2,3. The calculation should be repeated in the research mode with a lower value of the precision factor (10 or 1) and a reduced iteration interval. If the bad result persists it should be replaced by an interpolated value or ignored in any calculation of AUC or urinary recovery.

4. The oscillations have usually been found in very long runs in the study of drug interactions, and are due to the iteration interval becoming too long. As the maximum interval is linked to the minimum by a factor of 4, a remedy is to re-run in research mode with an iteration interval set at 1 minute or less.

Instability is found particularly with lignocaine, due to the very rapid metabolism of this drug. It is essential with lignocaine to use a much-reduced iteration interval and therefore the research mode is required with a reduction of this interval to 0.1 min. The precision factor should be set at 1.

5. Some exercises with *MacDope*

Much information about the general behaviour of the drugs may be obtained using the graphical output. For example the effects of changes in subject parameters on plasma levels of a given drug dosage scheme may be assessed.

Lists of normal doses and of target plasma levels for the drugs in *MacDope*

are given in Appendix 3, together with information about standard routes of administration and about metabolic type. In the following exercises it is suggested that you use the normal dose and the normal adult male subject, except where otherwise indicated. Start with the first drug on the list and look at the others later. Begin with graphical output; for more detail re-run with numerical output.

Use of differing subjects

Use the pre-set subjects 2 (3-year-old girl), 5 (the 80-year-old) and 6 (50-year-old in renal failure) to compare with the normal adult male.

Examine plasma levels (half lives, volumes of distribution) using indomethacin, theophylline, phenobarbitone, phenytoin, valproate, diazepam, notritptyline. (The glomerular filtration rate for each subject may be determined by using inulin and finding the urinary clearance at steady state plasma level.)

Stomach pH and emptying rate

Gastric pH is subject parameter 2 (sp2, normal value 3.5), while the emptying rate constant is sp1 (normal, 0.5 hr^{-1}). Determine the effects of raising the pH to 6.0 and of doubling or halving the emptying rate, on early plasma levels of aspirin and valproate.

Serum albumin

Study the effect of changing the plasma albumin concentration, sp3 (normal 5 g/dl), on plasma levels, half-lives and volumes of distribution of warfarin and diazepam.

Sustained release

Examine the effects of the three sustained release drug parameters, dp34, dp47 and dp48, on the shapes of plasma-level curves following oral doses, using Example 14 as a guide, with propranolol, oxprenolol, theophylline, indomethacin and paracetamol.

Drug pK_a

Raising the pK_a, drug parameter 1 (dp1), of an anionic drug to make it a very weak acid, say $pK_a = 10$, simulates the effect of using an ester of the drug as the dosage form (see example 9). Examine the effects of this change on absorption, as shown by early plasma levels following oral dose using phenobarbitone, ampicillin, phenytoin, valproate, aspirin and indomethacin.

Liver and kidney dysfunctions

Liver dysfunction is simulated by using subject parameter 8, sp8 (normal value 1.0). To reduce liver function to 10 % of normal, use the sequence '1/4/8/0.1'.

Kidney dysfunction is simulated by changing sp9, the GFR (normal value 7.5

litre/hr), sp12, the tubular excretory function (normal 1.0) and sp17, the tubular re-absorption function (normal 1.0). To reduce kidney function to 10 % of normal, enter '1/4/9 12 17/0.75/0.1/0.1'.

Examine the effects of liver and kidney dysfunctions on plasma levels of the following and decide which dysfunction(s) is important in treatment with the drug: nortriptyline, paracetamol, ampicillin and phentyoin. Examine by urine level studies the effects of the dysfunctions on the excretion patterns. None of the above drugs has an M form, see Appendix 3.

Routes of administration

Carry out runs to compare plasma levels following IV, PO and IM dosage. IV dose may be STAT or IVDRIP. For the IM dose it is best to operate in the research mode with the precision factor set to 1.0. Use the following drugs: kanamycin, benzpenicillin, ampicillin, diazepam, lignocaine* and phenytoin.
*Research mode with an iteration interval of 0.1 min and a precision factor of 1 is essential for runs with lignocaine.

Compare the metabolism of propranololm after IV and PO doses, by examining urine levels.

Varying dose

Examine the effects of successive doubling of the dose on plasma levels and AUC values of phenytoin and aspirin. Use nortriptyline as a comparison drug which does not show saturable effects.

Overdose, urine pH and diuresis

Urine pH is sp10 (normal value 5.5) and diuresis is simulated by increasing the urine flow rate, sp11 (normal 0.066 litre/hr). Examine the effects of raising urine pH to 7.5 and flow rate to 0.3 litre/hr, on plasma levels following overdose (say 20 g) of aspirin and paracetamol.

Digitalising

How quickly can you digitalise a patient, i.e. achieve a therapeutic level and maintain it while avoiding toxic reactions, with digoxin. Repeat with digitoxin and compare results. Use some of the preset subjects in an extension of this exercise.

Quantitative studies with single and multiple doses

A useful quantitative exercise is to evolve a multidose scheme from single-dose studies. A suitable single dose D is given (see Appendix 3) and a run is made to determine AUC, as in Example 13. A dosing interval, T, is decided based on the half-life of the drug and on the purpose for which it is being used. The mean steady-state plasma level after giving dose D at intervals T should be AUC/T mg/litre. If there is a target level, L, for the drug (see Appendix 3),

then to reach this level the dose should be altered to $D.L/(AUC/T)$.

The scheme is tried out with this altered dose given at intervals T, and if the mean plasma level differs significantly from L, there are three possibilities:

(a) Miscalculation — check as indicated in Section 4.8.
(b) Saturable effects cause the mean steady state level to be well above L and to increase beyond the point at which the steady state should be reached.
(c) Enzyme induction — may cause levels below L.

(b) and (c) call for modification of the multidose design. Saturable effects are best dealt with by using the 'Then' option in the prescription (see Example 3). Having established a suitable regime for the standard subject 1, the use of this scheme with other preset subjects and with the user's own subjects may be explored, making necessary modifications to maintain the target level.

The effects of dysfunctions and other changes in subject and drug parameters may then be examined. Some subject parameters of particular interest are:

1 gastric emptying rate,
2 gastric pH,
3 plasma albumin concentration,
8 hepatic enzyme function, ratio to normal 1.0,
9 glomerular filtration rate, 7.5 litre/hr normal,
10 urine pH, 5.5 normal,
11 urine output, 0.066 litre/hr normal,
12 excretory tubular function (ratio to normal, 1.0),
17 re-absorptive tubular function (ratio to normal, 1.0).

Some drug factors of particular interest are:

1 pK_a, see example 9,
34,47,48 sustained release parameters, see Example 14,
23,24 rate constants for formation of metabolite by possible saturable process,
25 rate constant for metabolite by first-order process,
9 renal tubular permeability, governs rate of re-absorption in the kidney from the urine.

Studies of urinary excretion and clearances may be made using a single dose, as outlined in example 11. The effect of changing some of the above parameters may then be assessed.

Values for the bio-availability of a drug when given by the oral route are estimated by carrying out runs with varying intervals to give AUC values as in Example 13 (see Section 4.5) using the same dose by both IV and PO routes. It is difficult to assess AUC by the IV route if a STAT dose is given, owing to high initial concentrations. It is better to give the dose as an IVDRIP over, say, one hour. The IV dose is considered to be fully available and so the bio-availability by the oral route is assessed as AUC (oral) divided by AUC (IVDRIP) with the same total dose in each case. The oral bio-availability is less than 1.0 due to incomplete absorption and to the first pass effect (Section 4.4).

Appendix 1. The kinetics of some drugs in *MacDope*

The simplest type of kinetics is shown by the physiological test substance inulin. It is not bound to plasma protein, it is not metabolized to any extent and it is neither re-absorbed nor specifically secreted in kidney tubules. It is a carbohydrate polymer of modest size and is filtered in the kidney glomeruli at the standard filtration rate; it is therefore used to measure this glomerular filtration rate in a given subject. As the elimination mechanism is so simple, the total clearance of inulin equals the urinary clearance which in turn equals the filtration rate.

$$\text{Clearance, } CL = VD \times KE$$

where KE = first-order elimination rate constant; VD = effective volume of distribution.

From the table of results from *MacDope*, renal clearance equals rate of elimination in the urine over an interval (mg/hr) divided by the mean plasma concentration during the interval, C_p (mg/litre).

In *MacDope* the urine concentrations C_u are mean values over the preceding time interval in the printout, corresponding to the experimental method of pooling urine samples for analysis. The clearance is therefore

$$CL = C_u.FU/C_p$$

where FU = urine flow rate (0.066 litre/hr for the normal subject). C_p is the mean of the plasma concentrations at the start and finish of the interval and C_u is the urine concentration shown at the end of the interval, which is the mean value over the interval. In order to avoid inaccuracies in determining C_p, inulin is given as an intravenous infusion so that a steady state with constant plasma levels is obtained.

The next simplest overall kinetics is that for kanamycin. This drug is also a moderately large molecule with negligible protein binding and metabolism. The clearance is, however, somewhat less than the filtration rate indicating possible tubular re-absorption or incomplete filtration. The elimination is rapid with a plasma half-life of about 2 hr which is greatly increased by kidney dysnfunction.

Rapid elimination may be considered to imply plasma half-lives of less than 3 hr. Ampicillin is only metabolized to a limited extent and its urinary clearance is greater than the glomerular filtration rate (GFR) due to an active tubular secretion process. The plasma half-life is about 1.3 hr and is again greatly affected by impaired kidney function.

Another type of rapid elimination is exemplified by paracetamol. The drug itself is almost non-polar and is substantially re-absorbed in the kidney tubules. It is however, rapidly metabolized in the liver to more polar conjugates which in turn are excreted rapidly in the urine. The plasma half-life is around 2.5 hr and is considerably increased by liver dysfunction. The plasma half-life of paracetamol has been used to assess liver impairment in cases of overdose with this drug. Paracetamol in very large doses has a toxic effect on the liver.

The beta-blockers, oxprenolol and propranolol, are also in the category of rapidly eliminated drugs due to rapid metabolism, as is lignocaine.

In the range of intermediate rapidity of elimination (half-lives of, say, 3 to 12 hr), the drug itself is eliminated more slowly than the filtration rate due to protein binding and to tubular re-absorption, and the metabolic processes are only of moderate speed. Examples here are: indomethacin (half-life 6 hr) which is mainly excreted as metabolites and has a protein binding around 80%; sulphasalazine (half-life 6 hr) is metabolized mainly by the intestinal flora; theophylline (half-life also around 6 hr) has a plasma protein binding of around 60%. Sodium valproate has a high protein binding of 90% and a half-life of 12 hr. The kinetics of all these drugs are affected by renal and hepatic impairment.

Salicylate from aspirin is an important member of this intermediate group. Aspirin itself is very rapidly metabolised to salicylate in plasma as well as in liver with a half-life of 0.3 hr. Aspirin is, therefore, in effect a prodrug, and the longer term effects of aspirin dosage are due to salicylate. At lower doses, up to 400 mg of aspirin, the plasma half-life of salicylate is 3 hr but at higher doses such as those used in the treatment of arthritis, the apparent half-life increases to 13 hr or more, evidence of a saturable, capacity-limited, dose-dependent process in the elimination. The dose-dependent kinetics arises from the saturation of enzymes in the liver. This effect is a problem in the use of repeated high doses of aspirin as it leads to drug accumulation which may cause toxicity.

The slowly eliminated drugs, with half-lives greater than 12 hr, owe their persistence to several factors. High protein binding reduces the filtration of drug in the kidney; an example where this effect is prominent is warfarin with a half-life of 40 hr and a binding of over 99%. Another factor causing persistence is tubular re-absorption; this process is seen with phenobarbitone, (half-life 90 hr). Phenobarbitone is only partly excreted as metabolite.

Phenytoin (half-life 22 hr at lower doses) is almost entirely excreted as the hydroxy-metabolite; the formation of this substance in the liver is saturable in the therapeutic dose range, and so the overall half-life is dose-dependent and drug accumulation may occur with repeated doses.

Diazepam, having a half-life around 40 hr, owes its persistence to high protein binding of over 97%, to tubular re-absorption and to slow metabolism. Its first metabolite, desmethyl-diazepam, is even more persistent than the parent drug, with a half-life of 90 hr. The kinetics of elimination of diazepam is somewhat complex: with single doses, saturable effects can be detected; at higher doses, however, with repeated dosing, enzyme induction occurs and the saturable effect is more than cancelled out.

Another factor causing drug persistence is extensive distribution outside the plasma. This effect is seen with nortriptyline (half-life around 30 hr). Nortriptyline has a high protein binding of 95% and is strongly re-absorbed in the tubules. It is eliminated mainly as a hydroxy-metabolite which is only formed slowly due to the very extensive distribution of nortriptyline outside the plasma. The apparent volume of distribution of several hundred litres indicates strong extravascular binding of the drug.

Appendix 2. Metabolism and the M suffix. Nomenclature. Units

In *MacDope* each drug which is metabolized to any extent has metabolite(s) associated with it. A minimum number of metabolites sufficient to give an adequate representation has been used in the simulations. With a drug such as aspirin, salicylate is first formed and is then further metabolized to give at least four products. In order to avoid over elaborate calculations and printout, these metabolites have been condensed into two groups, one showing saturable kinetics and the other showing first-order kinetics.

Whenever possible, only one metabolite has been used and no drug has been given more than three. Even with three metabolites, the printed output becomes clumsy and the full range of substances is usually only required for urinary recovery studies. For most purposes it is sufficient to have information on the unchanged drug and on one main metabolite. The drug nomenclature has been arranged so that on prescribing the drug by its usual name, the printout whether graphical or tabular, only shows the concentrations of unchanged drug and of the principal metabolite. For urinary recovery studies where all the metabolites are required, in cases where the drug has more than one metabolite, the letter M is added to the name of the drug in the prescription. There is no space between the drug name and M.

For example 'DIAZEPAM' will give printouts for diazepam and the active metabolite desmethyl-diazepam; while 'DIAZEPAMM' gives additionally levels of the main excretion product, oxazepam conjugate. For urinary excretion studies with diazepam it is essential to use the suffix M; otherwise most of the drug elimination which, is as the second metabolite, would be missed.

With phenytoin there is only one metabolite and therefore there is no drug name in the model with a suffix M for this substance.

Metabolites may be formed by first-order or by saturable processes. The processes may be distinguished by examining the variation of urinary clearance of original drug via each metabolite with dose. Clearance of drug as a first order metabolite is independent of dose; clearance of drug as a saturable metabolite decreases as dose increases.

The table in Appendix 3 shows the type of metabolism for each drug in *MacDope*, indicating where the use of the M suffix is required for a full account of the metabolism of a drug.

Nomenclature

In general, the drug names in *MacDope* are conventional except for 'BENZPENICILLIN' for benzyl penicillin and 'FENTANYLCIT' for fentanyl citrate. In the program, names are coded as negative numbers for subsequent reference. This arrangement has caused some problems with names for metabolites since no two substances in the model can have the same number codes. As a result, some of the metabolite names are unusual; however, they have been kept as descriptive as possible.

Units

Throughout the program, all concentrations are expressed as mg/litre; times as hours. In order to avoid any confusion with '1', wherever 'litre' is involved in a unit, it has been spelt out in full. First-order rate constants are in reciprocal hours 'hr^{-1}', whereas volume rates are 'litre/hr'; saturable rate constants are mg/hr for the maximum rate and litre/mg for the Michaelis constant. The plasma binding parameters are in μmol/g for the capacity and litre/μmol for the binding constant; plasma protein concentrations are in g/dl.

The metabolite concentrations are all expressed in terms of the parent drug, the concentrations are not corrected for the change of molecular mass following the conversion of drug to metabolite.

Appendix 3. List of drugs and metabolites in *MacDope*, 1987

Table I. Drugs held on disc file.

Paracetamol*	Conjugate		
Salicylate*			
Lignocaine*+	Megx		
Nortriptyline*	Hydroxynt		
Salicylatem*	Salicylurate	Salacgluc	
AspirinM*	SalicylateM*	Salicylurate	Salacgluc
Aspirin*	Salicylate*		
Oxprenolol*	Metaboxp		
Ampicillin*	Metabampi		
Phenytoin*	Hydroxypt		
Phenobarbitone*	Hydroxpnbrtn		
Diazepam*	Desmediazepam		
Propranolol*	Hydroxyprop		
Valproate*	Oxovpa		
Digoxin*	Metabdigox		
Fentanylcit*	Metabfent		
Kanamycin*			
DigitoxinM*	Digoxin*	Metabdigox	Metabdigit
Sulphapyridine*	Acetylsp		
Sulphasalazine*	Sulphapyridine*	Acetylsp	
Warfarin*	Warfalcohol		
Theophylline*	Methylxanthine		
Cimetidine*	Cimsulphox		
Thiopentone*	Metabthio		
Benzpenicillin*	Metabbenzpen		
Indomethacin*	Metabindo		
Inulin*			
DiazepamM*	DesmediazepamM	Oxazconjugate	
LignocaineM*	MegxM	HDMA	
Digitoxin*	Digoxinnometab		
PropranololM*	Hydroxyprop	Propconj	Napoxlac
TheophyllineM*	Methylxanthine	Methylurate	
WarfarinM*	Warfalcohol	Hydroxwarf	
ValproateM*	Oxovpa	Metabvpa	
CimetidineM*	Cimetab	Cimsulphox	

*Indicates the parent drug.
+With lignocaine, it is essential to use the research mode with an iteration interval of 0.2 min and a previous factor of 1.

Table 2. Parent drugs, usual doses and target levels.

Drug	Usual dose and route	Use	Target level (mg/l)	Metab. type
	PO			
Ampicillin	1 g/6hr	Bacterial infection	2.5	1
Aspirin	600 mg/4hr	Rheumatic disease	120	M
Cimetidine	200 mg/8hr	Peptic ulceration	0.5	M
Diazepam	10 mg/12hr	Tranquillizer	0.4	M
Digitoxin	0.6 mg + 0.2 mg/24hr	Heart failure	0.02	M
Digoxin	0.5 mg + 0.2 mg/24hr	Heart failure	0.0015	1
Indomethacin	25 mg/8hr	Anti-inflammatory	0.6	1
Nortriptyline	50 mg/8hr	Anti-depressant	0.05 – 0.15	1
Oxprenolol	40 mg/8hr	Beta blocker	0.09	1
Paracetamol	500 mg/4hr	Anti-pyretic	4	1
Phenobarbitone	100 mg/8hr	Anti-convulsant	10	1
Phenytoin	100 mg/8hr	Anti-convulsant	8	1
Propanolol	80 mg/8hr	Beta blocker	0.07	M
Sulphasalazine	1 g/6hr	Ulcerative colitis	*	1a
Theophylline	120 mg/6hr	Bronchodilator	8 – 20	M
Valproate	200 mg/8hr	Anti-convulsant	50	M
Warfarin	40 mg + 6 mg/24hr	Anti-coagulant	1.4	M
	IM			
Benzpenicillin	400 mg/8hr	Bacterial infection	2.0	1
Kanamycin	250 mg/8hr	Bacterial infection	10.0	0
	IV			
Fentanylcit	0.15 mg	Narcotic analgesic	<	
Lignocaine	100 mg + 3.0 mg/min.	Cardiac arrythmia	2.0	M
Thiopentone	125 mg	Short acting anaesthetic	<	
Inulin	3 mg + 7 mg/hr	To measure GFR		0

In the 'Metab. type' column: 1, is one metabolite; M, means add M to the name of the drug in the prescription to get all the metabolites; 0 means no metabolites; 1a, sulphasalazine gives 2 metabolites on normal prescription.
*The target level is 40 mg/l total sulphapyridine including the acetyl derivative.
<The pharmacodynamic action zone, PDZ, option is best used in these cases.

Appendix 4. Changeable subject parameters

Subject factor list

Rate constants with dimensions of reciprocal hours, hr^{-1}, are first order. Volume factors marked with an asterisk can only be meaningfully changed before a run has taken place.

Subject factor	Value for 70 kg man (subject 1)
1. Gastric emptying rate (hr^{-1})	0.5
2. Gastric pH	3.5
3. Plasma albumin concentration (g/dl)	5
*4. Volume of plasma compartment (litre)	3
*5. Lipid compartment size (kg)	12
*6. Interstitial space compartment size (litre)	14
*7. Intracellular fluid compartment size (litre)	26
8. Hepatic enzymatic catabolic function, gives the ratio of hepatic function to that of a normal 70 kg man, allowing simulation of hepatic dysfunction	1.0
9. Glomerular filtration rate (litre/hr) (7.5 litre/hr corresponds to 125 ml/min)	7.5
10. Urine pH	5.5
11. Urine output (litre/hr)	0.066
12. Renal tubular excretory function, ratio to normal (gives the ratio of renal tubular excretory function to that of a normal 70 kg man)	1.0
*13. Intestinal volume (litre)	0.4
14. Plasma globulin 1 fraction concentration (g/dl)	1
15. Ratio of body weight to 70 kg (standard subject)	1
16. Intestinal emptying rate (hr^{-1})	0.25
17. Renal tubular re-absorptive function, ratio to normal	1
18. Plasma globulin 2 fraction concentration (g/dl)	1
19. Blood pH	7.4
*20. Volume of liver plasma compartment (litre)	1.2
*21. Gastric volume (litre) (the fasting mean residual gastric volume of the subject)	0.2
22. Intestinal pH, normal range 5.5 to 8.5; bottom of range	5.5
23. Rate of exchange of liver compartment with plasma (hr^{-1})	23.0

Subject parameters grouped according to function

These parameters are not altered during the setting of the drug parameters which is usually done with the normal young adult male (subject 1). It is useful to have their values when setting drug parameters and they are grouped below as in Appendix 5 for the drug parameters, with the values for subject 1 given in brackets.

A *Miscellaneous*

4 volume of plasma (excluding liver, 3 litre)
19 blood pH (7.4)
15 ratio of bodyweight to 70 kg (1.0)

B *Absorption*

1 gastric emptying rate (0.5 hr^{-1})
21 gastric volume (fasting, 0.2 litre)
2 pH of gastric absorbing surface (3.5)
13 volume of intestine (0.4 litre)
16 intestinal emptying rate (0.25 hr^{-1})
22 pH of intestinal absorbing surface, range of 3 units (5.5 – 8.5)

C *Protein binding*

3 plasma albumin concentration (5 g/dl)
14 plasma globulin 1 concentration (1 g/dl)
18 plasma globulin 2 concentration (1 g/dl)

D *Liver*

8 hepatic enzyme function, ratio to normal (1.0)
20 volume of liver compartment (1.2 litre)
23 rate of exchange of liver with plasma, liver (blood flow) (23 hr^{-1})

E *Distribution*

5 weight of lipid compartment (12 kg)
6 volume of interstitial compartment (14 litre)
7 volume of intracellular compartment (26 litre)

F *Kidney*

9 glomerular filtration rate (7.5 litre/hr)
10 urine pH (5.5)
11 urine output (0.066 litre/hr)
12 renal tubular excretary function, ratio to normal (1.0)
17 renal tubular re-absorptive function, ratio to normal (1.0)

Appendix 5. Changeable drug parameters

List of drug factors

1. pK_a (if a drug is neither acid nor base, it is entered as an acid, factor 17 = 1, with a pK_a of 10).
2. Absorption rate from an intramuscular deposit (hr^{-1}) — also used as the first rate constant for the pharmacodynamic zone (PDZ) (see factor 50).
3. Lipid to plasma partition ratio.
4. Lipid distribution rate (hr^{-1}).
5. Intra/extracellular distribution ratio.
6. Intracellular distribution rate from interstitial fluid (hr^{-1}).
7. Intestinal absorption rate of non-ionized drug (hr^{-1}).
8. (Portal transfer ratio in original model) not used, set at 1.0.
9. Renal tubular permeability (litre/hr, amount of solution in the non-ionized drug which is diffused back per hour).
10. Maximum plasma binding capacity (μmol/g) — this indicates how many μmol of drug can maximally be bound by 1 g of the plasma protein specified (see factor 38).
11. Plasma binding constant (litre/μmol) — inverse of plasma protein concentration at which 50% of a very small drug concentration would be bound.
12. Usual administration route (no longer used in *MacDope*, 0 = un-restricted, 1 = oral only, 2 = parenteral only).
13. Maximum usual dose (mg) — largest dose that is usually recommended for a 70 kg man.
14. Minimum usually available oral dose (mg) (set to 1, no longer used in *MacDope*).
15. Interstitial distribution ratio to unbound drug in plasma.
16. Interstitial distribution rate (hr^{-1}).
17. Index specifying whether the drug is acid (1) or base (0) — specify pK_a by factor 1 above.

18. Graph median scale (mg/litre) — this determines the scale on the graphical display.
19. 50% lethal level (mg/litre).
20. Rate of destruction by gastric acid (hr^{-1}).
21. Gastric absorption rate of un-ionized drug (hr^{-1}).
22. Toxic level (mg/litre).
23. V_{max} of saturable liver enzymes (mg/hr).
24. Liver enzyme dissociation constant, saturable metabolism (litre/mg).
25. Liver first order conversion rate (hr^{-1}).
26. V_{max} of the renal secretory mechanism (mg/hr).
27. Renal secretory dissociation constant (litre/mg).
28. V_{max} of renal re-absorptive mechanism (mg/hr).
29. Renal re-absorptive dissociation constant (litre/mg).
30. Hepatic enzyme induction factor (if the drug has no enzyme-inducing capacities this factor is 0).
31. Renal secretory inhibition factor, non-competitive.
32. Renal reabsorptive inhibition factor, non-competitive.
33. Diuretic factor.
34. First time in hours for drug release in the GI tract (hr, see factor 47).
35. Route for product of first-order liver metabolic process (see 25, 0 = product not described, 1 = pass metabolite to plasma).
36. Drug code of product of saturable liver metabolism (see 23,24).
37. Drug code of metabolic product, first order (see 25).
38. Type of plasma protein binding, if present. (A value 1, 2 or 3, depending upon the main plasma protein fraction to which this drug binds.)
39. Type of interaction with a liver enzyme system. (0 = no liver degradation, 1 = non-specific microsomal system, 2 – 9 = additional enzymes in pathways of intermediary metabolism.)
40. Renal secretory system type (0 = no active secretion, 1 = acid, 2 = base).
41. Renal re-absorptive system type (same as above).
42. Site of toxic and lethal reactions (0 = plasma, 7 = interstitial fluid, 8 = intracellular fluid).
43. Default display for graphs and tables (1 = every 15 min. for 3 hr, 2 = every 30 min. for 6 hr, 3 = every hr for 12 hr, 4 = every 2 h for 24 hr).
44. Molecular mass.
45. Route code for product of saturable liver metabolism (see 23,24; 0 = not described, 1 = pass metabolite to plasma).
46. Site for metabolism (0 = liver, 1 = general, – 1 = intestine for saturable metabolism; any other metabolic process simultaneous with intestinal metabolism has to be first order).
47. Second time for drug release (hr, see 34).
48. Proportion of oral dose going to release route governed by factor 47 (rest via route 34).
49. Default precision factor (0 is taken to indicate the maximum value, 50).
50. Second rate constant for PDZ; when the PDZ option is not in use it is set equal to factor 2.

51. Drug serial code number.
52. Drug name code (used by system to recognise drug name, it is unique for each drug, calculated by adding codes for the letters in the drug name. Any currently unacceptable name code is given automatically as a negative error number if you try to prescribe it.)

Drug factors grouped according to function

A *Miscellaneous*

1 pK_a.
17 Acid–base index (1 = acid, 0 = base).
19 Lethal level.
22 Toxic level.
42 Site of toxic and lethal reactions (0 = plasma, 7 = interstitial, 8 = intracellular).
12 Usual administration route (0 = unrestricted, 1 = oral only, 2 = parenteral only).
13 Maximum dose.
18 Graph median scale.
43 Default display table (1 = every 15 min. for 3 hours; 2 = 30 min. for 6 hours; 3 = 1 hour for 12 hours; 4 = 2 hours for 24 hours).
44 Molecular mass.
49 Default precision factor; 0 is taken as the maximum value of 50.
51 Serial code number.
52 Drug name code.

B *Absorption*

2 Rate from IM deposit (or first rate constant for PDZ see Section 4.7; when PDZ is not in use, 50 and 2 are set equal).
7 Rate from intestine.
21 Rate from stomach.
34 Release time in GI tract.
47 Second time for release.
48 Proportion going to 47.
20 Rate of destruction by gastric acid.

C *Protein binding in plasma*

10 Capacity.
11 Binding Constant.
38 Type of binding (1, 2 or 3).

D *Liver, metabolism*

23 V_{max}, enzyme.
24 Dissociation constant, enzyme.
36 Code name, saturable metabolite.
45 Route code, saturable (0 = not described, 1 = pass to plasma).
25 First-order rate.

37 Code name, first-order metabolite.
35 Route code, first order (as for 45).
30 Enzyme induction factor.
39 Type of enzyme (1 = non-specific, other numbers to 10 may be used to define specific systems).
46 Site for metabolism (0 = liver, 1 = general, −1 = intestinal).

E *Distribution*

lipid	4 rate,	3 ratio
interstitial	16 rate,	15 ratio
intracellular	6 rate,	5 ratio

F *Kidney*

9 Renal tubular permeability.
33 Diuretic factor
Secretion: 26 V_{max}; 27 constant; 31 inhibition factor; 40 type (0 = no active secretion, 1 = weak acid, 2 = weak base).
Reabsorption: 28 V_{max}; 29 constant; 32 inhibition factor; 41 type (as for 40).

G *Pharmacodynamic zone (PDZ)*

2 Transfer rate, plasma to PDZ.
50 Transfer rate, PDZ to plasma; when the PDZ option is not in use, 50 is set equal to 2 (rate from intramuscular deposit).

H *Unused parameters*

8 was used for first pass effect, now set at 1 for all substances.
14 was used for minimum available dose, now set at 1 for all drugs.

Appendix 6. Setting up a new drug in *MacDope*

In this appendix, drug parameters (factors) are referred to by number, dp1, dp2 etc. Appendix 5 gives lists of parameters in numerical sequence and then in groups according to their function.

Only general comments are offered. Each new drug presents its own set of problems. It is often a prolonged operation to produce a satisfactory set of drug parameters (factors) and it is better to have a series of short sessions to achieve the simulation of experimental data rather than attempting it in one long session. A great deal can be learned from studying the parameters for drugs already stored on the disc file. Complete sets of parameters are obtained as described in Section 3.5.

The sequence of procedures suggested is as follows.

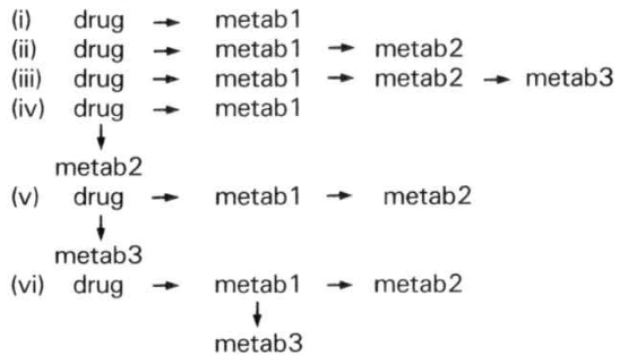
1. Carry out a literature search and a study of monographs on the drug to be set up, in the Extra Pharmacopoeia, Martindale. From this search, you should obtain values for the pK_a, for the protein binding at effective plasma concentrations, for the plasma levels or the doses which produce lethal and toxic effects, and the solubilities in lipid solvents. Ideally target

sets of plasma level, time data for IV, PO and IM dosage should also be obtained though with some drugs there may only be PO data available.

Information about the metabolism and the urinary excretion patterns for unchanged drug and metabolites following dosage by different routes and for the total recovery of drug plus metabolites from oral dosing should also be sought. Plasma levels of metabolites, if available, should be noted. The volume of distribution for the drug is helpful.

2. The information on metabolism should be grouped to give a metabolic scheme of minimum complexity which will account for the behaviour of the drug. The maximum number of metabolites should be three, and in cases where the metabolism is more complex than this (see Section 4.2), metabolites will have to be grouped together.

   In *MacDope*, two metabolites may be formed simultaneously from the parent, one by a first-order process and one by a saturable process. If there is no experimental evidence of saturation, dp23 (drug parameter or factor 23, maximum metabolic rate in mg/litre) is set to a high value so that the route becomes effectively first order. Consecutive metabolites are set up in chains; in some cases such as aspirin (Section 4.2), the first metabolite, salicylate, gives the branching. The possible metabolic schemes in *MacDope* are:



   If one metabolite is sufficient for the representation, scheme (i) is used. With a few drugs such as kanamycin, metabolism is negligible and no scheme is required.

3. The first computer step is to set up the metabolic sequence and to store it on the drug file with the names for the new drug and for its metabolites, without modifying parameters other than those required to establish the sequence. Since this will result in modifications to the drug data file, it is advisable to take a back up copy of this before attempting to store descriptions of new substances.

   All the computer work should be made in the research mode (Section 4.1) so that drug parameter changes may be carried forward from one run to another. Use should be made of the store/backtrack facility (section 3.2) in order to eliminate repetitive choice of subject and prescriptions.

   It is best to choose substances already on the disc file with properties

resembling those of the substances to be set up. Take as an example the simplest scheme, sequence (i).

Start by setting up the substance at the end of the chain, metab1. Prescribe some substance already on the disc file (metabolites as well as parent drugs may be prescribed), carry out the standard run by answering '2. Continue'. As this substance is to be at the end of a chain, no further metabolism is required, so set dp23, dp24 and dp25 to zero if they have non-zero values. To alter drug factors see Section 3.5

This substance is now stored on the disc file by entering '1. Change', '3. Store/Backtrack' and '3' to store the drug details on the disc file. You are then asked to:

```
Enter number of drug to be dumped
```

The numbers of the substances are given in the list under the graphical display. Type in the number of the substance for which you have been adapting the drug factors to be appropriate for your metab1 (e.g. '1' if it is the prescribed drug you are dumping).

```
This is <drug name>, enter new name to be used
```

and at this stage, an appropriate new name is entered. The program response then gives the automatically calculated drug code as a negative number; note this as it is required for the precursor in the chain. The next question asks for symptoms to be associated with toxicity. Be ready with the reply and enter an appropriate message. You are then asked:

```
Is drug to appear as a main entry
```

The reply is generally 'no' for a metabolite, 'yes' for a parent drug. A final question may or may not be asked. If on first entering a new substance, the question

```
Drug already stored. Is it to be overwritten?
```

appears, the answer should be 'no' because it means that there is already a substance on the disc file with the same code number. Unless the answer 'no' is given, it would be overwritten. If this question does appear, a new name has to be devised and the storing process is repeated starting with '1. Change', then '3. Store/Backtrack' etc. If the question does not appear, there is no substance on the disc file with this code number and a message

```
Drug added to file
```

is given.

The next substance to be stored is the main drug. Again prescribe a substance present on the drug file, use 'Continue' to give it the standard run and, if the connection of drug to metab1 is first order, enter the drug code number of metab1, noted on storing metab1, into dp37 for the parent drug, set dp35 to 1.0 to give a printout of concentrations for metab1 and set dp25 to some value, say 0.5 hr^{-1}, to give some formation of metab1. If the connection is by saturable metabolism, set dp36 to the code number of metab1, dp45 to 1.0 and assign values to dp23

and dp24 to give some formation of metab1, say 10.0 and 0.05. Now store the main (parent) drug parameters as for metab1, ensuring that there is no substance with the same code number as the parent drug.

Having stored both sets of parameters, choose the main option 'Restart', answer 'yes' to the question about resetting drug parameters and prescribe the new drug. Give it a standard run using the 'Continue' option to check that the loading is working correctly.

The procedure for the more extensive metabolic schemes is simply an extension of that described. Always start with the end substance of the longer chain so that the code number for this substance is found and may be entered into the parameters for its precursor. Always ensure that the end substance of the chain has zero values for dp23, dp24 and dp25 unless there is a reason for some unspecified further metabolism of this substance.

The procedure described assumes that metabolism is in the liver; however, dp46 permits metabolism to be sited generally, as with aspirin, by giving dp46 the value 1. If dp46 is given a value −1 metabolism by the saturable route occurs in the intestine. The default value of zero for dp46 gives liver metabolism.

4. At this stage, no simulation has been made. Print out all the parameters for drug and metabolites by entering the command '1/7' followed by '1' for the parent drug and '1/7' followed by '2' for the metabolite (see Section 3.5). The first step in the simulation is to set dp1 (pK_a), dp17 (acid − base index) and dp44 (molecular mass) to known values; dp49, the precision factor for numerical integration is set at the value of zero which then gives a maximum pecision factor of 50. This value may have to be reduced later if there are calculation difficulties (see Section 4.8).

   The protein binding parameters dp10, dp11 and dp38 are set at values which on short runs give approximately correct values for the drug and for the metabolites (experimental values for the metabolites may not be available and may have to be inferred).

   Toxic and lethal levels and site of toxicity should be entered with dp22, dp19 and dp42. The site is generally taken as plasma with dp42 equal to zero.

   Having altered drug and metabolite parameters to take in these values, it is advisable to store them on the disc file. Now the question

   Drug already stored. Is it to be overwritten?

   will appear in each case, to which the answer is 'yes'.

5. A first attempt at fitting experimental data is made with plasma data following IV dose. If such data are not available the procedure described here will have to be combined with step 9 using oral dose data.

   The balance between distribution, metabolic rate and excretion has to be struck so as to simulate the data. The distribution to lipid may be assessed from relative solubility in lipid solvents. The octanol/water partition ratio is normally much higher than the bodyfat/plasma ratio. Partition into bodyfat is more nearly represented, according to Brodie, by the

peanut oil/water partition coefficient. Direct studies in the dog indicate a bodyfat/plasma ratio for pentobarbitone of 1.1. The value of dp3 (the bodyfat/plasma ratio for a drug) may be assessed relative to pentobarbitone by the ratio of the solubility of the drug in a lipid solvent to the solubility of pentobarbitone in the same solvent. Pentobarbitone solubilities are 25% in chloroform, 20% in diethyl ether and 22% in ethanol. The rate constant for distribution to lipid, dp4, may be given a general value of 0.3 hr^{-1}.

The distribution ratio to interstitial space, dp15, will generally be 1.0; however, if there is extensive binding of the drug outside the plasma resulting in a high volume of distribution, dp15 may have to be larger. The value of dp16, the rate constant for transfer to interstitial space tends to govern the shape of the IV log(plasma concentration) − time curve. Lower values of dp16 give curved, biphasic log(C) − time plots; higher values give linear plots.

The distribution from interstitial to intracellular fluid may be small for more polar drugs; for lipophilic drugs particularly those acting on the central nervous system, dp5, the appropriate ratio, will have a value governed by the overall volume of distribution. The rate constant for distribution to the intracellular fluid, dp6, may be taken as intermediate between dp4 and dp16.

After distribution, the main factors governing plasma levels following IV dose are the metabolic rate constants, dp23 and dp24 (saturable) and dp25 (first order); the renal tubular permeability, dp9, which governs diffusion back in the kidney tubules, and dp26 and dp27 which control active secretion by the tubules. These tubule parameters act in opposite senses: if dp9 is given a value, dp26 and dp27 should be zero; if dp26 and dp27 have values, dp9 should be zero; when dp26 and dp27 are non-zero, dp40 is set at 1 for acid, 2 for base and dp41 is set to the same value.

In the first phase, the setting of the metabolism kinetic parameters has to be inferred from the amounts of metabolite(s) formed. For a first order metabolite, dp25 equal to 8.0 hr^{-1} gives a rapid formation while dp25 equal to 0.1 hr^{-1} is slow. For a saturable metabolite, dp23 is the maximum rate of metabolism in mg/hr and dp24 is the reciprocal of the plasma concentration which gives half this rate. The product of dp23 multiplied by dp24 governs the rate of metabolism at levels below those giving the maximum rate.

Using these parameters and modifying them appropriately, a series of runs are made to give a simulation of the target experimental data.

6. When urinary excretion data following IV dose are available, the metabolic rate and excretion parameters are next adjusted to fit these results. If IV data are not available, PO results have to be used. Urinary recoveries may be assessed in *MacDope* by making runs with long intervals (8, 12 or 24 hours) between results. The urine concentrations are mean values over the preceding time interval and so no loss of accuracy is involved in using long intervals (section 4.2). The total recoveries of drug and

metabolites are worked out and compared with experimental values. If too much unchanged drug is excreted, dp9 is increased to turn it back at the tubules; the relative proportions of the metabolites are adjusted by using the kinetic rate constants for their formation.

7. When there is information about plasma levels of metabolites, dp9 for a metabolite may be used to increase plasma levels, while dp26 and dp27 may be used to decrease these levels. Other adjustments to the metabolite parameters should be made at this stage.
8. The IV plasma and excretion levels are cycled to reach a suitable compromise. At this stage, or at the end of each simulation session, the parameters for drug and metabolites should be stored on the disc file.
9. If IV fitting has been achieved, the PO simulation with oral dose plasma concentration – time data should not be too difficult. If IV data are not available, the procedures outlined in steps 5, 6, 7 and 9 have to be combined with this step (9).

   The important oral dose parameters are dp21, the rate constant for the absorption of non-ionized drug from the stomach and dp7, the rate constant for absorption from the intestine. The stomach pH is a subject parameter, sp2 (equal to 3.5 for the normal subject), while the pH of the intestine, sp22, is a range of three units, 5.5 – 8.5 for the normal subject. This range accommodates the experimental fact that anionic drugs such as phenobarbitone are well absorbed in the intestine.

   The relative values of dp21 and dp7 govern the time of the peak plasma concentration; if this is soon after dosage dp21 will be high, say 1 to 5 hr^{-1}. The dp7 parameter controls the total urinary recovery of drug and metabolites; if this recovery is ~80% or more dp7 will probably be 0.5 hr^{-1} or more. Low values of dp21 and dp7 result in incomplete absorption.
10. Having settled a generally suitable set of parameters for the oral plasma data, the urinary excretion results following oral dose are considered. Drug parameter dp7 is adjusted to give correct total recovery and the metabolism kinetic parameters dp23, dp24, dp25 are adjusted to give correct proportions of metabolites; dp9 is used to give the required excretion of unchanged drug.
11. After alterations to simulate the PO data, it is necessary to go back to the IV data (if it exists) to achieve a compromise between IV and oral doses.
12. When IM dose data are available, dp2, the absorption rate constant from IM deposit, is adjusted to fit the data. Before storing, dp50 is set equal to dp2 for all substances, drug and metabolites (section 4.7).
13. If sustained release PO data are available, a fit is achieved by using dp34, dp47 and dp48 (section 4.6). However these values are only noted and are not stored on the disc file unless the simulation is to be for sustained release oral data only.
14. The parameters not yet mentioned may be divided into three groups. In the first group, values have not been changed for any of the drugs at

present on the *MacDope* drug file and so it is unlikely that they need to be considered further.

dp8 formerly used for first pass effect, now set to 1.0 for all drugs.
dp12 usual administration route, set to zero for unrestricted.
dp15 minimum available dose, set to 1.0 for all substances.
dp28 tubular re-absorption, V_{max}, set to zero.
dp29 tubular re-absorption, rate constant, set to zero.
dp32 inhibition factor, renal re-absorption, set to zero.
dp51 serial code number, not used.
dp52 drug code number, set in the computer.

The second group of parameters may require values in particular circumstances.

dp20 rate constant for destruction by gastric acid, required for most of the penicillins.
dp30 enzyme induction factor, required for phenobarbitone and diazepam, values around 0.01.
dp33 diuretic factor, required with a few drugs.
dp39 type of enzyme interaction, normally 1.0, other values may be used to avoid inhibition of metabolism of one drug by another.

The third group do require values but do not affect the calculations.

dp13 maximum dose; the value triggers off a warning message when the dose is substantially exceeded.
dp18 graph median scale. This parameter governs the semi-logarithmic scale used for the graphical presentation of results; it is best set by making some short graphical runs. If possible, use the same value for the drug and for all its metabolites.
dp43 default display, this value is set at 1 for drugs of short half-life, 4 for persistent drugs and 2 or 3 for intermediate drugs; the value governs the length and results interval for the standard run with the drug. It should be set at the same value for the drug and for the metabolites.
dp49 precision factor, normally zero, giving the maximum value of 50. Lower values may have to be set if calculation difficulties occur. Particularly for the IM route, the precision factor should be set at 1.0, this may be done in the dialogue of the research mode. Leave it at zero unless there are calculation problems with IV and oral routes. dp49 should be set at the same values for drug and for metabolites.

The development of parameters is probably best spread over a period with a number of sessions, re-storing the parameters at each session. The achievement of final values is a remote target and the designer of a new set of drug parameters needs to be ready to modify them as further information becomes available.