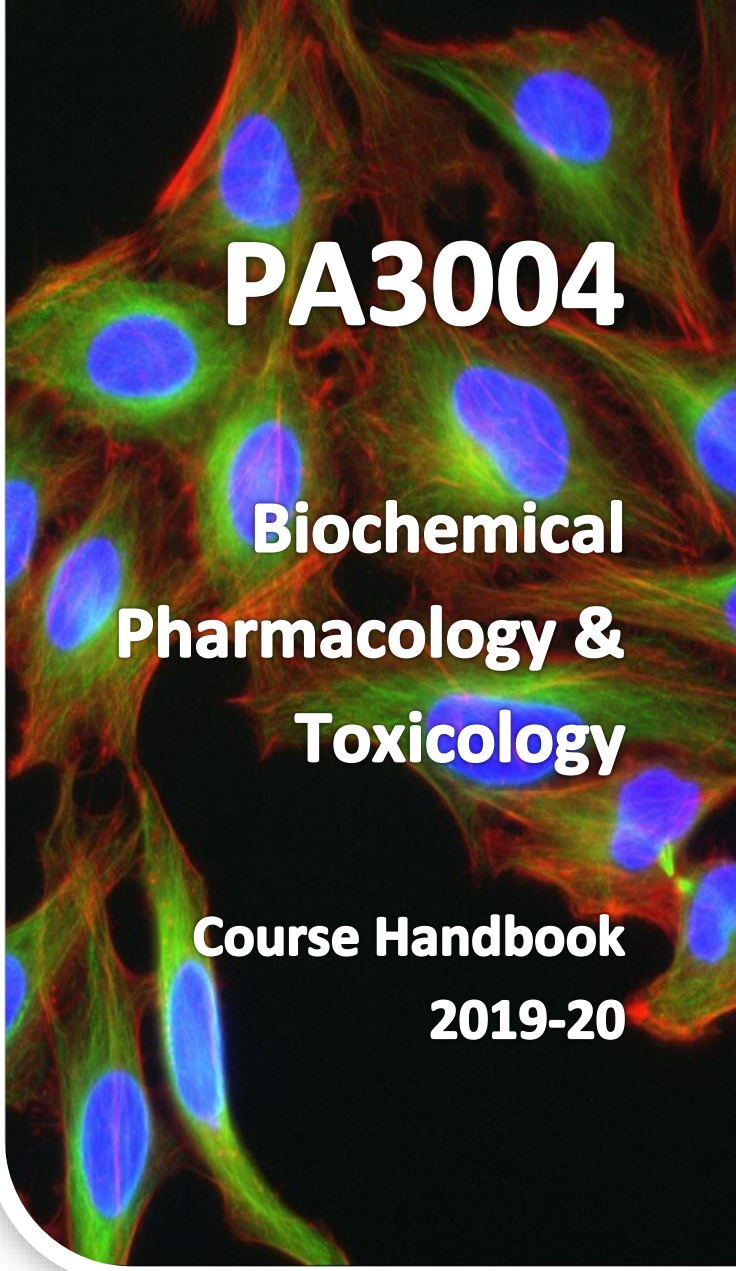
School Of Medicine, Medical Sciences & Nutrition



PA3004

Biochemical Pharmacology & Toxicology

Course Handbook
2019-20

UNIVERSITY OF ABERDEEN

Contents

Cover image:

Confocal micrograph of fluorescently labelled HeLa cells.
Nuclei are labelled in blue, tubulin in green and actin fibres in red.

Courtesy of:

Kevin Mackenzie
Microscopy and Histology Core Facility
Institute of Medical Sciences
University of Aberdeen
http://www.abdn.ac.uk/ims/microscopy-histology

Course Summary

This course covers an introduction to ADME, drug metabolism, pharmacokinetics, an introduction to toxicology, carcinogenesis, mutagenesis and biochemical mechanisms of drug action. It also covers the role of the immune system in toxicological context.

Course Co-ordinator: Dr Steve Tucker (437491; **s.j.tucker@abdn.ac.uk**)

Course Aims & Learning Outcomes

The students will be conversant with the principles of drug absorption, distribution, metabolism and excretion, pharmacokinetics, toxicology and some aspects of clinical and biochemical pharmacology. The course will close with 2 special topics applying the principles of the course to selected body systems and their specific pharmacological manipulation. The approach will be mechanism-based and will include problem solving and practicals to illustrate and reinforce the principles covered in the lectures.

Course Teaching Staff

Course Co-ordinator(s):

Dr S. Tucker (ST)

Other Staff:

Professor G I Murray (GIM)

Prof G Nixon (GFN)

Dr D Scott (DS)

Dr H Wilson (HW)

Professor H M Wallace (HMW)

Assessments & Examinations

Students are expected to attend the lectures, practicals and tutorials. Any period of absence must be covered by a medical certificate in accordance with University regulations (see Notice Boards). Practical reports and assignments must be handed in for marking by the dates indicated. A 100% attendance is required at practicals. If assignments are not handed in on time, e.g. more than 1 week late without good cause, it will not be marked.

The distribution of assessments is as follows:

1. Degree written exam (3h paper with 1 compulsory question + 2 out of 6 further questions) = 70% of CGS mark for this course.

2. Practical reports (3) = 30% of CGS mark for this course.

Past papers for PA3004 are available from the exam database.

Class Representatives

We value students' opinions in regard to enhancing the quality of teaching and its delivery; therefore in conjunction with the Students' Association we support the Class Representative system.

In the School of Medicine, Medical Sciences & Nutrition we operate a system of course representatives, who are elected from within each course. Any student registered within a course that wishes to represent a given group of students can be a class representative.

What will it involve?
It will involve speaking to your fellow students about the course you represent. This can include any comments that they may have. You will attend a Staff-Student Liaison Committee and you should represent the views and concerns of the students within this meeting. As a representative you will also be able to contribute to the agenda. You will then feedback to the students after this meeting with any actions that are being taken.

Training
Training for class representatives will be run by the Students Association. Training will take place within each half-session. For more information about the Class representative system visit **www.ausa.org.uk** or email the VP Education & Employability **vped@abdn.ac.uk**. Class representatives are also eligible to undertake the STAR (Students Taking Active Roles) Award with further information about this co-curricular award being available at: **www.abdn.ac.uk/careers**.

Problems with Coursework

If students have difficulties with any part of the course that they cannot cope with alone they should notify the course coordinator immediately. If the problem relates to the subject matter general advice would be to contact the member of staff who is teaching that part of the course. Students with registered disabilities should contact Mrs Jenna Reynolds (**medsci@abdn.ac.uk**) in the Medical Sciences Office (based in the Polwarth Building, Foresterhill), or Mrs Sheila Jones (**s.jones@abdn.ac.uk**) in the Old Aberdeen office associated with the teaching laboratories, to ensure that the appropriate facilities have been made available. Otherwise, you are strongly encouraged to contact any of the following as you see appropriate:

- Course student representatives
- Course co-ordinator
- Convenor of the Medical Sciences Staff/Student Liaison Committee (Professor Gordon McEwan)
- Medical Sciences Disabilities Co-ordinator (Dr Derryck Shewan)

All staff are based at Foresterhill and we strongly encourage the use of email or telephone the Medical Sciences Office. You may have a wasted journey travelling to Foresterhill only to find staff unavailable.

If a course has been completed and students are no longer on campus (i.e. work from second semester during the summer vacation), coursework will be kept until the end of Freshers' Week, during the new academic year. After that point, unclaimed student work will be securely destroyed.

Course Reading List

Books recommended for purchase

1. Rang & Dale; Pharmacology (eighth edition).
2. Golan *et al*.; Principles of pharmacology (third edition).
3. Harvey; Lippincott's Illustrated Reviews: Pharmacology (fifth edition).
4. Gibson & Skett; Introduction to Drug Metabolism (third edition).
5. Hedaya; Basic Pharmacokinetics (second edition).
6. Birkett; Pharmacokinetics Made Easy.
7. Timbrell; Principles of Biochemical Toxicology (third edition).
8. Clark and Smith; An Introduction to Pharmacokinetics (second edition). We have lots of these available for consultation if required.

Other books that may be useful and that are available at The Sir Duncan Rice & Medical School Library (Heavy Demand)

1. Tozer & Rowland; Introduction to Pharmacokinetics & pharmacodynamics.
2. Pratt & Taylor; Principles of Drug Action (third edition).
3. Casarett & Doull; Toxicology (fifth edition).
4. Lu; Basic Toxicology (seventh edition).

Lecture Synopsis

Lecture 1: Introduction to the course and what is biochemical pharmacology? - Dr S Tucker

Introduction to the course and the subject material that will be covered. There will also be an outline of the assessment criteria for the course, and the various exercises that constitute it. The lecture will finish with an introduction to what biochemical pharmacology is, how it will be explored through the course and why it is a key area of study.

Lecture 2-3: Absorption, distribution and excretion of drugs (ADE) - Dr S Tucker

Revision of pKa, partition coefficient, Henderson Hasselbach equation. Passage of drugs across membranes, diffusion, active transport, facilitated diffusion. Enteral administration, factors affecting absorption, including worked example. Non-parental routes of administration. Distribution of drugs, plasma protein binding, tissue reservoirs. Excretion of drugs in urine - tubular reabsorption, active secretion. Biliary secretion of drugs. Enterohepatic circulation.

Lecture 4: Pharmacokinetics I: Introduction - Dr S Tucker

Introduction to the subject of pharmacokinetics. Advice on studying the subject and also definitions of the primary and secondary pharmacokinetic variables.

Lecture 5: Pharmacokinetics II: Single dose IV kinetics - Dr S Tucker

The plasma concentration v time graph. Linear and semi-logarithmic plots, natural logarithms and exponential relationships. Zero order and first order processes. Calculating IV pharmacokinetic variables: plasma concentration at time 0, volume of distribution, elimination rate constant, elimination half time, clearance, AUC and the trapezoidal method.

Lecture 6: Pharmacokinetics III: Single extravascular dose kinetics - Dr S Tucker

The phases of oral pharmacokinetics; absorption vs elimination. Calculating oral pharmacokinetic elimination parameters. The use of residuals to calculate kabs and absorption t1/2. Bioavailability (absolute and relative), bioequivalence and factors that influence these.

Lecture 7: Pharmacokinetics IV: IV infusion and renal clearance - Dr S Tucker

The concept of infusion and the zero order nature of the infusion rate (Ko). The balance between Ko and elimination determines equilibrium/steady state. Calculation of infusion parameters: steady state concentration, time to steady state, loading dose. The effect of changing these parameters in isolation. Post infusion data and how to determine elimination parameters from it.

The concept of renal clearance and the different ways drugs can be handled by the renal system (filtration, secretion, reabsorption). Calculating renal clearance from urine and plasma sampling. Conclusions that can be drawn from renal parameters. Measurement of glomerular filtration rate (GFR) using creatinine handling data, and the relevance of this to renal clearance measures.

Lecture 8: Pharmacokinetics V: Multiple dose kinetics - Dr S Tucker

The concept of multiple doses and accumulation towards therapeutically relevant steady state. Calculation of IV parameters: $Cp_{max\ ss}$, $Cp_{min\ ss}$ and $Cp_{average\ ss}$ and the importance of scaling oral data using F. Time to steady state, and the role of half-life and dosing frequency. Loading doses and their role in rapid achievement of therapeutically relevant concentrations.

Lecture 9: Phase I metabolism (oxidation) - Dr S Tucker

Consequences and need for drug metabolism. Site of drug oxidation - liver (microsomes, mitochondria, cytosol). Microsomal oxidations - cytochrome P450-dependent oxidations, co-oxidation by PG synthetase, lipoxygenases. Non-microsomal oxidations - amine oxidases, alcohol and aldehyde oxidases, dehalogenation and purine oxidation. Enzymology - catalytic activity, co-factor requirements, substrate specificity, inhibitors. Relevance of drug oxidation to bioactivation and detoxification.

Lecture 10: Cytochrome P450 - Dr S Tucker

Catalytic cycle of cytochrome P450. Cytochrome P450 isozymes, mammalian isozymes, substrate specificity, implications for therapeutic effect and toxicity.

Lecture 11: Induction/inhibition of CYP450 - Dr S Tucker

Mechanisms of cytochrome P450 induction, receptor mediated (Ah, PXR, PPAR), species differences. Inhibition of cytochrome P450 by destruction of P450, formation of inactive complexes. Competition for active site of P450. Induction/inhibition of other drug metabolising enzymes.

Lecture 12: Phase II metabolism (conjugation) - Dr S Tucker

Role of phase II reactions in drug metabolism. Subcellular distribution of enzymes. Conjugation reactions - glucuronidation, sulphation, glutathione conjugation, acetylation, methylation, aminoacid conjugation. Enzymology - catalytic activity, co-factor requirements, substrate requirements, substrate specificity, inhibitors. Genetic polymorphisms - glucuronidation, acetylation. Glutathione transferases. Pharmacological and biological aspects of drug conjugation.

Lecture 13: Phase III metabolism (transporters) - Professor H Wallace

An overview of the basics of transport including drugs and nutrients and the importance of transport in relation to ADME and drug metabolising processes.

Lecture 14: Pharmacogenetics - Dr S Tucker

What is pharmacogenetics? What influence does genetic make-up have on drug metabolism and drug effects? Polymorphisms in the population. Case studies of aldehyde dehydrogenase, N-acetyl transferase and others. Polymorphic susceptibility based on endogenous role of enzymes.

Lecture 15: Introduction to toxicology/In vivo/In vitro toxicology - Professor H Wallace

Introduction to toxicology and its importance relating to human health. The drug discovery/development process will be outlined, with reference to regulatory aspects of drug development. The advantages and disadvantages of using In vitro and in vivo models to investigate and demonstrate toxicological profiles of poisons and drugs will be discussed. How are these very different models used to explore toxicology of substances and drugs.

Lecture 16: Pathology of drug toxicity - Professor G I Murray

Introductory pathology. Liver pathology - acute and chronic. Acute and chronic kidney, lung, GI pathology, illustrated with examples of appropriate histology.

Lecture 17: Carcinogenesis/mutagenesis - Professor H Wallace

Basic mechanisms of carcinogenesis and mutagenesis. The multistep process of carcinogenesis. Tests used to determine if a compound is a either a carcinogen or a mutagen.

Lecture 18: Target organ toxicity - Dr S Tucker

Concepts and reasons for site-specific toxicity. General mechanisms of nephro- and hepatotoxicity, illustrated with appropriate examples. Pulmonary toxicology - anatomy, response of lung to injury, fibrosis, emphysema, e.gs ozone, silica, asbestos, paraquat, bleomycin, toxic furans.

Lecture 19-20: Immunity – a controlled Toxicity System I & II - Dr H Wilson

The immune system is a sophisticated toxic killing machine. These two teaching sessions will look at the role of the Immune system one of the main defence systems of the body. How the cells of the adaptive and innate immune systems interact and communicate to protect us.

The recognition of non-self or altered self by the immune system protects us form overwhelming infection and cancer.

Lecture 21- Immune mediated toxicity –Hypersensitivity - Dr H Wilson

The immune system is tuned to destroy pathogens and protect us from infection, however these immune responses can also cause injury to the host. When immune responses go wrong and there is excessive inflammation or undesirable reactions caused by the immune system (hypersensitivity), it can have very serious consequences. This lecture will look at the hypersensitivity reactions particularly those that may lead to allergy and autoimmunity pathologies.

Lecture 22-23: Special topic I: Respiratory pharmacology - Professor G Nixon

The concepts and material of the course will be examined in the context of the respiratory system with focus on airway diseases and their treatment e.g. asthma, COPD.

Lecture 24-25: Special topic II: Renal pharmacology - Dr D Scott

Renal Pharmacology I

This lecture will begin by briefly reviewing the major functions of the kidneys that are important for drug handling in the body and those that can be targeted to achieve therapeutic outcomes. We will then review the major class of drugs that affect renal function - the diuretics. Topics to be covered include: diuretics acting on the proximal tubule, loop diuretics, diuretics acting on the distal tubule (e.g. thiazides, aldosterone antagonists), osmotic diuretics.

Useful reading: Rang *et al*. (2007), 6th Ed., Chapter 24 The Kidney.

Renal Pharmacology II

This lecture will review agents that can increase or decrease urinary pH and drugs that can alter the excretion of organic molecules. We shall also examine the various drugs that are used to treat various renal conditions such as renal failure i.e. targeting problems such as hyperkalaemia and hyperphosphataemia, with a brief introduction to aspects of cardiovascular drugs that may also be of use in such situations. Finally, we shall review drugs used in urinary tract disorders i.e. agents that may aid urination or prevent incontinence.

Useful reading: Rang *et al*. (2007), 6th Ed., Chapter 24 The Kidney.

Practical/Lab/Tutorial Work

Formative

These assessments do not count towards the final course mark but are designed to reinforce and apply the materials covered in lectures. As they are integrated with other aspects of the course, they are compulsory and failure to complete these, will deem you at risk of being withdrawn from the course.

There will be timetabled tutorial sessions studying various elements of the course. In addition, some computer-aided learning (CAL) exercises are available for reinforcing the drug metabolism and pharmacokinetic sections of the course. These are designed for students to work through in their own time and are very useful exercises. As well as developing understanding of the concepts, these exercises will help students direct their own learning, an important aspect of learning moving towards the latter stages of their degree programme. Details of these will be released through MyAberdeen. There will also be additional practice problems and exercises released through the course and a formative MCQ test at the end of term designed to test student knowledge and understanding of all aspects of the course.

Summative

These assessments do count towards the final course mark and are designed to assess practical skills and understanding of the lecture material.

There will be 3 practical sessions:

1. pKa determination
2. *In vitro* metabolism
3. Pharmacokinetics

These will each require a form of report to be completed after the practical session, details will be given in class.

Laboratory Work

The details of the practicals are given in the Practical Manuals (on MyAberdeen). Please ensure that you bring clean white laboratory coats to the practical and all students must read and observe the Notes on Behaviour and Safety in Laboratories enclosed with the laboratory manual.

Laboratory reports should be prepared with the aid of a word-processor and the data analysed with the aid of appropriate software packages.

The practical work required in this course may present difficulties to students with special educational needs. For such students, alternative arrangements will be made. Any student with special needs should make these known to the Course Co-ordinator when registering for the class and should then also discuss their needs with the Disabilities Co-ordinator, to ensure that they have the best possible outcome.

University Policies

Students are asked to make themselves familiar with the information on key institutional policies which been made available within MyAberdeen (**https://abdn.blackboard.com/bbcswebdav/institution/Policies**). These policies are relevant to all students and will be useful to you throughout your studies. They contain important information and address issues such as what to do if you are absent, how to raise an appeal or a complaint and indicate how seriously the University takes your feedback.

These institutional policies should be read in conjunction with this programme and/or course handbook, in which School and College specific policies are detailed. Further information can be found on the **University[1]s Infohub webpage** or by visiting the Infohub.

The information included in the institutional area for 2019/20 includes the following:

- Absence
- Appeals & Complaints
- Student Discipline
- Class Certificates
- MyAberdeen
- Originality Checking
- Feedback
- Communication
- Graduate Attributes
- The Co-Curriculum

Medical Sciences Common Grading Scale

Grade	Grade Point	Category	Honours Class	Description
A1	22	Excellent	First	• Outstanding ability and critical thought • Evidence of extensive reading • Superior understanding • The best performance that can be expected from a student at this level
A2	21			
A3	20			
A4	19			
A5	18			
B1	17	Very Good	Upper Second	• Able to argue logically and organise answers well • Shows a thorough grasp of concepts • Good use of examples to illustrate points and justify arguments • Evidence of reading and wide appreciation of subject
B2	16			
B3	15			
C1	14	Good	Lower Second	• Repetition of lecture notes without evidence of further appreciation of subject • Lacking illustrative examples and originality • Basic level of understanding
C2	13			
C3	12			
D1	11	Pass	Third	• Limited ability to argue logically and organise answers • Failure to develop or illustrate points • The minimum level of performance required for a student to be awarded a pass
D2	10			
D3	9			
E1	8	Fail	Fail	• Weak presentation • Tendency to irrelevance • Some attempt at an answer but seriously lacking in content and/or ability to organise thoughts
E2	7			
E3	6			
F1	5	Clear Fail	Not used for Honours	• Contains major errors or misconceptions • Poor presentation
F2	4			
F3	3			
G1	2	Clear Fail/ Abysmal	-	• Token or no submission
G2	1			
G3	0			

Course Timetable PA3004: 2019-2020

Date	Time	Place	Subject	Session	Staff
Week 7					
Mon 9 Sep					
Tue 10 Sep	14:00-15:00	FN3	Introduction to course	Lecture	SJT
	15:00-16:00	FN3	ADE 1	Lecture	SJT
Wed 11 Sep					
Thu 12 Sep					
Fri 13 Sep					
Week 8					
Mon 16 Sep	14:00-15:00	NK11	ADE 2	Lecture	SJT
Tue 17 Sep	14:00-16:00	FN112	ADE Tutorial	Tutorial	SJT
Wed 18 Sep					
Thu 19 Sep					
Fri 20 Sep	14:00-15:00	C11 Taylor	Pharmacokinetics I - Introduction	Lecture	SJT
	15:00-16:00	C11 Taylor	Pharmacokinetics II - Single dose IV kinetics	Lecture	SJT
Week 9					
Mon 23 Sep	14:00-15:00	NK3	Pharmacokinetics III - Single extravascular dose kinetics	Lecture	SJT
Tue 24 Sep	10:00-14:00	2:054, Polwarth	Practical-pKa determination	Practical	SJT
Wed 25 Sep					
Thu 26 Sep					
Fri 27 Sep	15:00-16:00	C11 Taylor	Pharmacokinetics IV - IV infusion and renal clearance	Lecture	SJT
Week 10					
Mon 30 Sep					
Tue 1 Oct	09:00-10:00	G08	Pharmacokinetics V - Multiple dose kinetics	Lecture	SJT
Wed 2 Oct					
Thu 3 Oct					
Fri 4 Oct	15:00-16:00	C11 Taylor	Phase I Metabolism (oxidation)	Lecture	SJT
Week 11					
Mon 7 Oct	14:00-15:00	NK3	Cytochrome P450	Lecture	SJT
Tue 8 Oct	09:00-10:00	G08	Induction/inhibition of CYP450	Lecture	SJT
	14:00-16:00	FN112	PK tutorial	Tutorial	SJT
Wed 9 Oct					
Thu 10 Oct					
Fri 11 Oct	14:00-15:00	C11 Taylor	Phase II Metabolism (conjugation)	Lecture	SJT
	15:00-16:00	C11 Taylor	Pharmacogenomics	Lecture	
Week 12					
Mon 14 Oct					
Tue 15 Oct	09:00-10:00	FN3	Transporters	Lecture	HMW
Wed 16 Oct					
Thu 17 Oct					
Fri 18 Oct					
Week 13					
Mon 21 Oct	14:00-15:00	NK3	Introduction to toxicology/In vivo/In vitro toxicology	Lecture	HMW
Tue 22 Oct	10:00-17:00	2:054, Polwarth	Practical –*in vitro* metabolism	Practical	SJT
Wed 23 Oct					
Thu 24 Oct					

Fri 25 Oct	14:00-15:00	C11 Taylor	Pathology of drug toxicity	Lecture	GIM
	15:00-16:00	C11 Taylor	Metabolism problem tutorial	Tutorial	SJT
Week 14					
Mon 28 Oct					
Tue 29 Oct					
Wed 30 Oct					
Thu 31 Oct					
Fri 1 Nov	14:00-15:00	C11 Taylor	Immunity: a controlled toxicity system I	Lecture	HW
Week 15					
Mon 4 Nov	14:00-15:00	NK11	Immunity: a controlled toxicity system II	Lecture	HW
Tue 5 Nov	09:00-10:00	FN3	Immune mediated toxicity –Hypersensitivity	Lecture	HW
	10:00-17:00	Polwarth 2:054	Practical – pharmacokinetics	Practical	SJT
Wed 6 Nov					
Thu 7 Nov					
Fri 8 Nov	14:00-15:00	C11 Taylor	Special topic 1:Respiratory pharmacology I	Lecture	GFN
Week 16					
Mon 11 Nov					
Tue 12 Nov	09:00-10:00	FN3	Special topic 1: Respiratory pharmacology II	Lecture	GFN
	11:00-12:00	MR051	Mutagenesis/carcinogenesis	Lecture	HMW
Wed 13 Nov					
Thu 14 Nov					
Fri 15 Nov	14:00-15:00	C11 Taylor	Target organ toxicity	Lecture	SJT
Week 17					
Mon 18 Nov	14:00-15:00	NK11	Special topic 2:Renal pharmacology I	Lecture	DS
Tue 19 Nov	09:00-10:00	FN3	Special topic 2:Renal pharmacology II	Lecture	DS
Wed 20 Nov					
Thu 21 Nov					
Fri 22 Nov	14:00-16:00	A21 (Taylor)	Formative MCQ, exam information and course round up	Lecture	SJT

Staff

Dr S Tucker (SJT) Course Co-ordinator
Professor GI Murray (GIM)
Professor GF Nixon (GFN)
Dr Derek Scott (DS)
Dr H Wilson (HW)
Professor HM Wallace (HMW)