255P A COMPUTER SIMULATION OF EXPERIMENTS DEMONSTRATING THE EFFECTS OF PHARMACOLOGICAL AGENTS ON THE CUTANEOUS INFLAMMATORY RESPONSE IN THE ANAESTHETISED RABBIT

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Computer programs, which simulate undergraduate pharmacological experiments, are now widely available and most undergraduate pharmacology courses in the UK employ examples of them in one form or another. Computer simulations such as that described here can be effective in presenting data in an interactive manner and encouraging students to use it to learn and practice data-handling, data-presentation, data-interpretation and report writing skills.

Here we demonstrate a computer simulation which simulates a range of experiments designed to demonstrate the action of inflammatory mediators and pharmacological agents on the *in vivo* inflammatory response in the anaesthetised rabbit. The program uses data obtained from actual experiments and is aimed at undergraduate students on courses in which pharmacology is a major component. It was developed using Macromedia Director (version 7) for PCs (minimum specification: Pentium PC, Windows 95/98/NT4, 16 Mb RAM, 10 Mb available HD space, 16 bit colour graphics).

'Introduction' and 'Methods' sections combine text and high-quality colour graphics to describe the animal preparation, the methods employed to measure oedema formation (extravascular accumulation of ^{125}I - albumin) and neutrophil accumulation, and to provide the student with the essential background information required to understand how the inflammatory response is triggered, and the mechanisms involved.
The 'Experiments' section allows the student to select, from a menu, to study the effects of the following agents on oedema formation (and, where appropriate, on neutrophil accumulation) in **normal rabbits**: (1) *a range of direct mediators of increased microvascular permeability* [histamine, bradykinin, platelet activating factor (PAF), substance P, leukotriene D_4], either alone (dose-response relation-ships), in the presence of a vasodilator (PGE_2) or with receptor antagonists; (2) *a range of agents which cause inflammation principally via neutrophil accumulation* [complement Factor C5a, cytokines interleukins IL-1 and IL-8, the bacterial peptide f-methyl-leucyl-phenylalanine (FMLP), leukotriene B_4, tumour necrosis factor (TNF_{alpha})], either alone (dose-response relationships) and in the presence of a vasodilator (PGE_2). The effects of neutrophil depletion and the importance of adhesion molecules are also covered; (3) *non-steroidal (local and systemic effects) and steroidal anti-inflammatory agents.*
A section describing the results of selected experiments using **sensitized rabbits** is also included and covers the IgG (Reverse Passive Arthus response) and IgE response.

The results are presented in graphical form either as bar-charts or line graphs. The program contains numerous self-assessment exercises which demand interpretation of experimental data presented to them, and an understanding of the underlying inflammatory mechanisms. These student-centred activities make the program useful for self-directed learning or, in the ideal situation, it would be incorporated into a structured teaching programme and used with a teacher-designed workbook.
It is envisaged that the program could be used in a number of ways: to better prepare students who will perform the practical at a later date; to debrief students after they have performed the practical; as a 'fallback' to provide data for students whose experiments were unsuccessful; as an alternative to the practical, though it should be remembered that different learning objectives may be achieved. It may be particularly useful as a student-centered alternative in those departments where there is a lack of equipment and/or technical expertise.

256P AN INTRODUCTION TO APOPTOSIS: A PICTURE IS WORTH A THOUSAND WORDS

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The term "apoptosis" was originally coined to describe a type of cell death distinct from classical necrosis. The first descriptions of apoptosis were entirely morphological in nature and applied to hepatic cells undergoing what was originally called "shrinkage necrosis", to prostate cells that die after withdrawal of androgen, to thymocytes exposed to corticosteroids, and to cells undergoing naturally-occurring developmental cell death. The morphology of apoptosis initially involves nuclear changes followed by cytoplasmic disintegration and rapid removal of cellular debris by phagocytosis not involving a significant inflammatory response. By contrast, classical necrosis initially involves cytoplasmic changes, distinct morphologies, and an inflammatory response.

From a functional perspective, the term apoptosis soon came to be thought of as a process of gene-directed cell suicide that occurs normally during development, and which can be triggered in adult cells by a variety of exogenous stimuli, e.g. corticosteroid- induced thymocyte death. This delayed process of gene-directed cell death is in contrast to the passive process by which an extrinsic stimulus directly and immediately kills a cell (necrosis).

An extraordinary degree of confusion is now evident in the literature regarding how to define and think about the terms "apoptosis" and "necrosis", whether they are definable entities, and whether apoptosis is synonymous with "programmed cell death (PCD)" (it is not, because apoptosis and necrosis are morphological terms whereas PCD refers to gene-directed cell death independent of morphology). Although this confusion about terminology may seem to be an unimportant semantic argument, the way in which these terms are used, and how we think about them, is of considerable pharmacological significance. For example, if we think about apoptosis as any cell death in which a biochemical process is involved, then virtually all brain cell death is apoptotic and undesireable. However, if the mechanism by which cancer cells die is also apoptosis, and desireable, then an "anti-apoptotic" compound developed to prevent brain cell degeneration would be expected to cause cancer. Or, perhaps, apoptosis is neither good nor bad, nor even a definable entity, and the carelessness with which terms are applied to biological processes requires impossible mental gymnastics.

This presentation will attempt to clarify these issues as they relate to neuronal degeneration and pharmacological intervention in particular. It will also attempt to undermine the audience members' confidence in their use of these confusing, misleading, and now impossible-to-define terms.