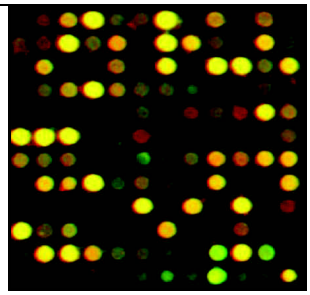
# Clinical pharmacology



CLINICAL PHARMACOLOGY is the clinical application of the action of drugs on the body, and involves understanding how the body handles and modifies drugs, and their side effects and interactions. Significant advances have occurred in the development of new drugs, and the genetics of drug actions, metabolism and transporters.

***Pharmacogenomics and new drug development.*** Pharmacogenomics[1,2] is the use of molecular biology techniques (eg, microarray chips, expressed-sequence tags and proteomics) to identify and study genes relevant to drug therapy. Thousands of potential new targets for drug therapy have been described. Combinatorial and computational chemistry and high-throughput screening allow the synthesis and evaluation of large numbers of compounds. These strategies have resulted in new antiangiogenic (SU5416) and antileukaemic (ST1571, or glivec) drugs for cancer. Increasing sophistication of in-vitro testing may lead to virtual studies and reduce the requirement for animal and human investigations.

***Pharmacogenetics and drug response.*** Pharmacogenetics, a subsection of pharmacogenomics, studies the genetic basis for differences in individual responses to drugs. Common alterations to gene structure are single-base changes in the genome (single-nucleotide polymorphisms). Examples include the lack of response of some people to certain drugs (eg, salbutamol) due to genetic variation in the $\beta_2$-adrenergic receptor;[2] polymorphisms in both the cholesteryl ester transfer protein and stromelysin-1 affecting the efficacy of pravastatin in coronary atherosclerosis; and the cardioprotective effect of ACE inhibitors being greater in whites than African-Americans.[2] Pretreatment genetic screening of patients will eventually enable this knowledge to be applied in clinical practice.

***Pharmacogenetics and drug metabolism.*** The genetics of the absorption, distribution, metabolism and elimination of drugs may also result in interindividual differences in treatment responses.[1,2] Functionally significant polymorphisms have been detected in the genes for cytochrome P450 (oxidising) enzymes (eg, CYP2D6, CYP2C9), and many genotypes have been identified for ultrarapid, extensive, and poor metabolisers,[3] with individuals with these genotypes requiring extremely high, average or low doses, respectively, of many drugs to achieve useful effects. Thus, extensive metabolisers for CYP2C19 need larger doses of protein-pump inhibitors (eg, omeprazole) to treat peptic ulcer and, conversely, poor metabolisers for CYP2D6 suffer from perhexilene toxicity caused by high blood levels even at low doses. Some analgesics (eg, codeine, tramadol) require activation by CYP2D6; poor metabolisers may not obtain any pain relief, but may suffer respiratory side effects.

***Drug transporters.*** Drug transporters are proteins that mediate the efflux of drugs from cells and tissues. They are widely expressed in normal tissues and also limit the uptake of foreign molecules (including drugs) across the blood–brain barrier and the gastrointestinal mucosa. They may contribute to the poor oral bioavailability of some drugs.

Interest in transporters followed the observation that overexpression of P-glycoprotein (PGP) in cancer cells imparted resistance to many anticancer agents (multidrug resistance). Inhibition of PGP by drugs (eg, verapamil) increases the retention of cytotoxic agents in cancer cells. Genetically engineered mice that no longer express PGP develop neurotoxicity when given drugs that normally do not cross the blood–brain barrier (eg, vinca alkaloids, ivermectin). Some opiates are substrates for PGP and differences in analgesic response to these drugs may relate to PGP.

***Drug interactions.*** Our understanding of drug interactions has increased by identifying the drugs metabolised by CYP450 enzymes[4] and/or excreted by PGP. Inducers and inhibitors of both these systems affect target drugs. CYP3A4 inhibitors (eg, ketoconazole, erythromycin) increase blood levels of drugs such as terfenidine, astemizole or cisapride and can provoke life-threatening arrhythmias. Coadministration of inhibitors with some "statins" increases the risk of rhabdomyolysis.

Many inhibitors and inducers of CYP3A4 act similarly on PGP. PGP pumps drugs (eg, digoxin) into the gut lumen, thereby reducing its bioavailability.[5] Consequently, blood levels of digoxin are increased when PGP is inhibited (eg, by macrolide antibiotics) or decreased when PGP is induced (eg, by rifampicin or St John's wort).

***The future.*** Rationally synthesised drugs and knowledge of molecular factors determining drug actions, toxicity and interactions may enable "individualised therapy", but will not remove the need for good clinical judgement.

**Glossary**

*Microarray chips:* Miniaturised assay systems enabling evaluation of structure and simultaneous expression of thousands of genes (Figure).
*Expressed-sequence tags:* Short sequences of cDNA from specific tissues that can be "mined" for genetic polymorphisms and novel proteins.
*Combinatorial chemistry:* Simultaneous synthesis of chemical compounds with multiple permutations of substituents.
*High-throughput screening:* High speed robotic, often miniaturised, testing of new compounds against purified receptors, enzymes and cellular systems.

**Gillian M Shenfield,* David G Le Couteur† Laurent P Rivory‡**

* Clinical Professor in Clinical Pharmacology, Department of Clinical Pharmacology, Royal North Shore Hospital, St Leonards, NSW 2065
† Professor of Geriatrics, Faculty of Medicine, University of Sydney, Sydney, NSW
‡ Senior Hospital Scientist, Sydney Cancer Centre, Department of Medical Oncology, Royal Prince Alfred Hospital, Camperdown, NSW
gilshen@med.usyd.edu.au

1. Destenaves B, Thomas F. New advances in pharmacogenetics. *Curr Opin Chem Biol* 2000; 4: 440-444.
2. Wolf CR, Smith G, Smith RL. Pharmacogenetics. *BMJ* 2000; 320: 987-990.
3. Rodrigues AD. Integrated cytochrome P450 reaction phenotyping. Attempting to bridge the gap between cDNA-expressed cytochromes P450 and native human liver microsomes. *Biochem Pharmacol* 1999; 57: 465-480.
4. Tanaka E. Clinically important pharmacokinetic drug-drug interactions: role of cytochrome P450 enzymes. *J Clin Pharm Ther* 1998; 23: 403-416.
5. Yu DK. The contribution of P-glycoprotein to pharmacokinetic drug-drug interactions. *J Clin Pharmacol* 1999; 39: 1203-1211. ❑