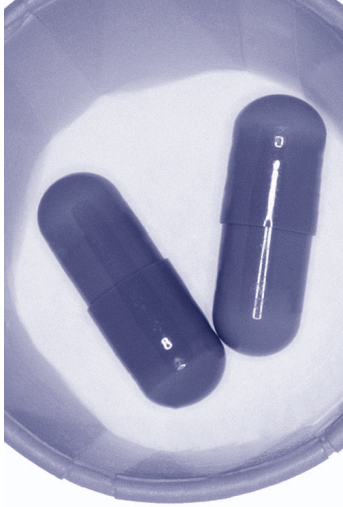
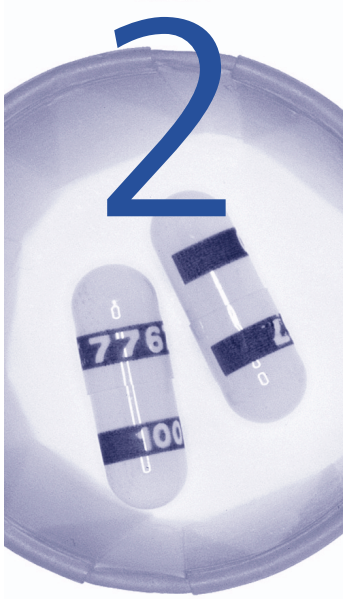
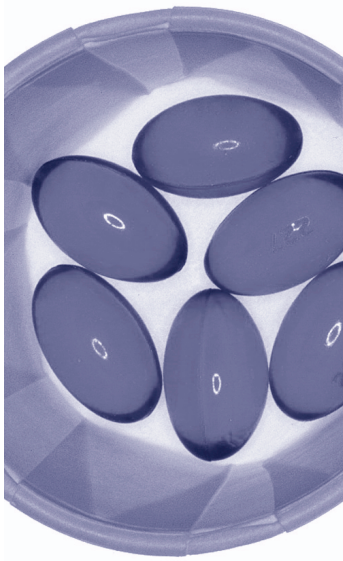
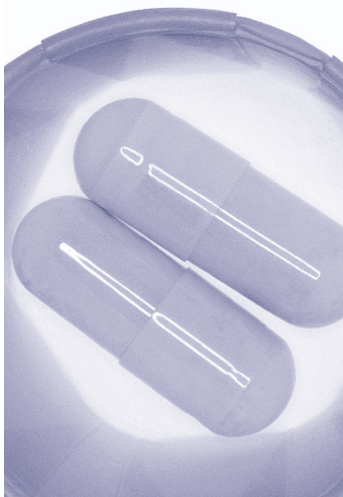
Chapter 2

Scientific background









Scientific background

Introduction

2.1 This chapter explains how genetic variation can affect response to medicines, and uses case studies to illustrate how information about such genetic variation can be applied to improving the safety and efficacy of medicines. We first describe the context for the modern development of pharmacogenetics.

2.2 Variation between individuals in their response to medicines has long been evident, and has posed significant challenges to scientific approaches in pharmacology. Sir William Osler observed in 1892 that 'if it were not for the great variability among individuals, medicine might as well be a science and not an art.'[1] In the 1950s, it was shown that some adverse reactions to certain medicines were caused by genetic variations that affected the metabolism of the medicine in the body.[2] In 1959, the term 'pharmacogenetics' was introduced to describe this phenomenon (see Boxes 1.1 and 2.1 for further definitions of the terms used in the Report).[3]

2.3 The Human Genome Project was established in 1990 to coordinate research that had been under way for some years to identify all the genes in human DNA. The map of the human genome, which identified the majority of the estimated 30,000-40,000 human genes, was completed in 2003. Scientists have made considerable advances in understanding how DNA functions, and how differences in DNA may lead to differences between people. These differences concern normal variation such as eye colour, or variation that causes diseases, such as cystic fibrosis or Huntington's disease. Researchers who have begun to examine the genome in more detail are now gaining a deeper understanding of how some variation between individuals in their responses to medicines can be explained in genetic terms.

2.4 This is a challenging enterprise, since the way in which medicines work in the body is complex (see Box 2.1). A number of different genes may be involved in the metabolism and processing of a particular medicine, and may affect different components of these processes. Environmental factors such as exposure to other medicines or chemicals can also influence the effectiveness of medicines, as can the health of the individual. For example, people with poor liver or kidney function are likely to differ from healthy people in how their body responds to a medicine. The compliance of patients with dosage schedules is also important; many failures or unexpected responses to medicines result from patients not taking the right amount of the medicine at the right time under the prescribed conditions. Medicines can even interact with common foods, for example, the consumption of grapefruit juice has been shown to influence the efficacy of some medicines.[4] All of these factors need to be taken into consideration if patients are to benefit fully from the medicines they are prescribed.

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1 Quoted in Roses AD (2000) Pharmacogenetics and the practice of medicine, *Nature* **405**: 857-65.

2 This phenomenon was described in Motulsky A (1957) Drug reactions, enzymes and biochemical genetics, *JAMA* **165**: 835-7.

3 Vogel F (1959) Moderne probleme der Humangenetik, *Ergeb Inn Med Kinderheilkd* **12**: 52-125.

4 Ameer B and Weintraub RA (1997) Drug interactions with grapefruit juice, *Clin Pharmacokinet* **33**: 103-21; Bailey DG *et al*. (1998) Grapefruit juice–drug interactions, *Br J Clin Pharmacol* **46**: 101-10. For a summary see UIC College-of-Pharmacy Drug Information Center Grapefruit Juice Interactions. Available: http://www.uic.edu/pharmacy/services/di/grapefru.htm. Accessed on: 14 Nov 2002.

Box 2.1: **How medicines work**

Pharmacology is the study of how a medicine acts in the body. It involves the consideration of both pharmacokinetics and pharmacodynamics.

Pharmacokinetics is the study of the processes and rate at which a medicine passes through the body:

- *Absorption* is the process by which a medicine enters the blood stream.
- *Distribution* refers to the transportation of a medicine to the site of action.
- *Metabolism* is the process whereby a medicine's structure and properties are altered, generally inactivating it and enabling it to be excreted by the body.
- *Excretion* is the removal of the medicine from the body through the kidneys and liver.

Genetic variation may influence all of these processes, since they involve numerous different molecules produced by genes, such as transport proteins and pumps, carriers and enzymes. Research in pharmacogenetics has traditionally focused on individual variation in the metabolism of medicines. The process of metabolism generally takes place in the liver where medicines are acted upon by enzymes. Variation in the rate of metabolism of a medicine by an enzyme can substantially alter how a person responds to that medicine. For example, rapid metabolism of a medicine can cause it to be ineffective, and slow or non-metabolism can lead to the accumulation of toxic amounts of the medicine in the body (See Box 2.2: Case study 1). Variation in proteins that metabolise medicines often affects response to more than one medicine.

Pharmacodynamics is the study of how a medicine works in the body. Most medicines work by interacting with the control systems of the body such as receptors, carrier molecules or enzymes. An individual's reaction to a particular medicine is therefore affected by genetic variation in these molecules. Historically, the development of medicines has proceeded on the presumption that these molecules are genetically homogeneous in the patient population. However, many studies in recent years have shown that this is not necessarily the case.

2.5 It is unrealistic to expect that by understanding the effects of genetic variation alone it will be possible to eliminate adverse reactions to medicines, or to ensure that we can all be treated more effectively. Research in pharmacogenetics is often welcomed as a step towards 'personalised' medicine. While this may be true in the sense that patients may be prescribed one medicine rather than another, or have the dosage of their medicine decided on the basis of information about their genetic make-up, it should not be taken to mean that individual patients will have medicines tailor-made for them. Moreover, one implication of developments in pharmacogenetics may be that some patients learn that it is very unlikely that the medicines available to treat their condition will be effective for them. In talking of personalised, targeted or tailor-made medicine, it is important not to mislead or to overestimate the possible benefits of pharmacogenetics.

The scientific basis of pharmacogenetics

2.6 Genetic factors may influence choice of medicine in several different ways. People are known to differ in the genetic variants they possess of a series of enzymes concerned with the absorption, metabolism and excretion of medicines (see Box 2.1). These are characteristics with which a person is born. They do not necessarily influence susceptibility to disease, but rather the way the individual body processes medicines to which it is exposed. They often affect classes of medicines rather than specific individual medicines (see Box 2.2: Case study 1).[5] People with particular genotypes may find some medicines ineffective, or may need higher or lower doses in order to achieve a therapeutic effect because they break the substances down either more or less rapidly. There are a large but finite number of these systems for processing medicines, and as our understanding of them advances, predictive genetic testing may be used to determine which medicines to prescribe, and in what doses.

2.7 Some diseases, notably cancers, develop in cells which have an altered genetic constitution, so that the genetic make-up of the diseased tissue is no longer the same as that of the person in which it is present. Specific genes present in the diseased tissue may play a critical role in determining the optimum treatment. To establish this, it will therefore be necessary to identify the genetic make-up of the cancer itself: testing the patient before a cancer has developed is of no use, because the genetic changes are only present in the cancer cells and not in the normal host tissues (see Box 2.3: Case study 2).

2.8 Genetic variation may also affect an individual's susceptibility to developing a particular disease. As more is learned about the vast subject of genetic variation which predisposes to disease, it is likely that newer, more precise classifications of common diseases will emerge (what has been called a molecular taxonomy of disease).[6] Although this is still at a very early stage, it is likely that some conditions which are now considered to be single disorders, with a common set of symptoms, will be discovered to be more heterogeneous, with several different biochemical disorders leading to a common set of clinical features. In some of these cases, it may turn out that the nature and efficacy of treatment depends on which type of the disease is present. Such heterogeneity may be behind some of the well-known variation in efficacy of medicines given to people who are affected by what appears superficially to be the same disorder.

2.9 This process of uncovering the genetic basis of predisposition to disease is also likely to lead to a better understanding of the biochemistry of disease processes, and of their corresponding healthy bodily functions. This knowledge of human biology in health and disease may help in designing and choosing which classes of chemical compounds are likely to be therapeutically useful and worth developing as medicines.

2.10 These different ways in which genetic variation can influence response to medicines are related and may often overlap. Nonetheless, they can raise different ethical issues, since the different kinds of information will be revealed by the various pharmacogenetic tests. In the following paragraphs (2.11 – 2.15) we explain each approach in more detail and provide examples. For simplicity, we divide the approaches outlined above into two broad

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5 For example, many substances, including medicines, are metabolised by a complex class of liver enzymes called cytochrome P450 (CYP). Genetic variation in some of these enzymes affects the rate of metabolism of many different medicines. Unlike this genetic variation in metabolising enzymes, genetic variation in receptors and other molecules more closely related to predisposition to individual diseases is more likely to affect a very small number of classes of medicine, perhaps just a single class.

6 For a summary of recent discoveries and future prospects in identifying subtypes of cancers on the basis of their genetic characteristics see Holmes B (2003) Stalking the enemy, *New Scientist* **179**: 52-5.

categories: those which examine differences in the DNA of individuals which are not related to the disease being treated, and those which examine differences in DNA which are related to the disease. We call the first approach 'differentiating people' and the second 'differentiating diseases'.

Differentiating people

2.11 Human beings share 99.9% of their DNA sequence with one another. It may seem quite extraordinary that such little variation can result in such great diversity. However, the 0.1% difference equates to 2–3 million individual differences in the DNA sequence of any two randomly selected people. On average, one in every 1,300 positions along the sequence will have different bases present in different people.[7] For example, some people might have an 'A' base whereas others have a 'G' base at a particular position. These two alternative possibilities are termed alleles. If the rarer of the two alleles is present in at least 1% of chromosomes in a population, it is termed a polymorphism. The simplest and most common type of variation, where a single base is substituted for another (as in the example above), is called a single nucleotide polymorphism (SNP). Some SNPs have a measurable effect on the individual; the majority have no effect. It is the former which are of primary interest in medicine, including in pharmacogenetics. These SNPs may be present in part of the gene that affects the production of a protein, or they may be in the regulatory region of the gene. Variation in the amount of product produced by a gene, rather than in the chemical nature of the product itself, can play an important role in determining how a patient responds to a medicine.[8]

2.12 There are numerous other forms of genetic variation that result in differences between people. Examples include:

- deletions: where a segment of DNA has been lost
- duplications: where an additional copy of a segment of DNA is present in the genome
- variable number of tandem repeats (VNTRs): a variable number of consecutively repeated sections of a short DNA sequence at a particular place in the genome

2.13 Genetic variation which does not influence the way a gene functions, or the proteins it produces, may still be relevant for research in pharmacogenetics. If a SNP or other polymorphism is closely associated with a genetic variant which affects response to a medicine, the two will be inherited together more frequently than would be expected by chance. The non-functional SNP can be used as a signpost, to help locate the important genetic variant. Groups of SNPs or genetic variants that are close together, so that they are often inherited together, are referred to as haplotypes.

2.14 Such genetic variation between people may affect how different individuals metabolise certain substances. A well-known example is the effect of variation in the aldehyde dehydrogenase (ALDH) gene on the response to alcohol. People with one variant of the gene are less efficient at breaking down alcohol once it enters the body. As a result, they suffer more severely from alcohol-induced nausea, facial flushing and headaches. Similarly, in the context of medical treatment, there are genetic variants which affect the metabolism

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[7] It is noteworthy that only a very small proportion of human DNA forms the genes. There is a considerable proportion of DNA whose function is at present not known; this kind of DNA is sometimes called 'junk DNA'. When comparing the genomes of different people, differences at the level of DNA are most commonly found in the areas that do not contain genes.

[8] See for example Drazen JM *et al*. (1999) Pharmacogenetic association between ALOX5 promoter genotype and the response to anti-asthma treatment, *Nat Genet* **22**: 168-70.

of certain classes of medicines (see Box 2.2: Case study 1). These variants may not have any noticeable effect on the individual until the particular medicine or substance is ingested, but they may make it possible to predict, to some extent, whether an individual will respond well to a medicine, whether it will have little effect on them, or whether it will cause an adverse reaction.

Box 2.2: **Case study 1 – CYP2D6**

CYP2D6 is an enzyme found in the human liver, which is involved in the metabolism of approximately 25% of all medicines that are currently prescribed, including some beta-blockers, used in the treatment of heart disease, and some of the tricyclic anti-depressant and anti-psychotic medicines. It is difficult to predict how a particular person will respond to a given dose of these medicines, in part due to the amount of variation in the CYP2D6 gene (over 70 alleles have been identified).

Approximately 7% of the Caucasian population has a genetic variant that results in reduced activity of the CYP2D6 enzyme: they are 'poor metabolisers'. A further 2%-30% have multiple copies of the CYP2D6 gene, arranged in tandem, so that these individuals metabolise the relevant medicines very quickly. In poor metabolisers, the medicine is not broken down quickly enough by the liver and accumulates in the body, which can have adverse consequences. A small number of medicines, such as codeine, only have an effect after they are processed by enzymes in the body. People who are deficient in the CYP2D6 enzyme may therefore derive no benefit from the normal dose of these medicines. Rapid metabolisers break down the medicine too quickly, and therefore require significantly increased concentrations of the medicine to achieve the desired pharmacological effect.

Although variation in the metabolism of a number of clinically important medicines is known to exist in populations due to differences in the CYP2D6 gene, pharmacogenetic testing for the relevant variants is not routinely performed in clinical practice (see paragraph 3.20). However, a P450 diagnostic chip that will test for a large number of 2D6 variants is to be introduced into the market in 2003.*

* Roche Diagnostics (2003) Roche Diagnostics launches the AmpliChip CYP450 in the US, the world's first pharmacogenetic microarray for clinical applications. Available: http://www.roche diagnostics.com/press_lounge/press_releases/division/2003_06_25.html. Accessed on: 25 June 2003.

Differentiating diseases

2.15 Genetic variation can affect an individual's susceptibility to a particular condition. It can also be an integral part of the process of disease, affecting only the diseased tissues, as in cancers. By understanding more about the genetic characteristics of a tumour, it may be possible to identify effective targets for medicines (see Box 2.3: Case study 2). In such cases, when viewed from the perspective of suitable therapy, a single disease such as breast cancer might be seen as a number of conditions which differ genetically. This genetic variation in the tumour may or may not turn out to be linked to genetic susceptibility to the disease.

Box 2.3: **Case study 2 – Herceptin**

Herceptin (trastuzumab) is used in the treatment of breast cancer and is an example of a medicine developed specifically to treat a subgroup of patients. In 1987, a connection was discovered between the expression of high amounts of a protein called HER2 and an aggressive form of breast cancer; 25 to 30% of patients with breast cancer express high amounts of HER2 due to a somatic mutation in the DNA of the cancerous cells, which contain many copies of the HER2 gene.* These women have a higher probability of metastasis, or spreading of the cancer; resistance to treatment with conventional chemotherapy; and a significantly shorter life expectancy. As a result of this discovery, the company Genentech developed the medicine Herceptin specifically to treat patients with this type of breast cancer by targeting over-expression of HER2. In determining whether a patient should receive Herceptin, the amount of HER2 in the tissue is measured (this does not involve examining the DNA directly). Patients with high levels of over-expression who receive Herceptin have an improved life expectancy compared to patients who receive standard chemotherapy.† Herceptin was licensed for use in the US in 1998 and in the UK in 2000, for patients with breast cancer who over-express HER2.

* Slamon DJ *et al.* (1989) Studies of the HER-2/neu proto-oncogene in human breast and ovarian cancer, *Science* **244**: 707-12.

† See prescription information about Herceptin: Genentech (2002) Herceptin full prescribing information. Available: http://www.gene.com/gene/products/information/oncology/herceptin/insert.jsp. Accessed on: 15 Nov 2002; National Institute for Clinical Excellence (2002) *Guidance on the use of trastuzumab for the treatment of advanced breast cancer,* Technology Appraisal Guidance - No.34 (London: National Institute for Clinical Excellence), pp. 3-5.

The application of pharmacogenetics

2.16 The application of pharmacogenetics has two main aspects: improvements in the safety and efficacy of medicines.

Improving safety

2.17 Pharmacogenetic tests that reveal genetic variations already known to be associated with adverse reactions could allow physicians to avoid exposing patients to medicines that would put them at risk. The majority of adverse reactions are caused because of an exaggerated effect of a medicine in the body.[9] Less often, an adverse reaction may be an idiosyncratic response to the medicine.

2.18 Adverse reactions to medicines have significant costs, in both human and monetary terms. However, it is difficult to ascertain the impact of genetic variation in response to medicines because data concerning adverse reactions often include problems caused by errors in prescription, and because information about other causes such as interaction between different medicines may be non-existent. According to one recent report, deaths in England and Wales from prescription errors and adverse reactions have increased by 500% over the past ten years: 1,100 people died for these reasons in 2002 at a cost to the NHS of more than £500 million.[10] In the US, approximately 400,000 adverse events associated with prescription or over-the-counter medicines were reported in 2001.[11] These events have been estimated

9 Phillips KA *et al*. (2001) Potential role of pharmacogenomics in reducing adverse drug reactions: a systematic review, *JAMA* **286**: 2270-9.

10 Audit Commission (2002) *A Spoonful of Sugar – Medicines Management in NHS Hospitals* (London: Audit Commission).

11 Quoted in O'Kane DJ, Weinshilboum RM and Moyer TP (2003) Pharmacogenomics and reducing the frequency of adverse drug events, *Pharmacogenomics* **4**: 1-4.

to be the fourth to sixth leading cause of death in the US.[12] It is difficult to estimate how many of these deaths, and what proportion of the financial costs could have been avoided through the use of pharmacogenetics. It is clear that pharmacogenetic testing has the potential to enable serious adverse reactions to medicines to be avoided in some cases (see for example Box 2.4: Case study 3), although it may be that programmes of education for physicians and patients would be more effective in reducing these problems.[13]

Box 2.4: Case study 3 – Abacavir

Abacavir is a medicine that is used widely in the treatment of HIV/AIDS. Clinical studies have shown that about 4% of patients experience a serious hypersensitivity reaction to the medicine, usually within the first six weeks of therapy. In rare cases, the adverse reaction is fatal.* In 2000, the company that makes abacavir, GlaxoSmithKline (GSK), announced the start of a research programme to identify genetic markers which would enable the prospective prediction of patients at an increased risk of a hypersensitivity reaction.

In 2002, two articles were published which linked a particular genetic variant called *HLA B5701* to the occurrence of hypersensitivity reactions.† The larger study, by the GSK group, found the *HLA B5701* SNP in 55% of Caucasian patients who had experienced a hypersensitivity reaction but only 1% of patients who were considered tolerant of abacavir.‡ While sample sizes for non-Caucasian patients were small, *HLA B5701* was not present in any of the nine black patients and in only one of the ten Hispanic patients who experienced the adverse reaction. Thus, many patients without the genetic variant experienced the hypersensitivity reaction.

The current position of GSK is that it would be premature to use *HLA B5701* testing to determine prospectively the risk of adverse response to abacavir. GSK also strongly recommends against testing once a patient has already experienced a hypersensitivity reaction. GSK aims to identify a set of genetic markers which might increase the predictive value of testing, with broad applicability across populations. Another group of researchers who have published similar results, however, have implemented genotyping of all patients in their hospital who have been prescribed abacavir on the basis of their research.§

* Hetherington S *et al*. (2001) Hypersensitivity reactions during therapy with the nucleoside reverse transcriptase inhibitor abacavir, *Clin Ther* **23**: 1603-14.

† Hetherington S *et al*. (2002) Genetic variations in HLA-B region and hypersensitivity reactions to abacavir, *Lancet* **359**: 1121-2; Mallal S *et al*. (2002) Association between presence of HLA-B*5701, HLA-DR7, and HLA-DQ3 and hypersensitivity to HIV-1 reverse-transcriptase inhibitor abacavir, *Lancet* **359**: 727-32.

‡ Hetherington S *et al*. (2002) Genetic variations in HLA-B region and hypersensitivity reactions to abacavir, *Lancet* **359**: 1121-2.

§ Mallal S *et al*. (2002) Association between presence of HLA-B*5701, HLA-DR7, and HLA-DQ3 and hypersensitivity to HIV-1 reverse-transcriptase inhibitor abacavir, *Lancet* **359**: 727-32.

12 Lazarou J, Pomeranz BH and Corey PN (1998) Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies, *JAMA* **279**: 1200-5.

13 We have already observed that many factors other than genetic variation affect the success or otherwise of medicines. In its response to our consultation paper, GeneWatch drew attention to a report by the Audit Commission which 'proposed a number of ways to improve medicines management, including increasing the role of pharmacists to ensure the optimal use of increasingly powerful medicines, encouraging patients to self-administer medicines whilst in hospital using individualized packs, and introducing better computer systems and monitoring.' Audit Commission (2002) *A Spoonful of Sugar – Medicines Management in NHS Hospitals* (London: Audit Commission).

Increasing efficacy

2.19 Results from pharmacogenetic tests may also inform physicians in selecting the medicine most likely to benefit a particular patient. Many medicines are effective in only a proportion of patients treated. Some common treatments for conditions including diabetes, depression and asthma are only effective in around 60% of patients, and for medicines used to treat cancer, this figure may be as low as 25%.[14] Sometimes, for a medicine to be effective, different doses are required for different patients. In the absence of a pharmacogenetic test for efficacy, the most appropriate medicine or dose is conventionally found by trial and error, although in some cases, tests of renal function may be used to predict the appropriate dose. It has been suggested that a 'trial and error' approach to prescription may reduce compliance for medicines that do work, since patients acquire a general aversion to taking medicines because of the unpleasant side-effects which they might experience.[15]

2.20 Bearing in mind the distinction made in paragraphs 2.6 – 2.10, there are two ways in which pharmacogenetics could improve this situation. First, it could enable medicines to be designed on the basis of information about the genetic characteristics of a disease (Box 2.3: Case study 2). Secondly, decisions about prescribing a medicine could be informed by knowledge of the genetic variation relevant to its metabolism in the body. In this latter case, the medicine itself may not have been developed with the genetic variation in mind, but its use could be restricted to those people whose genetic make-up identified them as being likely to respond well to the medicine, or the dosage adjusted to attain the maximum benefit (Box 2.2: Case study 1).

14 Spear BB, Heath-Chiozzi M and Huff J (2001) Clinical application of pharmacogenetics, *Trends Mol Med* **7**: 201-4.

15 Professor Robert Kerwin, Professor of Clinical Neuropharmacology, Institute of Psychiatry, London, UK, speaking at the British Association Science and Public Affairs Forum, 6 Feb 2003.