One of the promises of the human genome project is individualised pharmacological therapy. An individual's genetic type would be determined, and the resulting diseases which the person was susceptible to would be determined. In addition, the drugs to which an individual would respond well would be enumerated, and the drugs which were more likely to be toxic could be established. At present we are just beginning to determine those associations which would help us tailor an individual's pharmacological therapy so as to maximise efficacy and minimise toxicity. In this report we review the considerations involved in determining the pharmacogenetic profile of any given drug and to review the current level of understanding of the association between genetic polymorphisms and drug toxicity/efficacy in rheumatology.

Establishing an association between genetic types and toxicity is perhaps an easier task to accomplish than understanding the association between a given genetic type and drug efficacy. Drug toxicities are generally discrete events and a specific toxicity can often be traced to the agent in question. Thus, it is fairly easy to study a given population and define those with a specific drug toxicity. Nonetheless, a sufficiently large population must be studied to establish an association. Although this restates the obvious, most drugs for chronic conditions such as rheumatoid arthritis (RA) are toxic to only a modest proportion of the patients taking them otherwise they would have long ago been pulled off the market. To establish a relative risk association for a toxicity that occurs in only 5–10% of patients taking a given drug might require hundreds or even thousands of patients if the observed increase in risk of toxicity is modest.

There are many reasons why any given drug may fail in any given individual. Clearly, genetically associated resistance may account for failure of a given agent and being able to predict drug failure can both prevent unnecessarily prolonged suffering as the drug is given “a chance to work” as well as diminishing the exposure of the patient to a potentially toxic reaction. Nonetheless other factors can also account for drug failure in the treatment of a chronic disease. First, as we have found recently for RA, patients with longstanding, severe disease may not respond to any therapy because the disease has progressed too far. Some patients suffer a more severe form of the disease even from the outset and the susceptibility to more severe disease may also be genetic in origin. The best example of a genetic determinant of more severe disease in the rheumatic diseases is the presence of the “shared epitope” in human leucocyte antigen (HLA) molecules in patients with RA who suffer a more severe course.

Other drugs or even dietary substances may interfere with the action of a drug—for example, caffeine, an adenosine receptor antagonist present in coffee and other soft drinks, blocks the anti-inflammatory effects of methotrexate in animal studies and patients with RA who suffer a more severe course.1 Other drugs or even dietary substances may interfere with the action of a drug—for example, caffeine, an adenosine receptor antagonist present in coffee and other soft drinks, blocks the anti-inflammatory effects of methotrexate in animal studies and patients with RA who suffer a more severe course.1 Other drugs or even dietary substances may interfere with the action of a drug—for example, caffeine, an adenosine receptor antagonist present in coffee and other soft drinks, blocks the anti-inflammatory effects of methotrexate in animal studies and patients with RA who suffer a more severe course.1 Other drugs or even dietary substances may interfere with the action of a drug—for example, caffeine, an adenosine receptor antagonist present in coffee and other soft drinks, blocks the anti-inflammatory effects of methotrexate in animal studies and patients with RA who suffer a more severe course.1 Other drugs or even dietary substances may interfere with the action of a drug—for example, caffeine, an adenosine receptor antagonist present in coffee and other soft drinks, blocks the anti-inflammatory effects of methotrexate in animal studies and patients with RA who suffer a more severe course.1 Other drugs or even dietary substances may interfere with the action of a drug—for example, caffeine, an adenosine receptor antagonist present in coffee and other soft drinks, blocks the anti-inflammatory effects of methotrexate in animal studies and patients with RA who suffer a more severe course.1 Other drugs or even dietary substances may interfere with the action of a drug—for example, caffeine, an adenosine receptor antagonist present in coffee and other soft drinks, blocks the anti-inflammatory effects of methotrexate in animal studies and patients with RA who suffer a more severe course.1 Other drugs or even dietary substances may interfere with the action of a drug—for example, caffeine, an adenosine receptor antagonist present in coffee and other soft drinks, blocks the anti-inflammatory effects of methotrexate in animal studies and patients with RA who suffer a more severe course.1 Other drugs or even dietary substances may interfere with the action of a drug—for example, caffeine, an adenosine receptor antagonist present in coffee and other soft drinks, blocks the anti-inflammatory effects of methotrexate in animal studies and patients with RA who suffer a more severe course.1 Other drugs or even dietary substances may interfere with the action of a drug—for example, caffeine, an adenosine receptor antagonist present in coffee and other soft drinks, blocks the anti-inflammatory effects of methotrexate in animal studies and patients with RA who suffer a more severe course.1 Other drugs or even dietary substances may interfere with the action of a drug—for example, caffeine, an adenosine receptor antagonist present in coffee and other soft drinks, blocks the anti-inflammatory effects of methotrexate in animal studies and patients with RA who suffer a more severe course.1 Other drugs or even dietary substances may interfere with the action of a drug—for example, caffeine, an adenosine receptor antagonist present in coffee and other soft drinks, blocks the anti-inflammatory effects of methotrexate in animal studies and patients with RA who suffer a more severe course.1 Other drugs or even dietary substances may interfere with the action of a drug—for example, caffeine, an adenosine receptor antagonist present in coffee and other soft drinks, blocks the anti-inflammatory effects of methotrexate in animal studies and patients with RA who suffer a more severe course.1 Other drugs or even dietary substances may interfere with the action of a drug—for example, caffeine, an adenosine receptor antagonist present in coffee and other soft drinks, blocks the anti-inflammatory effects of methotrexate in animal studies and patients with RA who suffer a more severe course.1

Methotrexate is currently the most commonly used disease modifying antirheumatic drug (DMARD) in RA for which it is commonly administered alone or in combination with....
Methotrexate and cellular metabolism. 5-CH3-THF, 5-methyl-tetrahydrofolate; AICAR, aminoimidazolecarboxamidohexonucleotide; DHFR, dihydrofolate reductase; dTMP, deoxythymidine monophosphate; dUMP, deoxyuridine monophosphate; FAICAR, formyl aminoimidazolecarboxamidoribonucleotide; FPGS, folylpolyglutamate synthase; IMP, inosine monophosphate; MTHFR, methylene tetrahydrofolate reductase; MTX, methotrexate; MTXGl, methotrexate polyglutamate; RFC1, reduced folate carrier 1; THF, tetrahydrofolate; TS, thymidylate synthase.

Figure 2 Methotrexate and cellular metabolism. 5-CH3-THF, 5-methyl-tetrahydrofolate; AICAR, aminoimidazolecarboxamidohexonucleotide; DHFR, dihydrofolate reductase; dTMP, deoxythymidine monophosphate; dUMP, deoxyuridine monophosphate; FAICAR, formyl aminoimidazolecarboxamidoribonucleotide; FPGS, folylpolyglutamate synthase; IMP, inosine monophosphate; MTHFR, methylene tetrahydrofolate reductase; MTX, methotrexate; MTXGl, methotrexate polyglutamate; RFC1, reduced folate carrier 1; THF, tetrahydrofolate; TS, thymidylate synthase.

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CONCLUSION
It is now possible to predict which patients are susceptible to some forms of drug toxicity in the therapy of the rheumatic diseases. In particular, azathioprine toxicity can clearly be prevented by the avoidance of this drug in those patients who are incapable of eliminating its toxic metabolites. In patients treated with methotrexate the toxicities associated with genetic polymorphisms can also be prevented by avoiding the drug but most therapeutic series indicate that supplementation with either folic acid or folinic acid can prevent most of these toxicities as well.11–24 There is no complete evidence yet to indicate that we can predict which patients are most likely to respond to methotrexate, Nonetheless efforts are continuing to determine if genetic polymorphisms in enzymes or proteins of methotrexate's anti-inflammatory pathways determine response to the drug. Although not in a position yet to fully take advantage of the insights gained in the past few years, future studies will likely bring the benefits of the genetic revolution to patients with rheumatic diseases.

This work was supported by grants from the National Institutes of Health (AA13336, AR41911, GM56268), Scleroderma Foundation, King Pharmaceuticals, the General Clinical Research Center (M01RR00096), and by the Kaplan Cancer Center of New York University School of Medicine.

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Pharmacogenetics in the rheumatic diseases

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doi: 10.1136/ard.2004.028217

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