An additional mode for classifying idiosyncratic drug reactions is by the delay before the reaction presents (212). Classification by delay is:

- Almost immediate, such as urticaria, angioedema, rhinoconjunctivitis, or anaphylaxis (213,214);
- 1–2 weeks, such as simple rashes (215);
- 2–3 weeks, such as generalized hypersensitivity;
- 1–2 months, such as hepatotoxicity and agranulocytosis;
- 1 year or more, such as autoimmune reactions.

Idiosyncratic drug reactions can proceed by way of a pathway that does *not involve an immune response*, or by way of a pathway that *does involve an immune response*. The immune response can involve direct, spontaneous reaction of the drug with a protein, with the creation of a protein that bears a hapten group. Alternatively, the immune response can involve enzymatic activation of the drug, followed by condensation of the activated drug with a protein, with the creation of a hapten. Hepten-mediated immune reactions have been reviewed (216).

The spontaneous formation of haptens occurs with drugs such as penicillins and cephalosporins, which have a beta-lactam ring that can spontaneously react proteins to generate the hapten. Enzymatic activation of drugs can be mediated, for example, by cytochrome P450 or peroxidase (217). Enzymatic activation of drugs can result in the conversion of drug into a reactive epoxy compound.

Idiosyncratic drug reactions are a frequent cause of acute liver failure (218). In fact, idiosyncratic drug-induced liver injury is a common reason for not receiving FDA-approval, or for the FDA's withdrawal of a drug from marketing. Idiosyncratic drug reactions to the liver tend to arise from antibacterials and NSAIDs. Serious reactions of this type usually occur at doses greater than 10 mg/day.

The anticonvulsants carbamazepine and phenytoin are associated with idiosyncratic drug reactions, where these reactions include fever, neutropenia, and skin rash (including Stevens-Johnson syndrome) (219).

A number of animal models have been developed for use in studying idiosyncratic drug reactions. To be a valid model, the drug-induced

[212]Ng W, Lobach AR, Zhu X, et al. Animal models of idiopathic drug reactions. Adv. Pharmacol. 2012;63:81–135.

[213]Sanchez-Borges M, et al. Hypersensitivity reactions to non beta-lactam antimicrobial agents, a statement of the WAO special committee on drug allergy. World Allergy Org. J. 2013;6:18 (23 pp.).

[214]Andrade RJ, Tulkens PM. Hepatic safety of antibiotics used in primary care. J. Antimicrob. Chemother. 2011;66:1431–46.

[215]Ng W, Lobach AR, Zhu X, et al. Animal models of idiopathic drug reactions. Adv. Pharmacol. 2012;63:81–135.

[216]Erkes DA, Selvan SR. Hapten-induced contact hypersensitivity, autoimmune reactions, and tumor regression: plausibility of mediating antitumor immunity. J. Immunol. Res. 2014;2014:175265 (28 pp.).

[217]Lu W, Uetrecht JP. Peroxidase-mediated bioactivation of hydroxylated metabolites of carbamazepine and phenytoin. Drug Metabol. Disposition 2008;36:1624–36.

[218]Lammert C, et al. Relationship between daily dose of oral medications and idiosyncratic drug-induced liver injury: search for signals. Hepatology 2008;47:2003–9.

[219]Lu W, Uetrecht JP. Peroxidase-mediated bioactivation of hydroxylated metabolites of carbamazepine and phenytoin. Drug Metabol. Disposition 2008;36:1624–36.