

examined. It is tempting to speculate that the level of expression of cytochrome P450 enzymes might provide an explanation for the cardiomyopathy observed with certain drugs.⁵ In this context underexpression of a particular enzyme might be associated with excessive accumulation and toxic tissue concentrations of a drug, whereas overexpression might result in formation of a toxic metabolite.⁶ However, direct evidence linking gene expression, isoenzyme activity, and metabolite toxicity is essential in the testing of such a hypothesis. It is also possible that cytochromes P450 may be involved in either the anabolism or catabolism of endogenous substances such as steroids and eicosanoids.

Although the discovery of cytochromes P450 in the heart has numerous implications for pharmacotherapy, from both a safety and efficacy perspective, to define their role the quantitative relation between drug metabolism (in situ in the heart) and drug effect must be established. In particular, the metabolic capacity of the heart must be measured accurately. The actual types of cells that express the enzymes also need to be defined. Finally, levels of P450 expression similar to those in the heart have been found in the brain, where the functional significance of this group of enzymes is still under investigation.^{7,8} Hence the discovery of cytochromes P450 in the heart should not be overinterpreted.

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Antibiotic policies in neonatal intensive-care units

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Resistant strains of bacteria emerge in neonatal intensive-care units (NICUs) because of the need to use broad-spectrum antibiotics. Several approaches have been suggested to reduce the risk associated with the emergence of resistant bacteria, and in this issue of *The Lancet*, Peter de Man and colleagues report the results of a crossover study that compared two different empirical antibiotic regimens. Two NICUs participated in the study. In one NICU, babies received penicillin plus tobramycin for early-onset (first 48 h of life) sepsis and flucloxacillin plus tobramycin for late-onset sepsis; babies in the other NICU received amoxicillin plus cefotaxime. After 6 months the units switched regimens. The results were striking. Whereas babies treated with penicillin/tobramycin were, as expected, colonised or infected primarily by *Escherichia coli*,

Enterobacter spp predominated in the amoxicillin/cefotaxime group. The risk of colonisation with a resistant strain was 18 times higher with amoxicillin/cefotaxime treatment than with penicillin/tobramycin. The major clinical outcome that differed between the two regimens was a shorter stay in NICU in the penicillin/tobramycin group.

Many studies have found a strong association between the use of extended-spectrum cephalosporins (ESCs) and resistance of gram-negative bacteria to these agents; such resistance has commonly been associated with treatment failure.¹ Historically, resistance has occurred most often among organisms that have a chromosomally-encoded type 1 β -lactamase, such as *Enterobacter*, *Citrobacter*, *Serratia*, indole-positive *Proteus*, and *Pseudomonas aeruginosa*.

A more recent phenomenon reported with ESCs, especially among *Klebsiella*, is resistance due to plasmid-mediated β -lactamases, known as extended-spectrum β -lactamases (ESBLs). In a survey in the USA, 22% of *Klebsiella* isolates from ICU patients in teaching hospitals were ESBL producers.² In Europe, the frequency of organisms with ESBL has been highly variable, from 34% in Portugal to 3% in the Scandinavian countries. Many studies have shown a link between exposure to ESCs and colonisation and infection with bacteria that produce ESBL.³

Similar data exist about the relation between antibiotic use and resistance rates among gram-positive organisms. A Finnish study showed a substantial increase in macrolide resistance among group A streptococci linked to increased use of these agents: this increase was partly reversed by a nationwide educational programme to reduce the use of erythromycin.³ Investigators in Ontario, Canada, reported a large increase in the frequency of fluoroquinolone-resistant strains of pneumococci after the widespread use of agents in this class to treat respiratory infections.⁴ Colonisation and infection with meticillin-resistant strains of *Staphylococcus aureus* have been associated with exposure to cephalosporins. Vancomycin-resistant strains of enterococci have emerged worldwide in association with exposure to several agents, including glycopeptides and ESCs. A handful of cases of infection due to glycopeptide-resistant staphylococci have been reported from several countries in patients receiving treatment for long periods with these agents.

Scheduled changes in empirical antibiotic use (cycling) has been much debated, but there are few reports about the efficacy, safety, and cost-effectiveness of this approach.⁵ Early experiences involved the substitution of amikacin for gentamicin or tobramycin; most of these studies showed amikacin use led to lower gentamicin/tobramycin resistance. In one medical centre, use of an ESC instead of a fluoroquinolone as empirical therapy for presumed sepsis in the ICU was associated with a decline in the frequency of infections due to antibiotic-resistant gram-negative bacilli.⁶ Whether a cyclic change of antibiotics can affect the long-term development of resistance patterns in clinical settings such as the ICU needs further study.⁶ As a cautionary note, one medical centre that substituted imipenem for ceftazidime in an attempt to control a high frequency of ESBL producers noted an increased frequency of carbapenem-resistant strains of *Pseudomonas aeruginosa*.⁷

An antibiotic policy restricting the selection of empirical, prophylactic, or directed therapy is only one potential control measure.³ Evidence also suggests that giving the

antibiotic at the optimum dose and for the recommended duration are essential strategies for controlling antibiotic-resistant microorganisms. Infection-control policies and procedures remain a vital component in the surveillance and prevention of resistance and cannot be overemphasised.⁵ Whether improvements in infection-control standards is of greater benefit than a manipulation of antibiotic policies is not known. Probably both will be necessary to stem the spread of resistant pathogens worldwide.

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Medication errors, worse than a crime

In the wake of the Harold Shipman case—that of the general practitioner in Manchester, UK, found guilty last month of murdering 15 patients by injecting them with diamorphine¹—medicinal murder may briefly eclipse medicinal misadventure, but it will be much less important in the long run. The US Institute of Medicine has recently estimated that medical errors kill up to 98 000 Americans each year,² more than die in motor-vehicle accidents, and on Feb 9, US senators began to discuss the problem. “It’s not all that surprising”, said Dr Kenneth Kizer, the former head of the Veterans Administration, “that errors would occur. What is surprising is that health care has lagged so far behind other high-risk activities in risk reduction”.³

A medication error is “a failure in the [drug] treatment process that leads to, or has the potential to lead to, harm to the patient”.⁴ Up to 4% of inpatients will experience one.³ Most such cases arise from human error, the frequency of which depends on what people are trying to do and the circumstances in which they are doing it.^{5,6} In the formulation of avoidance strategies, a psychological approach can help (see p 994).

Psychologists distinguish between errors in the planning of an intentional act (“mistakes”) and errors in the execution of the act (“slips of action” or “lapses of memory”). Mistakes occur most often in unfamiliar circumstances, out of ignorance, or when someone chooses a familiar but incorrect strategy over an unfamiliar but correct one (“strong-but-wrong” errors)—in short, when the plan is wrong. Slips and lapses occur when execution of the plan does not follow the organised template (or “schema”) that specifies the sequence of steps in the plan.⁷ Examples of slips or lapses include the repetition or omission of a step, or an unwitting departure from the sequence specified in one schema to the sequence specified in a more familiar one. The likelihood of slips and lapses increases when people are tired, stressed, distracted, or in unfamiliar surroundings,⁸ almost a caricature of medical life.

The factors that increase the chances of a medication error are attributes of the complex mechanisms involved in the prescribing and giving of drugs. The drug-treatment system will fail if strategic decisions are wrong, or if conditions encourage error. Such failures can lead to unsafe acts, although the patient will be harmed only if defences, such as cross-checks, are inadequate.

So how can the chances of error be reduced? Teaching and training should help prevent mistakes. Yet many house officers are not taught how to administer drugs;⁹ such training should be part of the undergraduate curriculum.¹⁰ Specialist multidisciplinary teams are likely to make fewer mistakes than non-specialist staff, because they can concentrate on discrete features of care and become familiar with them; specialist pharmacists should thus form part of the team on, for example, paediatric, oncology, and intensive-care units.

Slips and lapses are defects in unconscious processes, so training, exhortation, and even threats are unlikely to reduce their incidence. However, technical changes can be made to improve the prescribing, dispensing, and giving of drugs, to remove some of the factors that impair performance, and to make thorough checks to detect errors

Psychological classification of medication errors

Mistakes

- Knowledge-based errors

Giving penicillin, without having established whether or not the patient is allergic.

- Rule-based errors

Mistakenly applying a good rule

Injecting diclofenac into the lateral thigh (the usually preferred site) rather than the buttock (which is preferred for diclofenac).

Applying a bad rule

Using excessive doses of captopril (as was done during early use of the drug).

Slips and lapses

- Slips of action (skill-based errors)

Setting out to write “chlorpromazine”, but instead writing the more familiar “chlorpropamide”.

Scrawling “chlorpromazine”, which is misread as “chlorpropamide”.

Picking a bottle of chlorpropamide from the pharmacy shelf when intending to take one of chlorpromazine.

- Lapses of memory (skill-based errors)

Giving penicillin, knowing, but forgetting, that the patient is allergic.