Pergamon

European Journal of Cancer, Vol. 34, No. 10, pp. 1493–1499, 1998

Printed in Great Britain
0959-8049/98/$—see front matter

PII: S0959-8049(98)00230-5

Clinical Oncology Update

Pharmacogenetics and Cancer Chemotherapy

L. Iyer[1] and M.J. Ratain[1,2,3]

[1]Committee on Clinical Pharmacology; [2]Department of Medicine; and [3]Cancer Research Center, The University of Chicago, 5841 South Maryland Avenue, MC 2115, Chicago, Illinois 60637, U.S.A.

Cancer chemotherapy is limited by significant inter-individual variations in responses and toxicities. Such variations are often due to genetic alterations in drug metabolising enzymes (pharmacokinetic polymorphisms) or receptor expression (pharmacodynamic polymorphisms). Pharmacogenetic screening prior to anticancer drug administration may lead to identification of specific populations predisposed to drug toxicity or poor drug responses. The role of polymorphisms in specific enzymes, such as thiopurine *S*-methyltransferases (TPMT), dihydropyrimidine dehydrogenase (DPD), aldehyde dehydrogenases (ALDH), glutathione *S*-transferases (GST), uridine diphosphate glucuronosyltransferases (UGTs) and cytochrome P450 (CYP 450) enzymes in cancer therapy are discussed in this review. © **1998 Elsevier Science Ltd. All rights reserved.**

Key words: pharmacogenetics, polymorphism, cancer, drug metabolism
Eur J Cancer, Vol. 34, No. 10, pp. 1493–1499, 1998

INTRODUCTION

INTER-SUBJECT VARIABILITY in therapeutic drug responses and drug toxicities is a major problem in clinical practice. Such variability is largely due to genetic factors leading to altered drug metabolism and/or receptor expression [1]. Polymorphisms in drug-metabolising enzymes, which appear to be more extensive than those of receptors [2], result in altered pharmacokinetics of therapeutic agents. Since the discovery of debrisoquine hydroxylase deficiency in the 1970s [3], pharmacogenetic polymorphisms of several drug metabolising enzyme systems have been identified and characterised [4–7]. Genetic variations in receptor expression systems, or pharmacodynamic polymorphisms, have been recently identified as major determinants of drug responses [8, 9].

The relationship between an individual's capacity to metabolise environmental carcinogens and other xenobiotics and susceptibility to cancer has been extensively studied [10–13]. The applicability of pharmacogenetics in cancer chemotherapy is critical due to the following reasons:

(1) anticancer agents generally have a narrow margin of safety;
(2) many of these agents are prodrugs and are biotransformed to active counterparts by enzyme systems that exhibit genetic polymorphisms;
(3) the active forms are usually also associated with toxicity;
(4) certain anticancer agents are detoxified by polymorphic enzyme systems; and
(5) most cancer chemotherapeutic drugs exhibit significant inter-patient variability in pharmacokinetics and toxicity.

This review will focus on the role of genetic polymorphisms of well-known classes of drug-metabolising enzymes in cancer chemotherapy.

THIOPURINE *S*-METHYLTRANSFERASE (TPMT)

TPMT catalyses the *S*-methylation of 6-mercaptopurine (6-MP) (also formed *in vivo* from the immunosuppressive prodrug, azathioprine), to form inactive metabolites. This competes with two other pathways of 6-MP metabolism that form inactive 6-thiouric acid and active 6-thioguanine nucleotides (6-TGN), catalysed by xanthine oxidase and hypoxanthine phosphoribosyltransferase (HPRT) enzymes, respectively [14]. 6-MP is commonly used as a component of maintenance therapy in acute lymphoblastic leukaemia (ALL) in children. 6-MP exhibits considerable inter-subject variation in oral bioavailability [15] and haematopoietic toxicities such as acute leucopenia, anaemia and pancytopenia [16]. This variation is largely due to variations in 6-MP metabolism, resulting from a genetic polymorphism of TPMT enzyme. In TPMT deficient patients, high concentrations of TGNs accumulate in haematopoietic tissues,

Correspondence to M.J. Ratain.
Received 25 Mar. 1998; accepted 1 Apr. 1998.

which is the basis for the haematopoietic toxicity observed in such patients [17]. TPMT deficient patients may require up to a 15-fold reduction in 6-MP doses to prevent fatal haematotoxicity [18]. In contrast, homozygotes with high TPMT activity may appear resistant to 6-MP therapy [19].

Population studies have shown a trimodal distribution of TPMT activity, with 89% of subjects having a high erythrocyte TPMT activity, 11% having intermediate activity and approximately 1 in 300 individuals having extremely low, or absent TPMT activity [20]. Similar polymorphic patterns have been observed in TPMT activity between Caucasians and Black subjects, with a reported 17% lower median TPMT activity in Blacks [21]. A unimodal distribution of TPMT activity has been observed in Japanese and Korean subjects [22, 23]. TPMT activity is age-related, with 50% higher activity reported in newborns compared with race matched adults, although the distribution of TPMT activity in newborns was similar to that seen in Caucasian and Black adults [24].

TPMT activity is usually assessed by monitoring red blood cell (RBC) TPMT activity which correlates with TPMT activity in leucocytes, liver, kidney, and leukaemic lymphoblasts [25, 26]. TPMT activity is inversely correlated to the concentration of TGNs in erythrocytes, which is another means to measure phenotypic activity of 6-MP [19], although recent reports indicate no correlation between TGN levels and TPMT activity [27]. The activities of the other enzyme systems involved in 6-MP metabolism may interfere with the phenotypic activity of TPMT activity [28], which is further complicated by intrasubject variation during therapy [14]. In addition, an accurate assessment of TPMT activity is not possible in patients who have received recent erythrocyte transfusions [17]. The functional TPMT gene has now been cloned and localised to human chromosome 6 [17, 29]. Two mutant alleles have been isolated from TPMT deficient [*TPMT**2, Ala to Pro substitution in codon 80) and heterozygous [*TPMT**3, Ala to Thr in codon 154 and Tyr to Cys in codon 240) patients [17, 30]. These mutations result in lower cellular levels of TPMT protein due to enhanced degradation of the proteins encoded by mutant *TPMT* alleles [31]. These findings have resulted in the development of polymerase chain reaction (PCR)-based methods to identify *TPMT* mutations, producing a 98% concordance between TPMT genotype and TPMT phenotype, which was determined by measuring RBC TPMT activity [30].

DIHYDROPYRIMIDINE DEHYDROGENASE (DPD)

DPD catalyses the initial, rate-limiting step in the catabolism of pyrimidines such as thymine and uracil and the fluoropyrimidine, 5-fluorouracil (5-FU). 5-FU is one of the most widely used anticancer agents in the treatment of breast, head and neck and colorectal cancers [32]. However, significant inter-individual variations in 5-FU clearance, tumour response and host toxicity have been reported after 5-FU therapy [32–34]. These variations may be due to genetic differences in the activity of DPD enzyme [35]. Deficiency in DPD activity can lead to severe 5-FU related toxicity which can be fatal [36, 37]. In contrast, high DPD activity (> 0.85 nmol/min/mg protein) in liver samples has also been reported [38], the significance of which is not clear, but may result in poor response to 5-FU treatment.

Tuchman and colleagues [39] were the first to report a case of DPD deficiency in a 27-year-old woman with breast cancer who exhibited myelosuppression, diarrhoea, stomatitis and neurological symptoms during 5-FU treatment. Measurement of uracil and thymine levels indicated 5–6 times higher levels in plasma and urine. Similar reports of DPD deficient cancer patients having familial pyrimidinaemia and pyrimidinuria and exhibiting severe 5-FU toxicity, emerged in the next few years [40, 41]. Currently, 17 cases of cancer patients with DPD deficiency have been reported in the literature [35]. The severe toxicity observed in 5-FU treated DPD deficient patients is believed to be due to alterations in 5-FU pharmacokinetics, with > 90% of 5-FU being recovered in urine, an apparent elimination half-life of approximately 160 min and a systemic clearance of 71 ml/min/m^2 [40]. Corresponding values in patients with apparently normal DPD activity are: < 20%, 13 ± 7 min and 594 ± 198 ml/min/m^2, respectively [34, 42].

Results from family studies suggest an autosomal recessive pattern of inheritance of DPD deficiency [40, 41]. Frequency of heterozygotes in the population may be as high as 3% [37] and that of homozygotes could be approximately 1/1000 [43]. Patients with low DPD activity have been identified as being at risk for severe toxic reactions to standard doses of 5-FU [37, 44]. Population studies indicate a normal distribution of DPD activity in peripheral blood mononuclear/PBMN cells [37, 45] and in human liver cytosolic preparations from donors [38]. DPD activity is not correlated with age or race [37, 38, 45, 46], but appears to be influenced by gender (15% lower DPD activity in women) [38, 45].

The gene encoding DPD has been recently cloned [47–49] and localised to chromosome region 1p22 [50]. The molecular basis for DPD deficiency is due to the deletion of a 165 bp segment in DPD mRNA due to exon skipping [51, 52] and a much rarer occurrence of a point mutation at codon 974 (aspartic acid to valine) of the DPD gene [53]. A diagnostic PCR-based genotyping assay is being developed to screen populations for the exon skipping mutation [54]. A recent report shows a lack of phenotype–genotype correlation for DPD enzyme, indicating the presence of DPD-deficient subjects in the population, who may be asymptomatic [55]. Hence, the contribution of a second gene, linked to the mutated DPD gene, in the complete manifestation of DPD deficiency may not be ruled out [55].

The clinical importance of DPD deficiency may diminish due to the availability of potent inhibitors of DPD such as 3-cyano-2,6-dihydropyridine (CNDP) [56], 5-benzyloxybenzyluracil [57] and 5-ethynyluracil (776C85) [58]. The use of such inhibitors may result in an improved therapeutic index of 5-FU by enabling the administration of smaller doses of 5-FU, as all patients would become DPD-deficient [59].

N-ACETYLTRANSFERASES (NAT)

Human acetylation polymorphism has been documented since the 1950s with the observation of slow and fast acetylators of isoniazid [60]. Two NAT genes (*NAT*1* and *NAT*2*) have been sequenced and located at distinct loci on chromosome 8, pter-q11 [61, 62]. Substrates of NAT1 include p-aminobenzoic acid and p-aminosalicylic acid and those of NAT2 include isoniazid, procainamide, hydralazine and sulphonamide [63–65]. NAT1 was initially believed to be monomorphic, but recent reports indicate that the *NAT*1 locus may be polymorphic [63, 66]. *NAT*2 exhibits a hereditarily determined polymorphism which shows substantial race-related differences [67], as 50% of Caucasians, but only 10% of Japanese subjects are slow acetylators. Fourteen

*NAT2** alleles have been found in Asian (excluding Japanese), Black, Hispanic and Caucasian subjects and four alleles have been found in Japanese subjects [61, 68, 69].

The association between carcinogenesis and NAT2 acetylator phenotypes is an area of continued research interest [64, 70, 71]. *N*-acetylation by NAT2 of the topoisomerase II inhibitor, amonafide, is of importance due to the considerable inter-patient variability in amonafide toxicity. *N*-acetyl-amonafide contributes to the toxicity (myelosuppression) of amonafide. Significantly different recommended phase II doses (RPTD) from two clinical trials (250 mg/m^2 and 400 mg/m^2) were reported for amonafide [72, 73]. Most phase II clinical trials used a dose of 300 mg/m^2/day for 5 days.

Recent studies have focused on the identification of fast and slow acetylators of amonafide and dosing the two groups separately [74–77]. Rapid acetylators of amonafide were shown to have significantly greater bone marrow toxicity than slow acetylators using a dose of 300 mg/m^2 over 60 min infusion, for 5 days [74, 76]. Using caffeine as a probe [78, 79], Ratain and colleagues [75] recommended doses of 250 and 375 mg/m^2 for fast and slow acetylators, respectively. Pharmacodynamic models using acetylator phenotype, pretreatment white blood cell (WBC) count, gender, and race have been suggested to permit individualised amonafide dosing in cancer patients [76, 77].

GLUTATHIONE *S*-TRANSFERASES (GST)

GSTs are a superfamily of enzymes that conjugate xenobiotics, such as herbicides, insecticides, carcinogens and anticancer agents (cyclophosphamide) with glutathione [80–83]. They have also been shown to play a role in multidrug resistance by direct binding to drugs and/or removing them from cells [84]. Increased levels of GST in tumour cells can contribute to the detoxification of the DNA-alkylating cytotoxic metabolite (phosphoramide mustard) of cyclophosphamide, resulting in the development of resistance [82].

Four GST families have been identified: α, μ (M), θ (T) and π [85]. GSTM1, GSTM3 and GSTT1 exhibit genetic polymorphisms [86–88]. A gene deletion occurring in *GSTM*1 gives rise to a polymorphism that results in deficient expression in 40–60% of Caucasians and 35% of American Blacks [86, 89, 90]. The GSTT1 null genotype occurs at a frequency of 15–38%, with a higher frequency among Blacks [85, 90].

GST polymorphisms appear to play an important role in the aetiology of several malignancies [85, 89, 91–93]. Interestingly, deficiency in GSTM1 or GSTT1 could also have a positive influence in cancer chemotherapy [85]. A lack of GSTM1 expression in leukaemic lymphoblasts correlated with event-free survival in children with ALL [94]. Recently, Chen and colleagues [90] have demonstrated the presence of both GSTM1 and GSTT1 null genotypes in black children with ALL.

ALDEHYDE DEHYDROGENASE (ALDH)

The ALDH family comprises of at least seven members: ALDH1 to ALDH5, betaine aldehyde dehydrogenase (BADH) and succinic semialdehyde dehydrogenase (SSDH) [95]. Genetic polymorphisms have been described in ALDH2, which is involved in the metabolism of alcohol [96]. ALDH1, ALDH2 and SSDH have been reported to oxidise aldophosphamide [95]. ALDH1 variants are prevalent up to 10% in the population [97]. A phenotypic deficiency in the excretion of carboxyphosphamide arising from ALDH polymorphism [98, 99] has been described. However, subsequent studies do not support this finding [100, 101].

URIDINE DIPHOSPHATE GLUCURONOSYLTRANSFERASES (UGTS)

UGTs are a superfamily of enzymes that catalyse the transfer of glucuronic acid moiety to a variety of endogenous substrates and xenobiotics [102–105]. Two major classes of UGT families have been identified: UGT1 and UGT2. UGT1 family members are formed by alternative splicing of exon 1 with the other exons [2–5], resulting in a conserved carboxyl region. UGT2 isoforms are separate gene products, eight of which have been identified so far [103–106]. UGT1 enzymes catalyse the glucuronidation of bilirubin and phenols, while substrates of UGT2 include zidovudine, morphine and non-steroidal anti-inflammatory agents [105].

The topoisomerase I inhibitor, irinotecan (CPT-11) has been shown to exhibit significant variability in pharmacokinetic parameters and toxicities, i.e. diarrhoea and myelosuppression [107]. This variability appears to be related to the glucuronidation of its active metabolite, SN-38, which is believed to be responsible for the diarrhoeal effects [108, 109]. Considerable inter-subject variability has been observed in the rates of *in vitro* glucuronidation of SN-38 [110]. We have recently demonstrated the role of UGT1A1 in the glucuronidation of SN-38 in our laboratory [111, 112]. This UGT isoform is also responsible for bilirubin glucuronidation in humans [113] and is absent in individuals with Crigler-Najjar type I (CN-I) syndrome [114, 115]. Patients who have milder hyperbilirubinaemia, such as those with Gilbert's syndrome [116] may also be at risk for CPT-11 induced toxicity [117]. Gilbert's syndrome, unlike CN-I disease, is common and is prevalent in up to 10–15% of the population [18, 19]. The molecular defect in Gilbert's syndrome is the presence of an additional 2 bp in the promoter region of UGT1A1 [118, 119]. Higher incidences (up to 19%) of the homozygotes {A(TA)$_7$TAA} have been recently reported in an Inuit population living in the Eastern Canadian Arctic [120]. Phenotype–genotype correlation studies are being initiated in our laboratory to relate UGT1A1 activity and CPT-11 toxicity and, thus potentially individualise CPT-11 therapy.

CYTOCHROME P*450* ENZYMES

CYP2D6

The *CYP2D6* polymorphism was originally suggested in the inter-subject variations observed in debrisoquine metabolism [3, 121]. *CYP2D6* activity is absent in 5–10% of European and North American Caucasian populations [122, 123]. Several alleles of *CYP2D6* have been described, such as *CYP2D6A*, *CYP2D6B*, *CYP2D6D*, *CYP2D6E* and *CYP2D6T* [122]. Correlation of poor metabolism phenotype with *CYP2D6* genotypes is being studied extensively for various therapeutic classes [124–127]. However, most anticancer agents are not subjected to *CYD2D6* metabolism at clinically relevant concentrations [128].

CYP2C

The CYP2C superfamily is responsible for metabolising a variety of therapeutic agents including mephenytoin [129], tobutamide [130], omeprazole [131–133], diazepam [134] and propranolol [135]. Polymorphisms in CYP2C19 and CYP2C9 have been described [129, 130, 136]. Frequencies of 3–5% in Caucasians and 18–23% in Oriental populations

have been described for CYP2C19 polymorphism [136]. CYP2C9 polymorphism is rarer, with an estimated frequency of 1 in 500 individuals [137]. Among the anticancer agents, teniposide is the only agent reported to interfere with *S*-mephenytoin metabolism on an *in vitro* level [128]. The MDR modulator, verapamil, has been reported to be metabolised by CYP2C9 [138], which may have an impact on the concomitant use of chemotherapeutic drugs and verapamil.

CYP3A

Polymorphism in CYP3A4 was initially described in connection with the variability in the oxidation of nifedipine [139]. However, subsequent studies have demonstrated a lack of clear evidence for CYP3A polymorphism [140]. With regard to anticancer agents, CYP3A enzymes are involved in the metabolism of teniposide and etoposide [141], ifosfamide [142, 143], vindesine [144], vinblastine [145, 146], vincristine [145], cyclophosphamide [142], paclitaxel [147] and docetaxel [148]. Verapamil has also been reported to be metabolised by CYP3A4 (and CYP1A1) [149], which may have an impact on development of resistance when used in conjunction with anticancer agents.

CONCLUSIONS

A major problem in cancer pharmacology is the prediction of the outcome of therapy, both in terms of tumour response and host toxicity [150, 151]. Pharmacogenetic variability in drug metabolising enzyme systems is a major determinant of variations in these outcomes. Unpredictable disposition of drugs may result in an undertreatment failing to provide therapeutic effects, or an overtreatment leading to excessive toxicity [152]. The current practice in oncology is to dose patients based upon height and body surface area, which may be imprecise. Other approaches include a more individualised approach using therapeutic drug monitoring and adaptive control [153]. Pharmacogenetically derived dosing regimens offer a new and exciting alternative to the above dosing approaches in oncology.

It is important for clinical researchers to identify and investigate therapeutic agents that exhibit unpredictable toxicity and variable pharmacokinetics/pharmacodynamics, which may be genetically determined. With the development of newer methods of molecular analysis to detect DNA polymorphisms, such as polymerase chain reaction (PCR) and restriction fragment length polymorphism (RFLP) techniques, genotyping screening approaches are increasingly becoming feasible [154–156]. Individualised dosing based upon phenotype and/or genotype of relevant drug-metabolising enzyme(s) may improve the therapeutic indices of chemotherapeutic drugs. Such methods have already proven to be beneficial, as seen with the studies on amonafide [77]. Pharmacogenetic screening prior to cancer therapy will enable the identification of patients who may be deficient in a critical detoxifying enzyme, as exemplified by the experiences with TPMT and DPD [14, 32]. More information is becoming available on genetic variations in other enzyme systems such as the UGTs and CYP, with respect to their role in cancer pharmacology.

1. Boddy A, Idle J. The role of pharmacogenetics in chemotherapy: modulation of tumor response and host toxicity. *Cancer Sur* 1993, **17**, 79–104.
2. Kalow W. Pharmacogenetics: its biological roots and the medical challenge. *Clin Pharmacol Ther* 1993, **54**, 235–241.
3. Dengler HJ, Eichelbaum M. Polymorphisms and deficient drug metabolism as triggers of toxic reactions. *Arzneimitt Forsch* 1977, **27**, 1836–1844.
4. Meyer UA. The molecular basis of genetic polymorphisms of drug metabolism. *J Pharm Pharmacol* 1994, **46**, 409–415.
5. Gonzalez F, Idle J. Pharmacogenetic phenotyping and genotyping: present status and future potential. *Clin Pharmacokin* 1994, **26**, 59–70.
6. Jacqz-Aigain E. Genetic polymorphisms of drug metabolism. *Dev Pharmacol Ther* 1989, **13**, 78–84.
7. Inaba T, Nebert DW, Burchell B, *et al.* Pharmacogenetics in clinical pharmacology and toxicology. *Can J Physiol Pharmacol* 1995, **73**, 331–338.
8. Propping P, Nothen MM. Genetic variation of CNS receptors—a new perspective for pharmacogenetics. *Pharmacogenetics* 1995, **5**, 318–325.
9. Boddy AV, Ratain MJ. Pharmacogenetics in cancer etiology and chemotherapy. *Clin Cancer Res* 1997, in press.
10. Nebert DW, McKinnon RA, Puga A. Human drug-metabolizing enzyme polymorphisms—effects on risk of toxicity and cancer. *DNA Cell Biol* 1996, **15**, 273–280.
11. Shields P. Pharmacogenetics: detecting sensitive populations. *Environ Health Perspect* 1994, **102**, 81–87.
12. Caporaso N, Landi T, Vineis P. Relevance of metabolic polymorphisms to human carcinogenesis: evaluation of epidemioloic evidence. *Pharmacogenetics* 1991, **1**, 4–19.
13. Ikawa S, Uematsu F, Watanabe KI, *et al.* Assessment of cancer susceptibility in humans by use of genetic polymorphisms in carcinogen metabolism. *Pharmacogenetics* 1995, **5**, S154–160.
14. Lennard L. The clinical pharmacology of 6-mercaptopurine. *Eur J Clin Pharmacol* 1992, **43**, 329–339.
15. Zimm S, Collins JM, Riccardi R, *et al.* Variable oral bioavailability of oral mercaptopurine. Is maintenance chemotherapy in acute lymphoblastic leukaemia being optimally delivered? *N Engl J Med* 1983, **308**, 1005–1009.
16. Lennard L, Van Loon JA, Weinshilboum RM. Pharmacogenetics of acute azathioprine toxicity: relationship to thiopurine methyltransferase genetic polymorphism. *Clin Pharmacol Ther* 1989, **46**, 149–154.
17. Krynetski EY, Tai HL, Yates CR, *et al.* Genetic-polymorphism of thiopurine S-methyltransferase. Clinical importance and molecular mechanisms. *Pharmacogenetics* 1996, **6**, 279–290.
18. Evans WE, Horner M, Chu YQ, Kalwinsky D, Roberts WM. Altered mercaptopurine metabolism, toxic effects and dosage requirement in a thiopurine methyltransferase-deficient child with acute lymphocytic leukemia. *J Ped* 1991, **119**, 985–989.
19. Lennard L, Lilleyman JS, van Loon J, Weinshilboum RM. Genetic variation in response to 6-mercaptopurine for childhood acute leukaemia. *Lancet* 1990, **336**, 225–229.
20. Weinshilboum RM, Sladek SL. Mercaptopurine pharmacogenetics: monogenic inheritance of erythrocyte thiopurine methyltransferase activity. *Am J Hum Gen* 1980, **32**, 651–652.
21. McLeod HL, Lin JS, Scott EP, Pui CH, Evans WE. Thiopurine methyltransferase activity in American white subjects and black subjects. *Clin Pharmacol Ther* 1994, **55**, 15–20.
22. Chocair PR, Duley JA, Sabbaga E, *et al.* Fast and slow methylators: do racial differences influence risk of allograft rejection? *Q J Med* 1993, **86**, 359–363.
23. Jang IJ, Shin SG, Lee KH, *et al.* Erythrocyte thiopurine methyltransferase activity in a Korean population. *Br J Clin Pharmacol* 1996, **42**, 638–641.
24. McLeod HL, Krynetski EY, Wilimas JA, Evans WE. Higher activity of polymorphic thiopurine S-methyltransferase in erythrocytes from neonates compared to adults. *Pharmacogenetics* 1995, **5**, 281–286.
25. Szumlanski C, Honchel R, Scott MC, Weinshilboum RM. Human liver thiopurine methyltransferase pharmacogenetics: biochemical properties, liver–erythrocyte correlation and presence of isozymes. *Pharmacogenetics* 1992, **2**, 148–159.
26. McLeod HL, Relling MV, Liu Q, Pui CH, Evans WE. Polymorphic thiopurine methyltransferase in erythrocytes is indicative of activity in leukemic blasts from children with acute lymphoblastic leukemia. *Blood* 1995, **85**, 1897–1902.
27. Bergan S, Rugstad HE, Klemetsdal B, *et al.* Possibilities for therapeutic drug monitoring of azathioprine: 6-thioguanine

nucleotide concentrations and thiopurine methyltransferase activity in red blood cells. *Ther Drug Monit* 1997, **19**, 318–326.
28. Lennard L, Hale HP, Lilleyman JS. Red blood cell hypoxanthine phosphoribosyltransferase activity measured using 6-mercaptopurine as a substrate: a population study in children with acute lymphoblastic leukaemia. *Br J Clin Pharmacol* 1993, **36**, 277–284.
29. Szumlanski C, Otterness D, Her C, Lee D, *et al.* Thiopurine methyltransferase pharmacogenetics: human gene cloning and characterization of a common polymorphism. *DNA Cell Biol* 1996, **15**, 17–30.
30. Yates CR, Krynetski EY, Loennechen T, *et al.* Molecular diagnosis of thiopurine S-methyltransferase deficiency: genetic basis for azathioprine and mercaptopurine intolerance. *Ann Intern Med* 1997, **126**, 608–614.
31. Tai HL, Krynetski EY, Schuetz EG, Yanishevski Y, Evans W. Enhanced proteolysis of thiopurine S-methyltransferase (TPMT) encoded by mutant alleles in humans (TPMT*3A, TPMT*2): mechanisms for the genetic polymorphism of TPMT activity. *Proc Natl Acad Sci USA* 1997, **94**, 6444–6449.
32. Diasio RB, Harris BE. Clinical pharmacology of 5-fluorouracil. *Clin Pharmacokin* 1989, **16**, 215–237.
33. Milano G, Etienne MC, Cassuto-Viguier E, *et al.* Influence of sex and age on fluorouracil clearance. *J Clin Oncol* 1992, **10**, 1171–1175.
34. Diasio RB, Lu Z. Dihydropyrimidine dehydrogenase activity and fluorouracil chemotherapy. *J Clin Oncol* 1994, **12**, 2239–2242.
35. Morrison G, Bastian A, Rosa TD, Diasio RB, Takimoto CH. Dihydropyrimidine dehydrogenase deficiency: a pharmacogenetic defect causing severe averse reactions to 5-fluorouracil-based chemotherapy. *Oncol Nurs Forum* 1997, **24**, 83–88.
36. Fleming RA, Milano GA, Gaspard MH, *et al.* Dihydropyrimidine dehydrogenase activity in cancer patients. *Eur J Cancer* 1993, **29A**, 740–744.
37. Lu Z, Zhang R, Diasio RB. Dihydropyrimidine dehydrogenase activity in human peripheral blood mononuclear cells and liver: population characteristics, newly identified deficient patients and clinical implication in 5-fluorouracil chemotherapy. *Cancer Res* 1993, **53**, 5433–5438.
38. Lu Z, Zhang R, Diasio RB. Population characteristics of hepatic dihydropyrimidine dehydrogenase activity, a key metabolic enzyme in 5-fluorouracil chemotherapy. *Clin Pharmacol Ther* 1995, **58**, 512–522.
39. Tuchman M, Stoeckeler JS, Kiang DT, *et al.* Familial pyrimidenemia and pyrimidimuria associated with severe fluorouracil toxicity. *N Engl J Med* 1985, **313**, 245–249.
40. Diasio RB, Beavers TL, Carpenter JT. Familial deficiency of dihydropyrimidine dehydrogenase—biochemical basis for familial pyrimidinemia and severe 5-fluorouracil-induced toxicity. *J Clin Invest* 1988, **81**, 47–51.
41. Harris BE, Carpenter JT, Diasio RB. Severe 5-fluorouracil toxicity secondary to dihydropyrimidine dehydrogenase-deficiency—a potentially more common pharmacogenetic syndrome. *Cancer* 1991, **68**, 499–501.
42. Heggie GD, Sommadosi JP, Cross DS, *et al.* Clinical pharmacokinetics of 5-fluorouracil and its metabolites in plasma, urine, and bile. *Cancer Res* 1987, **47**, 2203–2207.
43. Fernandez-Salguero P, Gonzalez FJ, Etienne MC, Milano G, Kimura S. Correlation between catalytic activity and protein content for the polymorphically expressed dihydropyrimidine dehydrogenase in human lymphocytes. *Biochem Pharmacol* 1995, **50**, 1015–1020.
44. Lyss AP, Lilenbaum RC, Harris BE, Diasio RB. Severe 5-fluorouracil toxicity in a patient with decreased dihydropyrimidine dehydrogenase activity. *Cancer Invest* 1993, **11**, 239–240.
45. Etienne MC, Lagrange JL, Dassonville O, *et al.* Population study of dihydropyrimidine dehydrogenase in cancer patients. *J Clin Oncol* 1994, **12**, 2248–2253.
46. McMurrough J, McLeod HL. Analysis of the dihydropyrimidine dehydrogenase polymorphism in a British population. *Br J Clin Pharmacol* 1996, **41**, 425–427.
47. Yokota H, Fernandez-Salgeuro P, Furuya H, *et al.* cDNA cloning and chromosome mapping of human dihydropyrimine dehydrogenase, an enzyme associated with 5-fluorouracil toxicity and congenital thymine uraciluria. *J Biol Chem* 1994, **269**, 23192–23196.
48. Albin N, Johnson MR, Diasio RB. cDNA cloning of bovine liver dihydropyrimidine dehydrogenase. *DNA Seq-J Seq Map* 1996, **6**, 243–250.
49. Johnson MR, Wang K, Tillmanns S, Albin N, Diasio RB. Structural organization of the human dihydropyrimidine dehydrogenase gene. *Cancer Res* 1997, **57**, 1660–1663.
50. Takai S, Fernandez-Salguero P, Kimura S, Gonzalez FJ, Yamada K. Assignment of the human dihydropyrimidine dehydrogenase gene (DYPD) to chromosome region 1p22 by fluorescence in situ hybridization. *Genomics* 1994, **24**, 613–614.
51. Meinsma R, Fernandez-Salguero P, van Kulenberg AB, van Gennip AH, Gonzalez FJ. Human polymorphism in drug metabolism: mutation in the dihydropyrimidine dehydrogenase gene results in exon skipping and thymine uracilurea. *DNA Cell Biol* 1995, **14**, 1–6.
52. Vreken P, Van Kuilenburg BP, Meinsma R, *et al.* A point mutation in an invariant splice donor site leads to exon skipping in two unrelated Dutch patients with dihydropyrimidine dehydrogenase deficiency. *J Inher Metab Dis* 1996, **19**, 645–654.
53. Ridge SA, Brown O, McMurrough J, *et al.* Mutations at codon 974 of the DPYD gene are a rare event. *Br J Cancer* 1997, **78**, 178–179.
54. Wei X, McLeod HL, McMurrough J, Gonzalez FJ, Fernandez-Salguero P. Molecular basis of the human dihydropyrimidine dehydrogenase deficiency and 5-fluorouracil toxicity. *J Clin Invest* 1996, **98**, 610–615.
55. Fernandez-Salguero PM, Sapone A, Wei X, *et al.* Lack of correlation between phenotype and genotype for the polymorphically expressed dihydropyrimidine dehydrogenase in a family of Pakistani origin. *Pharmacogenetics* 1997, **7**, 161–163.
56. Tatsumi K, Yamauchi T, Kiyons K, *et al.* 3-cyano-2,6-dihydroxypyridine (CNDP), a new potent inhibitor of dihydrouracil dehydrogenase. *J Biochem Tokyo* 1993, **114**, 912–918.
57. Naguib FN, Hao SN, el Kouni MH. Potentiation of 5-fluorouracil efficacy by the dihydrouracil dehydrogenase inhibitor, 5-benzyloxybenzyluracil. *Cancer Res* 1994, **54**, 5166–5170.
58. Baccanari D, Davis S, Knick V, Spector T. 5-ethynyluracil (776C85)—a potent modulator of the pharmacokinetics and antitumor efficacy of 5-fluorouracil. *Proc Natl Acad Sci* 1993, **90**, 11064–11068.
59. Adjei AA, Doucett M, Spector T, *et al.* 5-ethynyluracil (776C85), an inhibitor of dihydropyrimidine dehydrogenase, permits reliable oral dosing of 5-fluorouracil and prolongs its half-life. *Proc Am Soc Clin Oncol* 1995, **14**, 1478.
60. Evans DAP, White TA. Human acetylation polymorphism. *J Lab Clin Med* 1964, **63**, 394–403.
61. Ohsako S, Deguchi T. Cloning and expression of cDNAs for polymorphic and monomorphic arylamine N-acetyltransferases from human liver. *J Biol Chem* 1990, **265**, 4630–4644.
62. Blum M, Grant DM, McBride W, Heim M, Meyer UA. Human arylamine N-acetyltransferase genes: isolation, chromosomal localization, and functional expression. *DNA Cell Biol* 1990, **9**, 193–203.
63. Vatsis KP, Weber WW. Human N-Acetyltransferases. In Kaufman FC, ed. *Conjugation–Deconjugation Reactions in Drug Metabolism and Toxicity*. Berlin, Springer, 1994, 109–130.
64. Evans DAP. N-acetyltransferase. In Kalow W, ed. *Pharmacogenetics of Drug Metabolism*. New York, Pergamon Press, 1992, 95–178.
65. Grant DM, Blum M, Beer M, Meyer UA. Monomorphic and polymorphic human arylamine N-acetyltransferases: a comparison of liver isozymes and expressed products of two genes. *Mol Pharmacol* 1991, **39**, 184–191.
66. Vatsis KP, Weber WW. Structural heterogeneity of caucasian N-acetyltransferase at the NAT1 locus. *Arch Biochem Biophys* 1993, **301**, 71–76.
67. Okumura K, Kita T, Chikazawa S, *et al.* Pharmacokinetics and drug disposition-genotyping of N-acetylation polymorphism and correlation with procainamide metabolism. *Clin Pharmacol Ther* 1997, **61**, 509–517.
68. Lin HJ, Han CY, Lin BK, Hardy S. Slow acetylator mutations in the human polymorphic N-acetyltransferase gene in 786 Asians, Blacks, Hispanics, and Whites: application to metabolic epidemiology. *Am J Hum Genet* 1993, **52**, 827–834.

69. Lin HJ, Han CY, Lin BK, Hardy S. Ethnic distribution of slow acetylator mutations in the polymorphic N + acetyltransferase (NAT2) gene. *Pharmacogenetics* 1994, **4**, 125–134.
70. Weber WW. *The Acetylator Genes and Drug Response*. New York, Oxford University Press, 1987.
71. Martinez C, Agundez JAG, Olivera M, Martin R, Ladero JM, Benitez J. Lung cancer and mutations at the polymorphic NAT2 gene locus. *Pharmacogenetics* 1995, **5**, 207–214.
72. Legha SS, Ring S, Raber M, *et al.* Phase I clinical investigation of benzisoquinolinedione. *Cancer Treat Rep* 1987, **71**, 1165–1169.
73. Leiby JM, Malspeis L, Staubuo AE, Kraut EH, Grever MR. Amonafide (NSC 308847): a clinical phase I study of two schedules of administration. *Proc Am Assoc Cancer Res* 1988, **29**, 278.
74. Ratain MJ, Mick R, Berezin F, *et al.* Paradoxical relationship between acetylator phenotype and amonafide toxicity. *Clin Pharmacol Ther* 1991, **50**, 573–579.
75. Ratain MJ, Mick R, Berezin F, *et al.* Phase I study of amonafide dosing based on acetylator phenotype. *Cancer Res* 1993, **53**, 2304–2308.
76. Ratain MJ, Rosner G, Allen S, *et al.* Population pharmacodynamic study of amonafide: a Cancer and Leukemia Group B study. *J Clin Oncol* 1995, **13**, 741–747.
77. Ratain MJ, Mick R, Janisch L, *et al.* Individualized dosing of amonafide based on a pharmacodynamic model incorporating acetylator phenotype and gender. *Pharmacogenetics* 1996, **6**, 93–101.
78. Grant DM, Tang BK, Kalow W. . A simple test for acetylator phenotype using caffeine. *Br J Pharmacol* 1984, **17**, 459–464.
79. Tang DM, Kadar D, Qian L, Iriah J, Yip J, Kalow W. Caffeine as a metabolic probe: validation of its use for acetylator phenotyping. *Clin Pharmacol Ther* 1991, **49**, 648–657.
80. Hinson JA, Kadlubar FF. Glutathione and glutathione transferases in the detoxification of drug and carcinogen metabolises. In Sies H, Ketterer B, eds. *Glutathione Conjugation*. New York, Academic Press 1980, 235–280.
81. Tsuchida S, Sato K. Glutathione transferases and cancer. *CRC Crit Rev Biochem Mol* 1996, **27**, 337–384.
82. Dirven HAAM, van Ommen B, van Bladeren PJ. Involvement of human glutathione-S-transferase isoenzymes in the conjugation of cyclophosphamide metabolites with glutathione. *Cancer Res* 1994, **54**, 6215–6220.
83. Waxman DJ. Glutathione S-transferases: role in alkylating agent resistance and possible target for modulation chemotherapy—a review. *Cancer Res* 1990, **50**, 6449–6454.
84. Lautier D, Canitrot Y, Deeley RG, Cole SPC. Multidrug resistance mediated by the multidrug resistance protein (MRP) gene. *Biochem Pharmacol* 1996, **52**, 967–977.
85. Chen CL, Liu Q, Pui CH, *et al.* Higher frequency of glutathione S-transferase deletions in black children with acute lymphoblastic leukemia. *Blood* 1997, **89**, 1701–1707.
86. Board PG, Coggan M, Johnston P, *et al.* Genetic heterogeneity of the human glutathione transferases: a complex of gene families. *Pharmacol Ther* 1990, **48**, 357–369.
87. Inskip A, Elexperu-Camiruaga J, Buxton N, *et al.* Identification of polymorphism at the glutathione-S-transferase, GSTM3 locus: evidence for linkage with GSTM1*A. *Biochem J* 1995, **312**, 713–716.
88. Schroder KR, Wiebel FA, Reich S, Dannappel DMBH, Hallier E. Glutathione-S-transferase (GST) theta polymorphism influences background SCE rate. *Arch Toxicol* 1995, **69**, 505–507.
89. Anttila S, Luostarinen L, Hirvonen A, *et al.* Pulmonary expression of glutathione S-transferase M3 in lung cancer patients: association with GSTM1 polymorphism, smoking, and asbestos exposure. *Cancer Res* 1995, **55**, 3305–3309.
90. Chen C, Liu Q, Relling MV. Simultaneous characterization of glutathione S-transferase M1 and T1 polymorphisms by polymerase chain reaction in American whites and blacks. *Pharmacogenetics* 1996, **6**, 187–191.
91. Sun GF, Shimojo N, Pi JB, Lee S, Kumagai Y. Gene deficiency of glutathione s-transferase μ isoform associated with susceptibility to lung cancer in a Chinese population. *Cancer Lett* 1997, **113**, 169–172.
92. Katoh T, Nagata N, Kuroda Y, *et al.* Glutathione *S*-transferase M1 (GSTM1) and T1 (GSTT1) genetic polymorphism and susceptibility to gastric and colorectal adenocarcinoma. *Carcinogenesis* 1996, **17**, 1855–1859.
93. Yengi L, Inskip A, Gilford J, *et al.* Polymorphism at the glutathione *S*-transferase locus GSTM3: interations with cytochrome P450 and glutathione *S*-transferase genotypes as risk factors for multiple cutaneous basal cell carcinoma. *Cancer Res* 1996, **56**, 1974–1977.
94. Hall AG, Autzen P, Cattan AR, *et al.* Expression of μ class glutathione *S*-transferase correlates with event-free survival in childhood acute lymphoblastic leukemia. *Cancer Res* 1994, **54**, 5251–5254.
95. Dockham PA, Lee MO, Sladek NE. Identification of human liver aldehyde dehydrogenases that catalyze the oxidation of aldophosphamide and retinaldehyde. *Biochem Pharmacol* 1992, **43**, 2453–2469.
96. Nishiyori A, Fukuda K, Itoh K, Kato H. Genotype–phenotype agreement of aldehyde dehydrogenase 2 in 120 healthy Japanese. *Kurume Med J* 1994, **41**, 117–121.
97. Yoshida A. Molecular genetics of human aldehyde dehydrogenase. *Pharmacogenetics* 1992, **2**, 139–147.
98. Boddy AV, Furtun Y, Sardas S, Sardas O, Idle JR. Individual variation in the activation and inactivation metabolic pathways of cyclophosphamide. *J Natl Cancer Inst* 1992, **84**, 1744–1748.
99. Hadidi AHFA, Coulter CEA, Idle JR. Phenotypically deficient urinary elimination of carboxyphosphamide after cyclophosphamide administration to cancer patients. *Cancer Res* 1988, **48**, 5167–5171.
100. Yule SM, Boddy AV, Cole M. Cyclophosphamide metabolism in children. *Cancer Res* 1995, **55**, 803–809.
101. Boddy AV, Yule SM, Wyllie R, *et al.* Intrasubject variation in children of ifosfamide pharmacokinetics and metabolism during repeated administration. *Cancer Chemother Pharmacol* 1996, **38**, 147–154.
102. Burchell B, Nebert DW, Nelson DR, *et al.* The UDP glucuronosyltransferase gene superfamily: suggested nomenclature based on evolutionary divergence. *DNA Cell Biol* 1991, **10**, 487–494.
103. Tephly T, Green M, Pui J, Irshaid Y. Endogenous substrates for UDP-glucuronosyltransferases. *Xenobiot* 1988, **18**, 1201–1210.
104. Burchell B, Brierly CH, Rance D. Specificity of human UDP-glucuronosyltransferases and xenobiotic glucuronidation. *Life Sci* 1995, **57**, 1819–1831.
105. Clarke DJ, Burchell B. The uridine diphosphate glucuronosyltransferase multigene family: function and regulation. In Kaufman FC, ed. *Handbook of Experimental Pharmacology*. Berlin, Heidelberg, Springer, 1994, **112**, 3–43.
106. Parkinson A. Biotransformation of xenobiotics. In Klaassen CD, ed. *Casarett and Doull's Toxicology: The Basic Science of Poisons*. New York, McGraw, 1996, 113–186.
107. Gupta E, Mick R, Ramirez J, *et al.* Pharmacokinetics and pharmacodynamic evaluation of the topoisomerase inhibitor irinotecan in cancer patients. *J Clin Oncol* 1997, **15**, 1502–1510.
108. Gupta E, Lestingi TM, Mick R, *et al.* Metabolic fate of irinotecan in humans: correlation of glucuronidation with diarrhea. *Cancer Res* 1994, **54**, 3723–3725.
109. Araki E, Ishikawa M, Ligo M, *et al.* Relationship between development of diarrhea and the concentration of SN-38, an active metabolite of CPT-11, in the intestine and the blood plasma of athymic mice following intraperitoneal administration of CPT-11. *Jpn J Cancer Res* 1993, **84**, 697–702.
110. Iyer L, Roy SK, Ratain MJ. *In vitro* glucuronidation of SN-38, the active metabolite of irinotecan (CPT-11) in human liver microsomes. *Proc Am Soc Clin Oncol* 1996, **15**, 1589.
111. Iyer L, King C, Tephly T, Ratain MJ. UGT isoform 1.1 (UGT*1.1) glucuronidates SN-38, the active metabolite of irinotecan. *Proc Amer Soc Clin Oncol* 1997, **16**, 201a.
112. Iyer L, Whitington P, Roy SK, Ratain MJ. Genetic basis for the glucuronidation of SN-38: role of UGT*1 isoform. *Clin Pharmacol Ther* 1997, **61**, 164.
113. Bosma PJ, Seppen J, Goldhoorn B, *et al.* Bilirubin UDP-glucuronosyltransferase 1 is the only relevant bilirubin glucuronidating isoform in man. *J Biol Chem* 1994, **269**, 17960–17964.

114. Crigler JF, Najjar VA. Congenital familial nonhemolytic jaundice with kernicterus. *Pediatrics* 1952, **10**, 69–180.
115. Bosma PJ, Roy Chowdhury J, Huang T-J, *et al.* Mechanisms of inherited deficiencies of multiple UDP-glucuronosyltransferase isoforms in two patients with Crigler-Najjar syndrome, type 1. *FASEB J* 1992, **2**, 2859–2863.
116. Gilbert A, Lereboullet P. Travaux Originaux. *La Semaine Medicale* 1901, **21**, 241–243.
117. Wasserman E, Myara A, Paumier D, *et al.* Baseline bilirubin (bil) and its transient early increase predicts likelihood of severe neutropenia and diarrhea in CPT-11 based chemotherapy. *Proc Am Soc Oncol* 1997, **16**, 219a.
118. Monaghan G, Ryan M, Seddon R, Hume R, Burchell B. Genetic variation in bilirubin UDP-glucuronosyltransferase gene promoter and Gilbert's syndrome. *Lancet* 1996, **347**, 578–581.
119. Bosma PJ, Roy Chowdhury J, Bakker C, *et al.* The genetic basis of the reduced expression of bilirubin UDP-glucuronosyltransferase 1 in Gilbert's syndrome. *N Engl J Med* 1995, **333**, 1171–1175.
120. Monaghan G, Foster B, Jurima-Romet M, Hume R, Burchell B. UGT1*1 genotyping in a Canadian Inuit population. *Pharmacogenetics* 1997, **7**, 153–156.
121. Mahgoub A, Idle JR, Dring LG, Lancaster R, Smith RL. Polymorphic hydroxylation of debrisoquine in man. *Lancet* 1977, **2**, 584–586.
122. Daly AK, Brockmoller J, Broly F, *et al.* Nomenclature for human CYP2D6 alleles. *Pharmacogenetics* 1996, **6**, 193–201.
123. Lennard MS. Genetic polymorphism of sparteine/debrisoquine oxidation: a reappraisal. *Pharmacol Toxicol* 1990, **67**, 273–283.
124. Chen S, Chou W, Blouin R, *et al.* The cytochrome P450 2D6 (CYP2D6) enzyme polymorphism: screening costs and influence on clinical outcomes in psychiatry. *Clin Pharmacol Ther* 1996, **60**, 522–534.
125. Beyeler C, Daly A, Armstrong M, *et al.* Phenotype/genotype relationships for the cytochrome P450 enzyme CYP2D6 in rheumatoid arthritis: influence of drug therapy and disease activity. *J Rheumat* 1994, **21**, 1034–1039.
126. Funck-Brentano C, Thomas G, Jacqz-Algrain E, *et al.* Polymorphism of detromethorphan metabolism: relationships between phenotype, genotype and response to the administration of encainide in humans. *J Pharmacol Exp Ther* 1992, **263**, 780–786.
127. Tseng YC, Wang SL, Lai MD, Lai ML, Huang JD. Formation of morphine from codeine in Chinese subjects of different CYP2D6 genotypes. *Clin Pharmacol Ther* 1996, **60**, 177–182.
128. Relling MV, Evans WE, Fonne-Pfister R, Meyer UA. Anticancer drugs as inhibitors of two polymorphic cytochrome P450 enzymes, debrisoquin and mephenytoin hydroxylase, in human liver microsomes. *Cancer Res* 1989, **49**, 68–71.
129. Kupfer A, Desmond P, Patwardhan R, Schenker S, Branch RA. Mephenytoin hydroxylation deficiency: kinetics after repeated doses. *Clin Pharmacol Ther* 1984, **35**, 33–39.
130. Sullivanklose TH, Ghanayem BI, Bell DA, *et al.* The role of the CYP2C9-Leu(359) allelic variant in the tolbutamide polymorphism. *Pharmacogenetics* 1996, **6**, 341–349.
131. Balian JD, Sukhova N, Harris JW, *et al.* The hydroxylation of omeprazole correlates with S-mephenytoin metabolism—a population study. *Clin Pharmacol Ther* 1995, **57**, 662–669.
132. Marinac JS, Balian JD, Foxworth JW, *et al.* Determination of CYP2C19 phenotype in black Americans with omeprazole: correlation with genotype. *Clin Pharmacol Ther* 1996, **60**, 138–144.
133. Caraco Y, Lagerstrom P-O, Wood AJJ. Ethnic and genetic determinants of omeprazole disposition and effect. *Clin Pharmacol Ther* 1996, **60**, 157–167.
134. Bertilsson L, Henthorn TK, Sanz E, *et al.* Importance of genetic factors in the regulation of diazepam metabolism: relationship to S-mephenytoin but not debrisoquine hydroxylation phenotype. *Clin Pharmacol Ther* 1989, **45**, 348–355.
135. Ward SA, Walle T, Walle UK, Wilkinson GR, Branch RA. Propranolol's metabolism is determined by both mephenytoin and debrisoquin hydroxylase activities. *Clin Pharmacol Ther* 1989, **45**, 72–79.
136. Goldstein JA, de Morais SMF. Biochemistry and molecular biology of the human CYP2C subfamily. *Pharmacogenetics* 1994, **4**, 285–299.
137. Inaba T. Phenytoin: pharmacogenetic polymorphism of 4′-hydroxylation. *Pharmacol Ther* 1990, **46**, 341–347.
138. Busse D, Cosme J, Beaune P, Kroemer HK, Eichelbaum M. Cytochromes of the P450 2C subfamily are the major enzymes involved in the O-demethylation of verapamil in humans. *Naun-Schm Arch Pharmacol* 1995, **353**, 116–121.
139. Kleinbloesem CH, van Brummelen P, Faber H, *et al.* Variability in nifedipine kinetics and dynamics: a new oxidation polymorphism in man. *Biochem Pharmacol* 1984, **33**, 3721–3724.
140. Horsmans Y, Desager JP, Harvengt C. Absence of CYP3A genetic polymorphism assessed by urinary excretion of 6 beta-hydroxycortisol in 102 healthy subjects on rifampicin. *Pharmacol Toxicol* 1992, **71**, 258–261.
141. Relling MV, Evans R, Dass C, Desiderio DM, Nemec J. Human cytochrome P450 metabolism of teniposide and etoposide. *J Pharmacol Exp Ther* 1992, **261**, 491–496.
142. Chang TKH, Weber GF, Crespi CL, Waxman DJ. Differential activation of cyclophosphamide and ifosphamide by cytochromes P-450 2B and 3A in human liver microsomes. *Cancer Res* 1993, **53**, 5729–5737.
143. Walker D, Flinois JP, Monkman SC, *et al.* Identification of the major human hepatic cytochrome P450 involved in activation and N-dechloroethylation of ifosfamide. *Biochem Pharmacol* 1994, **47**, 1157–1163.
144. Zhou XJ, Zhou-Pan XR, Gauthier T, *et al.* Human liver microsomal cytochrome P450 3A isozymes mediated vindesine biotransformation. *Biochem Pharmacol* 1993, **45**, 853–861.
145. Wacher MJ, Chi-Yuan W, Benet LZ. Overlapping substrate specificities and tissue distribution of cytochrome P450A and p-glycoprotein: implications for drug delivery and activity in cancer chemotherapy. *Mol Carcinogen* 1995, **13**, 129–134.
146. Zhou-Pan XR, Seree E, Zhou XJ, *et al.* Involvement of cytochrome P450 3A in vinblastine metabolism: drug interactions. *Cancer Res* 1993, **53**, 5121–5126.
147. Harris JW, Rahman A, Kim BR, Guengerich P, Collins JM. Metabolism of taxol by human hepatic microsomes and liver slices: participation of cytochrome P450 3A4 and an unknown P450 enzyme. *Cancer Res* 1994, **54**, 4026–4035.
148. Royer I, Monsarrat B, Sonnier M, *et al.* Metabolism of docetaxel by human cytochrome P450: interactions with paclitaxel and other antineoplastic drugs. *Cancer Res* 1996, **56**, 58–65.
149. Kroemer HK, Gautier JC, Beaune P, *et al.* Identification of P450 enzymes involved in metabolism of verapamil in humans. *Naun-Schm Arch Pharmacol* 1993, **348**, 332–337.
150. Chabot GG. Factors involved in clinical pharmacology variability in oncology. *Anticancer Res* 1994, **14**, 2269–2272.
151. Calabrese EJ. Biochemical individuality: the next generation. *Reg Toxicol Pharmacol* 1996, **24**, S58–S67.
152. Kobayashi K, Ratain M. Individualizing dosing of cancer chemotherapy. *Sem Oncol* 1993, **20**, 30–42.
153. Gurney H. Dose calculation of anticancer drugs: a review of the current practice and introduction of an alternative. *J Clin Oncol* 1996, **9**, 2590–2611.
154. Weber JL. Human DNA polymorphisms and methods of analysis. *Curr Opin Biotech* 1990, **1**, 166–171.
155. Elrich HA, Arnheim N. Genetic analysis using the polymerase chain reaction. *Ann Rev Genetics* 1992, **26**, 479–506.
156. Vas Á. Polymerase chain reaction and other gene techniques in pharmacogenetics: an introduction and review. *Acta Physiol Hung* 1992, **79**, 253–260.

Acknowledgements—The authors would like to thank M. Mortell and H.Y. Tam for their assistance in the preparation of this manuscript. Supported in part by the Clinical Therapeutics Training grant, National Institutes of Health (T32-GM07019).