MINIREVIEW

Canadian Content in the Pages of Drug Metabolism and Disposition:
A Comprehensive Historical Analysis

David S. Riddick

Department of Pharmacology and Toxicology, Medical Sciences Building,
University of Toronto, Toronto, Ontario, Canada
Running title: History of Canadian content in the pages of DMD

Corresponding author: David S. Riddick, Department of Pharmacology and Toxicology, Medical Sciences Building, University of Toronto, Toronto, Ontario, Canada M5S 1A8

Tel: (416) 978-0813; Fax: (416) 978-6395;

E-mail: david.riddick@utoronto.ca

No. of text pages 35
No. of tables 4
No. of figures 2
No. of references 458
No. of words in Abstract 178
No. of words in Introduction 308
No. of words in Discussion Not applicable

ABBREVIATIONS: AB, Alberta; AHH, aryl hydrocarbon hydroxylation; AHR, aryl hydrocarbon receptor; ARNT, AHR nuclear translocator; BC, British Columbia; BCRP, breast cancer resistance protein; BHT, butylated hydroxytoluene; CAR, constitutive androstane receptor; CIHR, Canadian Institutes of Health Research; Cmax, peak serum drug concentration; DCE, 1,1-dichloroethylene; DEET, N,N-diethyl-m-toluamide; DEX, dexamethasone; DMD, Drug Metabolism and Disposition; EC, ethyl carbamate; FMO, flavin-containing monooxygenase; GH, growth hormone; GR, glucocorticoid receptor; GST, glutathione S-transferase; HIV, human immunodeficiency virus; MB, Manitoba; MC, 3-methylcholanthrene; MDR, multidrug resistance; MRC, Medical Research Council of Canada; MRP, multidrug resistance-associated protein; N-alkylPP, N-alkylprotoporphyrin IX; NAT, N-acetyltransferase; NF-κB, nuclear factor-κB; NL, Newfoundland & Labrador; NNK, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butane; NOS, nitric oxide synthase; NQO, NAD(P)H-quinone oxidoreductase; NS, Nova Scotia; NSAID, nonsteroidal anti-inflammatory drug; OAT, organic anion transporter; OATP, organic anion transporting polypeptide; ON, Ontario; P450, cytochrome P450; PAH, polycyclic aromatic hydrocarbon; PBPK, physiologically based pharmacokinetics; PK, pharmacokinetics; polyIC, polyinosinic/polyctydilic acid; POR, NADPH-cytochrome P450 oxidoreductase; PXR, pregnane X receptor; QC, Québec; SK, Saskatchewan; tBHQ, t-butylhydroquinone; TCDD, 2,3,7,8-tetrachlorodibenzo-p-dioxin; TCE, trichloroethylene; UAlberta, University of Alberta; UBC, University of British Columbia; UdeM, Université de Montréal; UGT, UDP-glucuronosyltransferase; UManitoba, University of Manitoba; U of T, University of Toronto; USask, University of Saskatchewan; UWO, University of Western Ontario; VC, vinyl carbamate.
Abstract

Scientists from Canadian institutions have a rich history of making interesting and important contributions to the journal *Drug Metabolism and Disposition* (DMD) over the past 51 years. A goal of this minireview is to highlight these contributions and pay tribute to many of the scientists at Canadian institutions that have aided in the evolution of the discipline through their DMD publications. We conducted a geographical and research sectoral analysis of the temporal trends of DMD publications originating from Canadian sources. The fraction of total DMD papers of Canadian origin achieved a peak during the 1990s and since that time, this metric has displayed a pronounced and steady decline to the present situation, where the country needs to be concerned about its potentially vulnerable global status within the realm of drug metabolism and disposition science. Stronger and timely investment by Canadian academic institutions in drug metabolism and disposition science may help to restore the nation’s research excellence in this discipline and ensure a more robust pipeline of appropriately trained scientists to take on careers in academia, industry, and government.

Significance Statement

The substantial contributions made by scientists at Canadian institutions to the journal *Drug Metabolism and Disposition* (DMD) are highlighted and celebrated in this minireview. Analysis of temporal trends in the fraction of total DMD papers of Canadian origin paints a concerning picture of Canada’s current global status in the realm of drug metabolism and disposition science. Further investment in this discipline at Canadian universities may be needed.
Introduction

Canada is the second largest country in the world, with a total area of approximately 10 million km²; however, its estimated population of 40 million places Canada just barely within the world’s top 40 countries. The Huron-Iroquois word “kanata” meaning “village” or “settlement” provides the likely origin of Canada’s name. The Dominion of Canada was officially born on July 1, 1867. Among other things, Canada is known for its scenery, natural resources, ice hockey, maple syrup, extreme politeness, and comedic and musical exports. The map shown in Fig. 1 aims to orient the reader to Canada’s expansive geography and illustrates the population distribution across the country’s various provinces and territories. Canada shares the longest international border in the world with its neighbor, the United States, mostly to the south and with the state of Alaska to the west of Canada’s Yukon territory. It is interesting to note that nearly 90% of all Canadians live within approximately 160 km of the American border.

The purpose of this minireview is to recognize the substantial contributions made by scientists at Canadian institutions to the published content of Drug Metabolism and Disposition (DMD) over the journal’s first 51 years of operation. As a point of clarification, only published papers contributed by a corresponding author from a Canadian institution are included. The content of the minireview is organized geographically, from west coast to east coast, and attention is also paid to the research sector (academia, industry, government) from which contributions originated. The fraction of total DMD papers coming from Canadian sources is analyzed throughout as an important metric. Based on the assumption that DMD represents a desirable venue for scientists in this discipline to publish their work, analysis of temporal trends in this publication metric paints a concerning picture of Canada’s current global status in the realm of drug metabolism and disposition science.
British Columbia

Canada’s Pacific coast features the province of British Columbia (BC), which accounts for about 13.7% of the country’s population (Fig. 1) and about 12.72% of Canadian DMD publications over the decades (Table 1).

University of British Columbia (UBC). UBC and its affiliated institutes are based in Vancouver, the third largest city in Canada. The most prolific contributor to DMD as corresponding author from this province is Frank Abbott (Table 2), whose work has contributed greatly to our understanding of the metabolism and toxicity of the broad-spectrum antiepileptic agent, valproic acid (Singh et al., 1988; Kassahun et al., 1991; Kassahun and Abbott, 1993; Tang et al., 1996; Tang and Abbott, 1997; Gopaul et al., 2000; Gopaul et al., 2003; Surendradoss et al., 2014). In addition to characterizing cytochrome P450 (P450) induction by carbamazepine and its 10,11-epoxide (Panesar et al., 1996), the Abbott group has also studied the metabolism of toxic and carcinogenic N-methylformamides (Mutlib et al., 1990; Mutlib and Abbott, 1992), the large animal tranquilizer xylazine (Mutlib et al., 1992), antineoplastic chloroethylnitrosoureas (Borel and Abbott, 1993a), and clobazam, a benzodiazepine with anticonvulsant properties (Borel and Abbott, 1993b). As frequent collaborators, the groups of Dan Rurak and Wayne Riggs have used a sheep model to characterize the pharmacokinetics (PK) and disposition of the following drugs, often with a focus on the maternal-placental-fetal unit: the antihypertensive labetalol (Yeleswaram et al., 1993), the histamine H1-receptor antagonist diphenhydramine (Tonn et al., 1996; Kumar et al., 1999a; Kumar et al., 1999b; Kumar et al., 2000a; Au-Yeung et al., 2006; Au-Yeung et al., 2007), the antiepileptic valproic acid (Gordon et al., 1995; Kumar et al., 2000c; Kumar et al., 2000b; Wong et al., 2000; Wong et al., 2001), and the selective serotonin reuptake inhibitor fluoxetine (Kim et al., 2004). As well, the Riggs group has studied metabolism of
antineoplastic anthracyclines by allelic variants of aldo-keto reductases (Bains et al., 2008; Takahashi et al., 2008) and carbonyl reductase (Bains et al., 2009).

Several interesting topics have been covered in DMD articles contributed by the group of Gail Bellward, including the induction of hepatic drug-metabolizing enzymes by narcotic analgesics (Bellward et al., 1977; Finlayson and Bellward, 1982), the demonstration of aryl hydrocarbon hydroxylation (AHH) and epoxide hydrolase activities in rat hepatic nuclei (Gontovnick and Bellward, 1981), testosterone metabolism in hepatic cytosolic androgen binding assays (Sunahara and Bellward, 1986), and P450 inhibition by the histamine H2-receptor antagonist cimetidine (Levine and Bellward, 1995; Madeira et al., 2004). Studying the regulation of expression of rat hepatic P450s by gonadal steroids, the Bellward group showed that ovariectomy and androgen treatment influences the induction of CYP2B enzymes by phenobarbital (Chang et al., 1997), manipulation of androgen levels during puberty alters subsequent hepatic P450 expression in adults (Anderson et al., 1998), and the neonatal administration of tamoxifen can also impact adult hepatic P450 levels (Kawai et al., 1999). The group of Thomas Chang characterized the variation in mRNA levels for the constitutive androstane receptor (CAR) and the pregnane X receptor (PXR) in human liver (Chang et al., 2003), as well as the developmental expression and endocrine regulation of CYP1B1 in rat testis (Leung et al., 2009). Another focus of the Chang group has been on the modulation of drug-metabolizing enzymes by natural herbal remedies, and this work has considered P450 inhibition (Chang et al., 2002) and induction (Yu et al., 2005) by ginseng extracts and individual constituents, as well as P450 inhibition (Lau and Chang, 2009) and induction primarily via PXR agonism (Chang et al., 2006; Yeung et al., 2008; Lau et al., 2012a; Lau et al., 2012b) by *Ginkgo biloba* extracts and individual constituents. Work from the group of Stelvio Bandiera has
characterized the metabolism of both primary (Deo and Bandiera, 2008b) and secondary (Deo and Bandiera, 2008a; Deo and Bandiera, 2009) bile acids in rat and human liver systems.

Other UBC scientists have studied the metabolism of acetylhydrazine, a hepatotoxic isoniazid metabolite (Wright and Timbrell, 1978), the metabolism of biologically active vitamin D₃ by mouse and human liver CYP3A enzymes (Deb et al., 2012), the presence of active UDP-glucuronosyltransferase 1A (UGT1A) proteins in the mouse blastocyst (Collier et al., 2014), and the ontogeny and variability of human hepatic NAD(P)H-quinone oxidoreductase 1 (NQO1) (Rougee et al., 2016). A recent study developed a physiologically based pharmacokinetics (PBPK) model to predict the absorption profiles of vismodegib, an antineoplastic agent with unique nonlinear oral PK properties (Lin et al., 2022).

Simon Fraser University. Research from this institution located in Burnaby, BC has resulted in two DMD publications; the first reported the PK and metabolism of 4-chlorodiphenyl ether in rats (Chui et al., 1987) and the second developed a PBPK model for matrine, a bioactive marker constituent of a complex botanical drug prepared from six different Chinese herbs (Gao and Law, 2009).

Prairie Provinces (Alberta, Saskatchewan, Manitoba)

Moving eastward across the prairies, the provinces of Alberta (AB), Saskatchewan (SK), and Manitoba (MB) account for about 11.8%, 3.1%, and 3.6%, respectively, of Canada’s population (Fig. 1) and have contributed 10.31%, 5.04%, and 2.63%, respectively, of Canadian DMD papers to date (Table 1).

University of Alberta (UAlberta). Edmonton, the capital city of AB and Canada’s fifth largest city, is home to UAlberta and its affiliated institutes. The leading contributor to DMD as
corresponding author from the province of AB is Ayman El-Kadi (Table 2), who identified \textit{t}-butylhydroquinone (tBHQ) as an activator of the aryl hydrocarbon receptor (AHR) (Gharavi and El-Kadi, 2005), studied the transcriptional regulation of drug-metabolizing enzymes by various toxic metals and metalloids (Korashy and El-Kadi, 2006; Anwar-Mohamed and El-Kadi, 2008; Anwar-Mohamed et al., 2012), and documented sex differences in P450 expression in various rat tissues (Gerges and El-Kadi, 2023). A major interest of the El-Kadi group is the role of P450s in arachidonic acid metabolism (El-Sherbeni and El-Kadi, 2014) and alterations in these pathways in various disease models including: doxorubicin nephrotoxicity, hepatotoxicity (Zordoky et al., 2011), and cardiotoxicity (Alsaad et al., 2012); isoproterenol-induced cardiac hypertrophy (Zordoky et al., 2008; Altherwi et al., 2015); and angiotensin II-induced cardiac hypertrophy (Shoieb and El-Kadi, 2018; Alammari et al., 2023). Interestingly, this group also showed that 19(S)-hydroxyeicosatetraenoic acid is a more potent endogenous noncompetitive inhibitor of human CYP1B1 than the R-enantiomer (Shoieb et al., 2019).

The group of Yun Tam, along with UAlberta colleagues, made extensive use of isolated perfused rat liver models to characterize the disposition kinetics of lidocaine (Gray et al., 1987; Saville et al., 1987; Tam et al., 1987; Ngo et al., 1995; Zaman et al., 1996), diltiazem (Hussain et al., 1994b), and the kinetic interactions of lidocaine and other drugs with diltiazem (Hussain et al., 1994a). This group also developed a series-compartment model for the hepatic elimination of drugs (Gray and Tam, 1987). With interests in the stereochemical aspects of drug action and disposition and the influence of pathophysiological conditions on drug disposition, the group of Fakhreddin Jamali has contributed DMD articles addressing the PK of the catecholamine and serotonin depletor, tetrabenazine (Mehvar et al., 1987), and the stereoselective PK of nonsteroidal anti-inflammatory drugs (NSAIDs) such as ketoprofen (Foster and Jamali, 1988).
and etodolac (Brocks and Jamali, 1990). The Jamali group has also used rat arthritis models to study the effect of inflammation and anti-inflammatory drug treatment on the PK of propranolol (Piquette-Miller and Jamali, 1995) and verapamil (Ling and Jamali, 2005).

Early DMD papers from UAlberta scientists analyzed the human PK of the carcinostatic agent, 9-ß-D-arabinofuranosyladenine (LePage et al., 1973), human urinary metabolites of 13C-labeled butylated hydroxytoluene (BHT) (Wiebe et al., 1978), and the metabolism in rat systems of the antispasmodic agent, isometheptene (Taylor and Coutts, 1977), as well as amphetamines, derivatives and metabolites (Coutts et al., 1976a; Coutts et al., 1976b). Moving into the 1990s, work from UAlberta characterized the metabolism of the ß-adrenergic receptor agonist, methoxyphenamine, by human CYP2D6 (Coutts et al., 1994), the metabolism by human CYP3A4 of the antidepressant trazodone (Rotzinger et al., 1998), the metabolism of racemic mexiletine, an antiarrhythmic drug, by the fungus Cunninghamella echinulata (Freitag et al., 1997), and the mouse PK of an antiherpetic drug, 5-ethyl-2’-deoxyuridine, and its prodrug forms (Cheraghali et al., 1995). Other research from this institution examined the role of rat CYP3A enzymes in the metabolism of the antiarrhythmic drug, amiodarone (Shayeganpour et al., 2006), and the handling of tecadenoson, an adenosine A1-receptor agonist, by equilibrative nucleoside transporters (Lepist et al., 2013). The group of Elaine Leslie studied the transport by multidrug resistance-associated protein 1 (MRP1) of various methylated arsenical species (Carew et al., 2011; Banerjee et al., 2018), and demonstrated the association of glutathione S-transferase P1 (GSTP1) with the intracellular surface of the plasma membrane in human cell lines (Qazi et al., 2011).

*Agriculture & Agri-Food Canada.* Government scientists at this research facility located in Lethbridge, AB have contributed to our understanding of the metabolism and disposition of
chemicals of agricultural interest. Using primarily rat liver microsomes, the group of Wesley Taylor studied the metabolism of the following insect repellents: the citronellal derivative, 3-acetyl-2-(2,6-dimethyl-5-heptenyl)oxazolidine (Taylor, 1983); N,N-diethyl-\textit{m}-toluamide (DEET) (Taylor, 1986; Yeung and Taylor, 1988); and N,N-diethylbenzamide, a compound closely related to DEET (Taylor et al., 1993). The Taylor group also reported a PK assessment of DEET dermal absorption in cattle (Taylor et al., 1994) and detected metabolites of N,N-diethylbenzamide and related compounds in rat urine (Taylor et al., 1995). Colleagues at this government agency also studied the clearance and demethylation of caffeine in sheep and cattle (Danielson and Golsteyn, 1996).

\textit{University of Saskatchewan (USask).} The city of Saskatoon, SK provides the setting for USask. The most frequent contributor to DMD as corresponding author from the province of SK is Edward Hawes, with a long-standing interest in quaternary ammonium-linked glucuronide metabolites of various drugs (Hawes, 1998) such as the antidepressant doxepin (Luo et al., 1991), the model aromatic tertiary amine 1-phenylimidazole (Vashishtha et al., 2000) and other 1-substituted imidazoles (Vashishtha et al., 2001), as well as nicotine and cotinine (Ghosheh et al., 2001; Ghosheh and Hawes, 2002b; Ghosheh and Hawes, 2002a). The Hawes group also studied the N-oxygenation of the antipsychotic clozapine by human liver flavin-containing monooxygenase (FMO) enzymes (Tugnait et al., 1997). The group of Kamal Midha contributed several DMD publications reporting the measurement in urine and other biological matrices from multiple species of the following drugs and/or metabolites: the hallucinogen \textit{p}-methoxy-amphetamine (Hubbard et al., 1981), the antidepressant doxepin (Shu et al., 1990a; Shu et al., 1990b), and the antipsychotics chlorpromazine (Chaudhary et al., 1988), \textit{cis}-flupentixol (Shu et al., 1991) and fluphenazine (Jackson et al., 1991).
Other USask scientists have reviewed drug glucuronidation in patients with renal failure (Verbeeck, 1982), characterized the N-methylation of the antidepressant phenelzine (Yu et al., 1991), and studied the disposition of the β-adrenergic receptor blockers propranolol and metoprolol in isolated perfused rat liver models (Semple and Xia, 1994; Semple and Xia, 1995; Wang and Semple, 1997). The rat metabolism and PK of the monoamine oxidase inhibitor and antiapoptotic agent, (R)-N-(2-heptyl)-N-methylpropargylamine, was reported (Durden et al., 2000), as was the inhibition of rat liver microsomal CYP1A2 and 2B1 by this and related compounds (Dyck and Davis, 2001). Reaction phenotyping studies suggested a prominent role for CYP3A4 in the metabolism of the antipsychotic haloperidol (Fang et al., 2001) and collected data revealed important inconsistencies with the underlying assumptions of a rat hepatic P450 ontogeny model (Alcorn et al., 2007).

University of Manitoba (UManitoba). Winnipeg, the capital city of MB and Canada’s seventh largest city, is home to UManitoba and its affiliated institutes. The leading contributor to DMD as corresponding author from this province is Brian Hasinoff, whose group contributed substantially to our understanding of the metabolism of the anthracycline cardioprotective agent dexrazoxane (ICRF-187), including pathways involved in the drug’s conversion to the active iron-chelating form (Hasinoff et al., 1991; Hasinoff, 1993; Hasinoff and Aoyama, 1999; Schroeder et al., 2002; Schroeder and Hasinoff, 2005; Schroeder et al., 2005; Schroeder et al., 2008). The inaugural DMD issue published in January 1973 featured the first contribution from a corresponding author from a Canadian institution, Brent Schacter at UManitoba, who reported that stimulated microsomal lipid peroxidation triggers the rapid degradation of heme and hemoproteins (Schacter et al., 1973).

Other UManitoba investigators reported the metabolism of the diuretic furosemide in
patients with acute pulmonary edema (Perez et al., 1979), the rabbit metabolism and PK of a monohydroxylated metabolite of the immunosuppressant cyclosporine (Copeland et al., 1990), the acetylation of the antiviral amantadine by spermidine/spermine $N_1$-acetyltransferase (Bras et al., 2001), and a comparison of blood-brain barrier models for their drug efflux transport kinetics (Bachmeier et al., 2006).

**Ontario**

The province of Ontario (ON) makes up about 39.0% of Canada’s population (Fig. 1) and has contributed about 44.74% of Canadian DMD publications since the journal was launched (Table 1). Several institutions will be considered in this section, moving from west to east across the province.

*University of Windsor.* As one of my undergraduate teachers in the mid-1980s, Bruce Virgo was the first person that I ever heard speak the words “cytochrome P450”. Based at this institution in Canada’s southernmost city, the Virgo group studied the effects of somatostatin and testosterone on hepatic P450s in castrated male rats (Virgo, 1985) and the neonatal imprinting of rat hepatic P450s and steroid 5α-reductase by gonadal steroids (Reyes and Virgo, 1988).

*University of Western Ontario (UWO).* Working at UWO located in the city of London, ON, the group of John Bend characterized the mechanism-based inactivation of guinea pig hepatic and pulmonary P450s by various derivatives of 1-aminobenzotriazole (Woodcroft et al., 1990; Sinal and Bend, 1996; Sinal et al., 1998). The Bend group also studied the selectivity of human GSTs toward alkene and polycyclic arene oxide substrates (Dostal et al., 1988) as well as the effects of arsenite on NQO activity in rat liver, lung, kidney, and heart (Falkner et al., 1993). Of great significance to this author, Prof. Bend served as the external examiner for my Ph.D.
thesis defense at Queen’s University in 1990.

Other scientists from UWO or affiliated institutes in London demonstrated the ability of liposomal amphotericin B and phospholipase A2-II to enhance cisplatin and carboplatin cytotoxicity in human oral squamous cell carcinoma cell lines (Ferguson et al., 1999), and the efflux transport by P-glycoprotein (multidrug resistance 1, MDR1) of endoxifen, the active metabolite of tamoxifen (Teft et al., 2011). Rats with moderate chronic kidney disease show down-regulated hepatic CYP2C and 3A enzyme levels (Velenosi et al., 2012) and protein restoration elevates hepatic CYP2C11 and 3A activity in adulthood in low-birth-weight rat offspring born to dams fed a low-protein diet (Sohi et al., 2014). CYP3A expression and activity were shown to be decreased in human subjects with nonalcoholic fatty liver disease as well as in mouse and in vitro cellular models (Woolsey et al., 2015), whereas this condition does not appear to affect the human PK of apixaban, a direct-acting oral anticoagulant, or rosuvastatin (Tirona et al., 2018). Use of a newly developed knockout mouse model characterized organic anion transporting polypeptide 2B1 (OATP2B1) as a determinant of oral fexofenadine absorption but not rosuvastatin disposition (Medwid et al., 2019).

University of Waterloo. This institution is in the sister cities of Kitchener-Waterloo, together ranked as Canada’s tenth largest city. Use of meta-regression analyses suggested that mean small intestinal transit time does not differ between children and adults (Maharaj and Edginton, 2016).

University of Guelph. Just a half-hour down the highway in the city of Guelph, ON, researchers studied the P450-mediated metabolism of the microbial tryptophan metabolite, 3-methylindole, by pig liver microsomes (Diaz et al., 1999) and primary cultured porcine hepatocytes (Terner et al., 2006), as well as the effects of cytochrome b5 on the metabolism of
chlorzoxazone by pig P450s (Wiercinska and Squires, 2010). In addition, interleukin-1β was shown to down-regulate α-class GSTs in cultured human Caco-2 cells (Romero et al., 2002).

*University of Toronto (U of T).* Toronto, the capital city of ON and Canada’s largest city, is home to U of T and its affiliated institutes. The leading contributor to DMD as corresponding author from the province of ON and all of Canada by a rather impressive margin is Sandy Pang (Table 2), whose contributions to the journal span across five decades from the 1980s to the 2020s. During the 1980s, the Pang group made good use of perfused rat liver systems to study the kinetics of formation of active metabolites from quinidine (Yu et al., 1982), the kinetics of procainamide N-acetylation (Pang et al., 1984b), the kinetics of meperidine N-demethylation (Babiak et al., 1984), and the lack of a compensatory increase in glucuronidation when acetaminophen sulfation is inhibited (Fayz et al., 1984). Also using a perfused rat liver preparation, data suggested the presence of a diffusional barrier into hepatocytes for enalaprilat, the diacid metabolite of enalapril (Pang et al., 1984a); this diffusional barrier was found to retard the entry of preformed enalaprilat into hepatocytes (de Lannoy and Pang, 1986) and the effects of diffusional barriers were extended to a broader consideration of drug and metabolite kinetics (de Lannoy and Pang, 1987). The metabolism of acetaminophen and phenacetin by isolated rat hepatocytes was characterized (Pang et al., 1985) and a perfused rat small intestinal preparation was used to study the absorption and metabolism of acetaminophen (Pang et al., 1986). The first-pass metabolism of salicylamide was investigated in a once-through vascularly perfused rat intestine-liver preparation (Xu et al., 1989), and a commentary was contributed on methods and assumptions in kinetic estimates of metabolite formation (Pang and Kwan, 1983).

The early 1990s saw a commentary from the Pang group addressing the effects of hepatic blood flow on metabolite formation (Pang and Mulder, 1990), as well as experimental work on
the intestinal vs. liver first-pass metabolism of gentisamide, the hydroxylated metabolite of salicylamide, using the once-through vascularly perfused rat intestine-liver preparation (Hirayama and Pang, 1990) and in vivo approaches (Hirayama et al., 1990). The localization of glutathione conjugation activity toward bromosulfophthalein was investigated in the perfused rat liver (Zhao et al., 1993), the kinetics of glutathione depletion by acetaminophen was reported in a simulation study (Chiba and Pang, 1995), the uptake of sulfate conjugates by isolated rat hepatocytes was studied (Hassen et al., 1996), and the use of enriched periportal and perivenous isolated rat hepatocytes revealed a lack of zonal uptake of estrone sulfate (Tan et al., 1999). Isolated perfused rat kidney models were used to examine the glycine conjugation of benzoic acid (Poon and Pang, 1995), the intracellular esterolysis of enalapril (Sirianni and Pang, 1998), and the increased urinary clearance of enalapril when its esterolysis is inhibited (Sirianni and Pang, 1999). In terms of kinetics of sequential metabolism, the contributions of parallel primary metabolic pathways to the formation of a common secondary metabolite were considered (Pang, 1995), and a sequestered endoplasmic reticulum space for the sequential hydroxylation and glucuronidation of salicylamide was proposed (Tirona and Pang, 1996). A detailed comparison of dispersion and Goresky models for hepatic clearance was contributed (Tirona et al., 1998). Further work from the Pang group during the 2000s employed zonal isolated rat hepatocytes to study uptake of enalapril and expression of OATP1 (Abu-Zahra et al., 2000), enalapril hydrolysis (Abu-Zahra and Pang, 2000), and the rate-limiting nature of sulfation in the futile cycling between estrone and estrone sulfate (Tan and Pang, 2001). An isolated perfused rat liver system revealed the role of haptoglobin in the uptake of native and cross-linked human hemoglobins (Chow et al., 2008). Several DMD papers focused on various aspects of intestinal drug absorption and/or metabolism: a new physiologically based, segregated-flow model to
explain route-dependent intestinal metabolism (Cong et al., 2000); the impact of segmental intestinal transporters and enzymes on intestinal drug absorption (Tam et al., 2003b); and the use of the vascularity perfused rat small intestine preparation to characterize the segmental absorption of benzoic acid (Cong et al., 2001) and the involvement of MDR1 and an unstirred water later in barring digoxin absorption (Liu et al., 2006). The Pang group also reviewed modeling of the roles of transporters and metabolic enzymes in intestinal drug absorption (Pang, 2003) and contributed a commentary on the roles of transporters and enzymes in hepatic drug processing (Liu and Pang, 2005). Theoretical analyses addressed influences of MDR1, transfer clearances and drug binding on intestinal metabolism (Tam et al., 2003a), permeability, transport and metabolism of solutes in Caco-2 cell monolayers (Sun and Pang, 2008), and the disparity in intestinal disposition between formed and preformed metabolites (Sun and Pang, 2009).

More recent work from the Pang group has had a strong focus on various aspects of PBPK modeling: nonlinear PK of verapamil and the drug’s fractional clearance by hepatic N-demethylation (Yang et al., 2015); a segregated flow model describing the in vivo rat intestinal and hepatic glucuronidation of morphine (Yang et al., 2016); theoretical predictions of flow effects on intestinal and systemic availability (Pang and Chow, 2012); and PBPK-pharmacodynamic modeling of active vitamin D₃ and its receptor-mediated actions in mice (Ramakrishnan et al., 2016; Yang et al., 2018). Other contributions examined MRP2-mediated excretion of estradiol conjugates to illustrate the interplay of phase II enzymes and transporters in futile cycling (Sun et al., 2010), characterization of enzyme zonation, physiologic spaces and enzymes and transporters in the liver of chimeric humanized mice (Chow et al., 2016), and approaches for determination of peak serum drug concentration (Cmax) and time to achieve Cmax in multi-compartmental models (Han et al., 2018). Finally, the in vivo rat PK of human amyloid-β₄₀, a
precursor of Alzheimer’s neuritic plaques, was studied following different routes of administration and in the absence or presence of active vitamin D₃ (calcitriol), an inducer of MDR1-mediated brain efflux of amyloid-β₄₀ (Peng et al., 2020).

The group of Micheline Piquette-Miller (Table 2) has reported effects of endotoxin-induced inflammation on several aspects of drug disposition in rodent models: suppressed expression and activity of intestinal MDR1, MRP2 and CYP3A in rats (Kalitsky-Szirtes et al., 2004); altered doxorubicin clearance in mice via differential MDR1 regulation in liver and kidney (Hartmann et al., 2005); suppressed placental expression of several drug transporters and increased fetal accumulation of the hypoglycemic sulfonylurea glyburide in pregnant rats (Petrovic et al., 2008); down-regulation of several hepatic transporters and metabolic enzymes in human immunodeficiency virus (HIV)-1-transgenic rats (Ghoneim and Piquette-Miller, 2016); and suppression of numerous mouse hepatic transporters via a mechanism involving nuclear factor-κB (NF-κB) but not dependent on PXR (Abualsunun and Piquette-Miller, 2017). The polyinosinic/polycytidylic acid (polyIC) model of viral infection results in altered expression of several placental and hepatic transporters in pregnant rats (Petrovic and Piquette-Miller, 2010) and altered maternal and fetal disposition of the HIV protease inhibitor lopinavir due to changes in plasma protein binding, drug metabolism and transport (Petrovic and Piquette-Miller, 2015). Increased hepatobiliary clearance results in reduced maternal and fetal exposure to lopinavir in a rat model of gestational diabetes (Anger and Piquette-Miller, 2011) and pregnant mice infected with the malarial parasite Plasmodium berghei show altered expression of hepatic and fetal drug transporters (Cressman et al., 2014). PXR activators were shown to induce expression of hepatic MRP3, an important bile acid efflux transporter (Teng et al., 2003), the induction of mouse hepatic P450s and transporters by the hepatocarcinogen 2-acetylaminoﬂuorene was found to be
PXR-mediated (Anapolsky et al., 2006), and a repressive role of PXR in the basal expression of several placental transporters in pregnant mice was demonstrated along with a lack of induction of placental transporters by exogenous PXR activators (Gahir and Piquette-Miller, 2011). The Piquette-Miller group also reported altered glyburide transport by the Q141K variant of the human breast cancer resistance protein (BCRP) (Pollex et al., 2010) and recently reviewed the regulation of expression of placental amino acid transporters by inflammation and infection (McColl et al., 2022).

The group of Jack Uetrecht (Table 2) has contributed greatly to our understanding of the roles of metabolism, covalent binding, and the immune system in a range of idiosyncratic drug reactions. The bioactivation of several drugs by the myeloperoxidase system, the major oxidative enzyme in activated neutrophils, has been studied along with implications for adverse reactions including drug-induced agranulocytosis or lupus: oxidation to reactive metabolites of the antithyroid drug propylthiouracil (Waldhauser and Uetrecht, 1991); oxidation of the antiarrhythmic procainamide to a reactive hydroxylamine (Uetrecht and Sokoluk, 1992); metabolism of the tuberculostatic agent isoniazid to isonicotinic acid (Hofstra et al., 1992); N-chlorination of the antibiotics sulfamethoxazole and dapsone (Uetrecht et al., 1993); oxidation of 5-aminosalicylic acid, a treatment for inflammatory bowel disease, to a reactive iminoquinone (Liu et al., 1995); covalent binding of oxidative metabolites of the anticonvulsant carbamazepine (Furst et al., 1995); conversion of desmethyldeschlorobenzoylindomethacin, a metabolite of the NSAID indomethacin, to a reactive intermediate (Ju and Uetrecht, 1998); bioactivation and covalent binding of hydroxyfluperlapine, a metabolite of the non-marketed atypical antipsychotic fluperlapine (Lai et al., 2000); and metabolism of the antiplatelet drug ticlopidine (Liu and Uetrecht, 2000). The Uetrecht group also explored potential bioactivation pathways for the
anticonvulsant lamotrigine (Lu and Uetrecht, 2007) and studied the role of bioactivation of hydroxylated metabolites of carbamazepine and phenytoin by peroxidases in idiosyncratic drug reactions (Lu and Uetrecht, 2008). Roles of minocycline bioactivation in drug-induced lupus and hepatitis were discussed (Mannargudi et al., 2009) and the paradoxical attenuation of experimental autoimmune hepatitis by isoniazid in mice immunized with isonicotinic acid-modified hepatic proteins was reported (Metushi et al., 2014). Most recently, the Uetrecht group reviewed the value, or lack thereof, of in vitro assays for prediction of idiosyncratic drug-induced liver injury (Kenna and Uetrecht, 2018).

Early work by the group of Tadanobu (Ted) Inaba (Table 2) focused on rat biliary excretion of diazepam (Inaba et al., 1974) and phenytoin (Inaba and Umeda, 1975), as well as the identification of N-hydroxylation as an important pathway for metabolism of amobarbital (Tang et al., 1975) and pentobarbital (Tang et al., 1977) in human subjects. Using in vitro preparations derived from human livers, the Inaba group studied the P450-mediated metabolism of mephenytoin (Jurima et al., 1985b), screened compounds for inhibition of mephenytoin hydroxylation and sparteine monooxygenation (Inaba et al., 1985), showed independent variation in the N-demethylation vs. 3-hydroxylation of diazepam (Inaba et al., 1988), and used the large interindividual variation in sparteine oxidation kinetics to suggest the presence of multiple alleles in extensive metabolizer populations (Tyndale et al., 1989). Focusing on reductive metabolism, the Inaba group reported that haloperidol reductase of human and guinea pig liver shows characteristics of a ketone reductase (Inaba and Kovacs, 1989), studied structure-activity relationships among substrates of human liver cytosolic carbonyl reductase (Wong et al., 1992), and documented the metabolism of acetohexamide, an oral antidiabetic drug, in human erythrocytes (Kishimoto et al., 1994). Colleagues at U of T (Werner Kalow, Bing-Kou Tang,
Dezso Kadar) also studied the metabolism and disposition of isoproterenol in cats (Kadar et al., 1978), N-glucoside formation as a major metabolic pathway for phenobarbital in human subjects (Tang et al., 1979), and identification of 5-acetylamino-6-formylamino-3-methyluracil as a major caffeine metabolite in human subjects (Tang et al., 1983). Further experiments with in vitro preparations derived from human livers screened steroids as inhibitors of mephenytoin hydroxylation (Jurima et al., 1985a), demonstrated a role for a polycyclic aromatic hydrocarbon (PAH)-inducible P450 in the metabolism of caffeine and its primary dimethylxanthine metabolites (Campbell et al., 1987), screened substrates to distinguish cytosolic alcohol dehydrogenase variants (Kassam et al., 1989), and resulted in a sensitive assay for bupranolol hydroxylation as an index of CYP2D6 activity (Appanna et al., 1996). Finally, Prof. Kalow contributed a commentary putting pharmacogenetics, ecogenetics, and inborn resistance to infectious diseases into a broad perspective (Kalow, 2001).

Several interesting findings have emerged from Rachel Tyndale’s group, including a characterization of the enzyme kinetics for dextromethorphan conversion to dextrorphan by CYP2D1 in rat brain (Tyndale et al., 1999), and a summary of the early studies on the metabolism of nicotine and alteration of smoking behavior and risk by genetically-variable CYP2A6 and the potential for therapeutic applications of CYP2A6 inhibitors (Tyndale and Sellers, 2001). Various aspects of nicotine pharmacology have been a focus of DMD papers from the Tyndale group: the induction and recovery time course of rat brain CYP2E1 after nicotine treatment (Joshi and Tyndale, 2006); induction of hepatic CYP2E1 and chlorzoxazone hydroxylation in African green monkeys by chronic nicotine treatment (Lee et al., 2006a); increased hepatic CYP2E1 and chlorzoxazone hydroxylation in African green monkeys by ethanol self-administration and nicotine treatment, alone and in combination (Ferguson et al.,
2011); and age-dependent changes in nicotine PK in rats (Craig et al., 2014). This group also characterized nicotine PK in the zebra finch, an established behavioral model, and demonstrated that CYP2B enzymes mediate nicotine metabolism in this species (Miksys et al., 2013). As well, CYP2C19 genetic variants were shown to influence bupropion PK but not smoking cessation outcomes (Zhu et al., 2014). The group of Edward Sellers demonstrated key roles for CYP2C19 in the N-demethylation and CYP3A4 in the 3-hydroxylation of flunitrazepam (Kilicarslan et al., 2001), conducted in vitro testing of methoxsalen, tranylcypromine, and tryptamine as CYP2A6 inhibitors (Zhang et al., 2001), and characterized the nonselective inhibition of multiple human P450s by antifungal imidazole derivatives (Zhang et al., 2002b). The Sellers group also identified the O-demethylation of 18-methoxycoronaridine, an ibogaine analog, as a potential selective probe of CYP2C19 activity (Zhang et al., 2002a) and studied the inhibition of CYP2D6 and CYP3A4 by buprenorphine and its major metabolite norbuprenorphine (Zhang et al., 2003).

Other U of T colleagues of Profs. Tyndale and Sellers reported the catalytic and immunologic similarities between human CYP2D6 and its counterpart in African green monkeys (Otton et al., 1992) and the tissue distribution of CYP2D6 and endogenous murine CYP2D enzymes in CYP2D6-transgenic mice (Miksys et al., 2005).

Other U of T scientists characterized the P450-mediated oxidation of sulfamethoxazole to a hydroxylamine by mouse liver microsomes (Cribb and Spielberg, 1990), the PAH inducibility of CYP1A enzyme activities in three long-term human hepatocyte lines cocultured with rat liver epithelial cells (Roberts et al., 1993), glutathione conjugate formation from dietary dihydroxy-cinnamic acids (Moridani et al., 2001), and the metabolic activation by isolated rat hepatocytes of 4-hydroxyanisole, a depigmenting phenolic melanocytotoxic prodrug (Moridani et al., 2002). The group of Denis Grant generated and characterized novel mouse models with genetic
manipulations of N-acetyltransferase (NAT) enzymes: double Nat1/2-null mice were used to characterize the in vitro and in vivo metabolism of arylamine procarcinogens (Sugamori et al., 2006); Nat3-null mice were used to show minimal roles for this enzyme in the N-acetylation of arylamines (Sugamori et al., 2007); and human NAT2-transgenic mice on the double Nat1/2-null background show liver-selective expression of the human transgene (Sugamori et al., 2011). The Grant group also discovered that CYP2E1 is a novel 4-aminobiphenyl N-oxidizing enzyme in mice and that CYP1A2 plays a more important role in detoxification and clearance (Wang et al., 2015). Allan Okey, my postdoctoral supervisor in the early-1990s, later reported the AHR-dependent induction of mouse hepatic FMO2 and FMO3 mRNAs by 2,3,7,8-tetrachlorodibenzo-\(p\)-dioxin (TCDD) (Celius et al., 2008).

Our laboratory (Table 2) studied the transcriptional down-regulation of the male-specific growth hormone (GH) pulse-regulated rat hepatic CYP2C11 by TCDD and 3-methylcholanthrene (MC), a prototypical PAH, using luciferase reporter plasmids driven by the gene’s promoter and 5’-flanking region in cultured cells (Bhathena et al., 2002) and in rat liver in vivo (Sawaya and Riddick, 2008). The regulation of constitutive hepatic P450s and GH signaling components by MC was also studied in wild-type mice (Lee et al., 2006b) and in mice with conditional hepatic depletion of NADPH-cytochrome P450 oxidoreductase (POR) (Lee et al., 2013b; Lee et al., 2013a). MC also suppresses CYP3A4 expression and activity in the liver of humanized PXR-CAR-CYP3A4/3A7 mice (Crosby and Riddick, 2019). With a focus on regulation of AHR response pathway components by hormonal factors, we studied the glucocorticoid receptor (GR)-mediated induction of the AHR by dexamethasone (DEX) in mouse Hepa-1 cells (Bielefeld et al., 2008), alterations in the AHR pathway and MC response in the liver of adrenalectomized rats (Mullen Grey and Riddick, 2011), and the role of the GR and
PXR in the induction by DEX of rat hepatic AHR nuclear translocator (ARNT) and POR (Hunter et al., 2017). We also contributed symposium reports addressing the transcriptional suppression of P450s by endogenous and exogenous factors (Riddick et al., 2004), cancer chemotherapy and drug metabolism (Riddick et al., 2005), and the roles of POR in physiology, pharmacology, and toxicology (Riddick et al., 2013). Most recently, we reviewed the history of AHR research from a DMD perspective as part of the journal’s 50th anniversary celebration (Riddick, 2023).

Queen’s University. The population of Kingston, ON grows by about 30% each fall with the influx of students, distinguishing this as a proverbial “college town”. Despite the relatively small size of the city housing it, Queen’s University has certainly “punched above its weight” in terms of contributions to DMD over the years. The group of Poh-Gek Forkert (Table 2) examined biochemical and anatomical aspects of the pulmonary and hepatic toxicity for various chemicals. Regarding trichloroethylene (TCE), an industrial solvent, the Forkert group studied covalent binding and morphological features of TCE-induced lung toxicity in mice (Forkert and Birch, 1989), measured TCE and its metabolites in seminal fluid of workers exposed occupationally (Forkert et al., 2003), and compared the activities of expressed recombinant CYP2E1, 2F, and 2B1 enzymes for conversion of TCE to chloral hydrate (Forkert et al., 2005). Studies with 1,1-dichloroethylene (DCE), used in the manufacture of plastics, showed the following: the preferential damage to club cells from exposed mouse lungs correlates with the high monooxygenase capacity and covalent binding in this cell population (Forkert et al., 1990); dose-dependent relationships between covalent binding of DCE metabolites, glutathione depletion, and hepatocellular necrosis in mice (Forkert and Moussa, 1991); preferential sensitivity of club cells with low glutathione levels to DCE-induced cytotoxicity (Forkert and Moussa, 1993); tumor foci in mouse lung show diminished CYP2E1 expression and decreased
formation of the glutathione conjugate derived from the DCE epoxide (Forkert et al., 1999); the high CYP2E1 expression in liver of A/J mice, compared to CD-1 and C57BL/6, coincides with increased DCE bioactivation and hepatotoxic severity (Forkert and Boyd, 2001); and CYP2E1 and CYP2F2 catalyze bioactivation of DCE to its epoxide in mouse lung (Simmonds et al., 2004). Other work focused on ethyl carbamate (EC), also known as urethane, and a primary metabolite of EC, vinyl carbamate (VC): the metabolism of EC in mouse liver microsomes is carried out by CYP2E1 and the carboxylesterase hydrolase A (Lee et al., 1998); VC inactivates CYP2E1, a VC-activating enzyme, and the carboxylesterase hydrolase A, a VC-detoxifying enzyme, in mouse lung microsomes (Lee and Forkert, 1999); similar roles for CYP2E1 and carboxylesterase enzymes in VC metabolism were demonstrated in human lung microsomes (Forkert et al., 2001); and CYP2E1 bioactivates VC to an epoxide that alkylates DNA to form the 1,N6-ethenodeoxyadenosine adduct in mouse lung (Forkert et al., 2007). Other findings from the Forkert group included an immunohistochemical delineation of the mouse lung regional and cellular selectivities for the major MC- and phenobarbital-inducible P450s (Forkert et al., 1989), induction of mouse hepatic CYP2E1 by acute vs. chronic acetone treatment (Forkert et al., 1994), and inactivation of mouse lung and liver CYP2E1 by the garlic derivative diallyl sulfone results in conversion of the heme moiety to an N-alkylprotoporphyrin IX (N-alkylPP) (Black et al., 2006).

The mention of P450 heme modification and N-alkylPP formation provides an ideal segue into the work of Gerald Marks, my doctoral supervisor in the late-1980s. In their DMD publications, the Marks group used sex differences and selective inducers and inhibitors to identify the specific rat liver P450 sources of N-alkylPP formation from various porphyrinogenic xenobiotics (McNamee and Marks, 1996; Wong et al., 1998; Wong et al., 1999). As well,
expressed recombinant human P450s were used to identify the targets for mechanism-based inactivation (McNamee et al., 1997) and the sources of N-alkylPP formation from porphyrinogenic xenobiotics (Lavigne et al., 2002; Gamble et al., 2003). The inhibitory potency of N-methylPP toward human vs. chicken ferrochelatase was also compared (Gamble et al., 2000). Together with other Queen’s colleagues, Prof. Marks also screened various metalloporphyrins for selective heme oxygenase inhibition (Appleton et al., 1999), compared nitric oxide formation from four nitrovasodilators in rabbit aortic strips (Marks et al., 1995), and provided evidence against a role for nitric oxide itself as the vasorelaxant metabolite produced by glycercyl trinitrate (Hussain et al., 1996; Kearney et al., 1998).

Other Queen’s scientists studied the disposition of ethanol and its proximate metabolite, acetaldehyde, in near-term pregnant ewes (Clarke et al., 1988), the disposition of the antiarrhythmic drug amiodarone and its proximate metabolite, desethylamiodarone, in dogs (Brien et al., 1990), and the P450-mediated biotransformation of 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) in human lung microsomes (Smith et al., 2003) with an emphasis on CYP2A enzymes (Brown et al., 2007). The group of Susan Cole showed that flavonoids stimulate human MRP1-mediated glutathione transport (Leslie et al., 2003), glutathione-conjugated catechol metabolites modulate the transport activity of human MRP1 and 2 (Slot et al., 2008), the transport activity of human MRP1, 2, and 4 is modulated by chalcogenopyrylium dyes (Myette et al., 2013), human MRP1 polymorphic variants impact drug resistance and inhibitor sensitivity (Conseil and Cole, 2013), and leukotriene modifiers nonselectively modulate transport by human MRP1-4 (Csandl et al., 2016). The Cole group also conducted mutational analyses of a highly conserved proline residue in human MRP1, 2, and 3 (Letourneau et al., 2007) and the estrone sulfate transport and modulator sensitivity of human MRP1 (Maeno et al.,
Additional mutational analyses of human MRP1 were reported by the group of Roger Deeley (Zhang et al., 2006; Qin et al., 2012; Trofimova and Deeley, 2018), as well as the structural determinants of the substrate specificity differences between human MRP1 and 3 (Grant et al., 2008) and the cloning and characterization of rat MRP1 (Nunoya et al., 2003).

Health Canada and Agriculture & Agri-Food Canada. These federal government institutions are located in Ottawa, ON, Canada’s national capital and sixth largest city. Early studies emphasized the identification of urinary metabolites of various chemicals: metabolites of methoxyphenamine, a ring-methoxylated amphetamine, in humans and monkeys (Midha et al., 1976); 3-O-methyl-α-methyldopamine (Midha et al., 1977) and α-methyldopamine (Midha et al., 1978) as metabolites of 3,4-methylenedioxyamphetamine in dogs and monkeys; O-demethylated metabolites of p-methoxyamphetamine in dogs and monkeys (Hubbard et al., 1977); and 2,6-diamino-5-hydroxy-3-(phenylazo)pyridine as a metabolite of the urinary tract analgesic phenazopyridine in rats (Bailey et al., 1983). There were also investigations of the disposition in rats of various compounds: the phthalate ester plasticizer mono-2-ethylhexyl phthalate (Chu et al., 1978); photomirex, a photodecomposition product of mirex (Chu et al., 1979); and the environmental contaminant octachlorostyrene (Chu et al., 1982). Other government scientists reported the following: extensive first-pass removal of imipramine in the isolated perfused rat liver (Beaubien and Pakuts, 1979); the diphenyl ether cleavage of 3-phenoxypybenzoic acid, a common metabolite of pyrethroid insecticides, by chicken kidney microsomes (Akhtar and Mahadevan, 1992); inhibition of the CYP3A-mediated metabolism of terfenadine in human liver microsomes by macrolide antibiotics andazole antifungals (Jurim-Romet et al., 1994); and quantitative trait loci affecting caffeine metabolism in mice (Casley et al., 1999).
Québec

Scientists from the province of Québec (QC) have contributed about 21.05% of Canadian DMD publications (Table 1), approximately proportional to the province’s share of about 22.1% of the country’s population (Fig. 1).

Université de Montréal (UdeM). This university and its affiliated institutes are based in Montréal, the second largest city in Canada. The group of Patrick du Souich (Table 2) studied the contributions of organs such as liver, small intestine, and lung to the first-pass effect in a rabbit model for drugs such as salbutamol (Perreault et al., 1993), propranolol (du Souich et al., 1995), morphine (Abdallah et al., 1995), and lidocaine (Lê et al., 1996). As well, this group showed the following: sulfamethazine acetylation is induced in rabbits by complete Freund’s adjuvant and high doses of hydrocortisone (du Souich and Courteau, 1981); a nitric oxide precursor and an inhibitor of nitric oxide synthase (NOS) both inhibit rabbit P450-mediated metabolism of theophylline (Barakat et al., 1997); the roles of intestine and liver in the dose-dependent enantioselective disposition of propranolol in rabbits (Marier et al., 1998); and the influence of plasma protein binding (Pichette et al., 1999), fluid replacement and hypoalbuminemia (Castaneda-Hernandez et al., 2000) on the pharmacodynamics of furosemide in rabbits. A major theme of the work from the du Souich group is the effect of inflammation and hypoxia on hepatic drug metabolism, with the relevant DMD papers reporting: increased seromucoid levels and decreased hepatic P450 catalytic activities without an alteration in sulfamethazine acetylation in a rat turpentine-induced inflammation model (Kobusch et al., 1986); increased rabbit blood propofol concentrations by both inflammation and hypoxia due to a decrease in the rate of drug elimination (Audibert et al., 1993); and modulation of multiple hepatic P450s and transporters by acute moderate hypoxia in rabbits and rats (Fradette et al., 2007). Finally, serum
from rabbits with turpentine-induced inflammation and serum from humans with a viral infection
decrease rabbit hepatocyte P450 activities via reactive oxygen intermediates (El-Kadi et al.,
2000), with CYP3A6 showing preferential vulnerability to down-regulation vs. CYP1A1 and
1A2 (Bleau et al., 2001), and roles for signal transduction pathways involving Janus-associated
protein tyrosine kinase, extracellular signal-related kinase 1/2, and NOS2 (Kourylko et al.,
2006). Together with other UdeM colleagues, Prof. du Souich also contributed to work
addressing: the in vivo intrahepatic disposition of propranolol and its metabolites (Ong et al.,
1981); increased serum digoxin concentrations via inhibited uptake into hepatocytes by
amiodarone (Lambert et al., 1989); the role of neutral endopeptidase 24.11 in regulating
endogenous atrial natriuretic factor plasma levels in rabbits (Marleau et al., 1991); decreased
hepatic P450 content and activity in a dog congestive heart failure model (Lambert et al., 1991);
and the rat disposition of hexarelin, a GH secretagogue (Roumi et al., 2000).

Using a rat chronic renal failure model, the group of Vincent Pichette demonstrated
decreased hepatic P450 content and impaired drug metabolism (Leblond et al., 2000), decreased
hepatic uptake transporters and increased efflux transporters (Naud et al., 2008), altered
expression and activity of several kidney transporters leading to intrarenal drug accumulation
(Naud et al., 2011), decreased levels of some brain transporters without compromising the blood-
brain barrier integrity and function (Naud et al., 2012), and down-regulated brain P450 levels via
a mechanism involving hyperparathyroidism (Naud et al., 2016). Prof. Pichette also reported
decreased hepatic P450s and NAT2 at the protein and mRNA levels in a mouse model of chronic
renal failure (Dani et al., 2010) and contributed with other UdeM colleagues to an optimal
experimental design for the in vivo use of 1-aminobenzotriazole as an irreversible and
nonselective inhibitor of intestinal and hepatic P450s while avoiding its confounding effects on
drug absorption (Boily et al., 2015).

Other UdeM scientists reported altered kinetics of sulfacetamide tissue distribution in tumor-bearing rats (Nadeau and Marchand, 1975), the use of P450 spectrophotometric measurements to correct for losses occurring during differential centrifugation (Joly et al., 1975), the role of enterohepatic circulation in phenytoin elimination in rats (El-Hawari and Plaa, 1978), and the increase in hepatic microsomal epoxide hydrolase, glutathione content, and cytosolic GST activities following chronic ethanol administration to rats (Hetu et al., 1982). As well, glucuronidation and biliary excretion are not saturated at high pharmacological doses of isotretinoin (Meloche and Besner, 1986), the beneficial effects of cyclosporine A on liver regeneration after partial hepatectomy do not translate into overall accelerated recovery of liver P450s (Provencher et al., 1999), and CYP3A5 allele frequencies vary across different ethnic populations (Roy et al., 2005).

**McGill University.** Also based in Montréal, scientists at McGill University showed a prolonged methadone half-life in pregnant and lactating guinea pigs (Pak and Ecobichon, 1981), increased clearance of salicylate in protein-deficient rats (Yue and Varma, 1982), altered relative enantioselectivity of ifosfamide N-dechloroethylation by phenobarbital treatment in rats (Granvil et al., 1994), and effects of two prevalent FMO3 polymorphisms on enzymatic activity toward nitrogen-containing substrates (Cashman et al., 2000). There was also a theoretical analysis of the multiple indicator-dilution method for the study of hepatic enzyme heterogeneity (Schwab and Pang, 1999) and reviews of the history of the natural resistance-associated macrophage protein 1 and its role as a determinant of natural resistance to mycobacterial pathogens (Buschman and Skamene, 2001) and characterization of infectious disease susceptibility genes using tuberculosis and leprosy as examples (Marquet and Schurr, 2001).
Université du Québec à Montréal. The single DMD paper from this Montréal-based institution reported the maintenance of basal and inducible P450 activities in rat hepatocytes cryopreserved with wheat protein extract (Grondin et al., 2008).

Université Laval. Based in Québec City, the provincial capital and Canada’s eighth largest city, Université Laval is home to the leading contributor to DMD as corresponding author from the province of QC, Chantal Guillemette (Table 2). The Guillemette group has contributed in multiple ways to our understanding of the pharmacogenomics of the human UGT enzymes. Regarding matching substrates to UGT enzymes, UGT1A4 was shown to be a major contributor to the glucuronidation of tacrolimus (Laverdiere et al., 2011) and abiraterone and its active metabolites (Vaillancourt et al., 2020). As well, UGT2B7 was shown to play a major role in efavirenz glucuronidation and the glucuronidation of efavirenz and zidovudine is inhibited by one another (Bélanger et al., 2009); there is a primary role for UGT2B7 and lesser roles for UGT1A3 and 1A9 in the hepatic glucuronidation of fenofibric acid (Tojcic et al., 2009). This group also reported the metabolism of mycophenolic acid, an active immunosuppressive agent, by UGT1A9 and naturally occurring variants (Bernard and Guillemette, 2004) and several identified UGT1A8 variants (Bernard et al., 2006), the impact of a novel UGT1A9 intronic polymorphism on the glucuronidation of SN-38, the active metabolite of irinotecan (Girard et al., 2006), and specific UGT concentrations and glucuronidation potential of livers assessed accurately by multiplexed targeted quantitative proteomics (Margaillan et al., 2015b). Other findings from the Guillemette group include decreased glucuronidation capacity of neoplastic kidney vs. normal kidney paralleled by decreased UGT1A9 and 2B7 mRNA and protein levels (Margaillan et al., 2015a), impaired enzyme activity of a rare UGT2B7 variant due to creation of a novel N-glycosylation site (Girard-Bock et al., 2016), and development of a specific
monoclonal antibody to UGT2B17 leading to the identification of the transcription factor forkhead box A1 as a key driver of this UGT’s liver expression (Emond et al., 2019). The Guillemette group also uncovered a novel regulatory paradigm for human UGTs, initially showing that the $UGT1A$ gene locus generates alternatively spliced inactive protein products that inhibit the enzymatically active UGTs via protein-protein interactions (Bellemare et al., 2010) and that the relative abundance of the alternative splice variants is a determinant of UGT activity in cellular models (Rouleau et al., 2013). Alternative splicing has been shown to contribute to the variable expression and activity toward various drug substrates for UGT1A6 (Benoit-Biancamano et al., 2009), 2B7 (Menard et al., 2013), and 2B10 (Labriet et al., 2018).

The group of Pierre Bélanger characterized the reduction of 1-nitrosoadamantane, an amantadine metabolite, by rabbit liver microsomes (Bélanger and Grech-Bélanger, 1979), and studied multiple aspects of circadian variations: rat hepatic enzymes involved in the formation and degradation of glucuronide and sulfate conjugates (Bélanger et al., 1985); rat PK of isoniazid and N-acetylisoniazid (Bélanger et al., 1989); and rat hepatic glutathione concentrations and lipid peroxidation (Bélanger et al., 1991). This group also documented species differences in the formation of meta-hydroxymexiletine, a metabolite of the antiarrhythmic drug mexiletine (Grech-Bélanger et al., 1991). Laval colleagues of Prof. Bélanger identified N-hydroxy-mexiletine glucuronide as a mexiletine metabolite in human and rabbit urine (Turgeon et al., 1992), characterized the deacetylation of diltiazem by a rat liver microsomal esterase (LeBoeuf and Grech-Bélanger, 1987), and studied CYP2D6 inhibition by clinically relevant concentrations of classic histamine H$_1$-receptor antagonists (Hamelin et al., 1998).

Other scientists at Laval studied the human urinary metabolites of 9-deoxo-16,16-dimethyl-9-methylene prostaglandin E$_2$ (Steffenrud, 1983), the rat neuropharmacokinetics of
S18986, a positive allosteric modulator of AMPA-type receptors (Bourasset et al., 2005), involvement of GR in the induction of mouse CYP2B genes by DEX (Audet-Walsh and Anderson, 2009), and the decrease in guinea pig hepatic CYP3A expression and activity in a model of diet-induced metabolic syndrome (Patoine et al., 2013). Quinacrine, a lipophilic cationic antiprotozoal agent, is concentrated in cells via vacuolar ATPase-mediated ion trapping (Marceau et al., 2009). Multiple aspects of NNK metabolism were also investigated: the impact of pregnancy and/or ethanol treatment (Jorquera et al., 1992) and tobacco smoke condensate (Jorquera et al., 1993) on NNK metabolism in adult and fetal hamster liver and lung microsomes; and inhibition of NNK activation in mouse lung explants by NSAIDs (Bouchard and Castonguay, 1993). Screening of over 55 xenobiotics as potential substrates for human UGT2B17 revealed a different substrate selectivity compared to other UGT2B enzymes (Turgeon et al., 2003). Other studies from Laval focusing on human UGT enzymes showed: a key role for UGT2B7 in the glucuronidation of 3’-azido-3’-deoxythymidine (Barbier et al., 2000); an essential role of isoleucine at position 211 for the catalytic activity of UGT1A10 (Martineau et al., 2004); and the high activity of UGT2A1 and 2A2 in bile acid glucuronidation (Perreault et al., 2013).

Merck Frosst Canada. Located in Kirkland, QC, a suburb of Montréal, scientists at this company were leading contributors to DMD from the Canadian industrial sector. The group of Deborah Nicoll-Griffith studied the rat biotransformation of verlukast, a leukotriene D4 receptor antagonist (Nicoll-Griffith et al., 1992), including elucidating the role of CYP1A1 in the generation of an epoxide intermediate leading to the production of multiple metabolites (Nicoll-Griffith et al., 1993) and glutathione conjugation of the drug in liver and kidney cytosol (Nicoll-Griffith et al., 1995). This group also published on various aspects of lactone-containing
cyclooxygenase-2 inhibitors: the utility of a lactol derivative as a prodrug form (Nicoll-Griffith et al., 1999); the prediction of in vivo metabolic auto-induction from CYP3A induction data in rat hepatocyte cultures (Nicoll-Griffith et al., 2001); and the suitability of a benzyloxy-substituted lactone as a fluorogenic CYP3A-selective probe substrate in both rat and human cultured primary hepatocytes (Nicoll-Griffith et al., 2004).

The group of Nathalie Chauret contributed two DMD papers on metabolism of 5-lipoxygenase inhibitors showing: the role of CYP3A4 in biotransformation of the naphthalenic lignan lactone L-702,539 (Chauret et al., 1995a); and the importance of the dioxabicyclo moiety of L-739,010 and L-746,530 in microsomal metabolism to reactive intermediates that bind covalently to protein (Chauret et al., 1995b). Important practical investigations from this group compared P450-mediated activities in human, dog, cat, and horse liver microsomes (Chauret et al., 1997), documented the effects of common organic solvents on P450-mediated activities in human liver microsomes (Chauret et al., 1998), and established a novel fluorogenic substrate, 3-[2-(N,N-diethyl-N-methylammonium)ethyl]-7-methoxy-4-methylcoumarin as a selective CYP2D6 probe substrate (Chauret et al., 2001). Other Merck Frosst colleagues optimized culture conditions for assessing P450 induction in rat and human hepatocytes (Silva et al., 1998), conducted in vitro metabolism studies supporting the structural optimization of the phosphodiesterase-IV inhibitor, CDP-840 (Li et al., 2001), showed that rat hepatocytes cryopreserved by a programmed-freezing protocol retain drug transport activities (Houle et al., 2003), and reported a comparison of the metabolism and disposition of paraherquamide, a broad-spectrum anthelminthic, in sheep, gerbils, and dogs (Aloysius et al., 2008).

Ayerst Research Laboratories. Scientists at this company based in Montréal, QC studied the NSAID furobufen, including the disposition in mice, rats, and humans (Cayen et al., 1981b)
and the distribution and excretion in rats and dogs (Cayen et al., 1981a).

*AstraZeneca R&D Montréal.* Located in Ville Saint-Laurent, QC, a borough of Montréal, this company showed important roles for CYP2C8, 3A4, and 2D6 in the N-desethylation of the antimalarial chloroquine (Projean et al., 2003).

**Atlantic Provinces (Nova Scotia, Newfoundland & Labrador)**

Two of the provinces on the Atlantic coast of Canada, Nova Scotia (NS) and Newfoundland & Labrador (NL), have contributed DMD papers over the years: NS and NL account for about 2.6% and 1.3%, respectively, of the country’s population (Fig. 1) and have contributed 3.07% and 0.44%, respectively, of Canadian DMD papers (Table 1).

*Dalhousie University.* Dalhousie and its affiliated institutes are based in Halifax, the provincial capital of NS. The most prolific contributor to DMD as corresponding author from this province is Kenneth Renton, whose group showed that the interferon inducer polyIC modulates the induction of rat hepatic CYP3A1 (Delaporte et al., 1993) and that the animal species and the duration/level of P450 induction influence the suppressive response to polyIC (Anari et al., 1995). This group also showed that fluoroquinolone antibiotics competitively inhibit CYP1A- and CYP3A-mediated drug metabolism in rat and human liver microsomes (McLellan et al., 1996). Further work from the Renton group demonstrated that acute phase cytokines mediate the endotoxin-induced depression of CYP1A activity in cultured astrocytes (Nicholson and Renton, 2002) and the hepatic P450 down-regulation seen in an endotoxin-induced model of central nervous system inflammation involves the actions of hepatic NF-κB and CAAT-enhancer binding protein as well as the rapid transfer of central lipopolysaccharide to the periphery (Abdulla et al., 2005).
Other Dalhousie investigators reported the uptake and metabolism of $\Delta^1$-tetrahydro-cannabinol in the isolated perfused rabbit lung (Law, 1978), compared the metabolism of the animal tranquilizer phencyclidine by isolated perfused lung, liver and lung microsomes of rabbit (Law, 1982), and compared the metabolism and PK of diltiazem in humans, dogs, rabbits, and rats (Yeung et al., 1990). The nitroso and hydroxylamine metabolites of sulfamethoxazole were shown to react with glutathione (Cribb et al., 1991) and developmental changes in $Mdr1a$ expression were found to be important in determining brain cyclosporine A levels in mouse models (Goralski et al., 2006). The organic anion transporter 2 (OAT2) was shown to be expressed in human kidney and to mediate the tubular secretion of guanine-containing antivirals (Cheng et al., 2012) and multiple mechanisms for the inhibition of OAT1 transport activity were analyzed (Hotchkiss et al., 2015). Drug transport at the blood-aqueous humor barrier of the eye was reviewed (Lee and Pelis, 2016) and a symposium report addressed the impact of the COVID-19 virus and vaccines on drug metabolism and PK (McColl et al., 2023).

Memorial University. St. John’s, the capital city of the province of NL, is home to Memorial University. Two DMD papers from this institution addressed the metabolism, covalent binding, and glutathione depletion by the environmental contaminant 2,6-dimethylnaphthalene (Shamsuddin and Rahimtula, 1986) and the hydrolytic activation of the anthracycline cardioprotectant dexrazoxane (ICRF-187) (Hasinoff, 1990).

Concluding Comments

This minireview has strived to illustrate Canada’s rich history of substantial contributions to DMD over the journal’s first 51 years of publication. The main goal of this article is to highlight these contributions and to celebrate the scientists working at Canadian institutions that
have helped to shape our current thinking in the discipline of drug metabolism and disposition. It is important to point out, however, that our analysis has revealed a troubling temporal trend in Canadian DMD publications. As shown in Table 1 and Fig. 2, the fraction of total DMD papers coming from Canadian sources reached a peak of 7.02% in the 1990s, and this metric showed a substantial decline in the 2000s, a further strong decline in the 2010s, and the data for the 2020s show that only 1.55% of DMD papers come from Canadian sources. Overall, this represents a 78% decline in the journal’s Canadian content. The country’s expertise in drug metabolism and disposition is supported by the fact that about 10% of DMD’s current roster of Associate Editors and Editorial Advisory Board members are based at Canadian institutions, but Canada’s current status in the discipline on the global stage appears to be somewhat vulnerable. It is worth noting that our inclusion of only published papers contributed by a corresponding author from a Canadian institution may not fully capture contributions of Canadian scientists in other situations, including those working in labs in Canada or elsewhere with a corresponding author from outside Canada.

To provide context and comparative data for the closely allied discipline of toxicology, we conducted a similar analysis of the temporal trends for Canadian content in the journal *Toxicological Sciences*, which has a comparable 43-year publication history starting in 1981 as *Fundamental & Applied Toxicology*. Data in Supplemental Table 1 and Supplemental Fig. 1 show that the fraction of total papers in this journal coming from Canadian sources has remained relatively constant, ranging from about 3.3 to 4.9%, over the same timeframe that DMD’s Canadian content has shown a precipitous decline. It is also interesting to note that contributions from Canadian government scientists in the realm of toxicology, although declining, have remained relatively strong over time (Supplemental Table 2), whereas publications in DMD from
Canada’s government sector and industrial sector have been completely absent since the 1990s and 2000s, respectively (Table 3).

One of our hopes in presenting these intriguing data is to initiate conversations around the potential causes of the ongoing decline in Canadian contributions to DMD. Some ideas are presented here as questions rather than answers since additional data beyond the scope of this minireview will be required to gain a fuller understanding. Has there been a decline in the number of Canadian investigators working in the field? Are Canadian investigators in the field choosing to publish findings in journals other than DMD? How important was the loss of major pharmaceutical companies from the Canadian landscape and have there been shifts in the priorities of Canadian government labs away from drug metabolism and disposition? A major source of funding for Canadian academic biomedical and health scientists is the Canadian Institutes of Health Research (CIHR), originally called the Medical Research Council of Canada (MRC) prior to the year 2000. Table 4 shows that about 68% of the DMD papers of Canadian origin acknowledge operating grant support from this agency over the years and this index has remained relatively constant throughout several decades. The comparative funding data for the journal *Toxicological Sciences* show that the fraction of Canadian toxicology papers acknowledging MRC/CIHR support jumped noticeably in the 2000s and beyond as contributions shifted from government to academic labs (Supplemental Table 3). Throughout this minireview we have pointed out that the total relative contributions of DMD papers by province (Table 1) parallel rather closely the population distribution among provinces (Fig. 1), suggesting that regional differences may not explain the declining Canadian contributions to DMD.

An ASPET-sponsored symposium held over 20 years ago considered the supply-demand balance for scientists in drug metabolism and disposition research, mostly in an American
context (Stevens et al., 2003). It was suggested that an increased demand for industrial and regulatory scientists with expertise in drug metabolism and disposition may have contributed to challenges for academic programs to attract and retain students, postdoctoral scientists, and faculty in this discipline. Although it isn’t clear how these factors have impacted the Canadian context, it is absolutely clear that the characterization of drug metabolism and disposition continues to be a critically important aspect of the development and regulation of drug candidates (Cerny et al., 2023). Stronger and timely investment by Canadian academic institutions in drug metabolism and disposition science may help to restore the nation’s research excellence in this discipline and ensure a more robust pipeline of appropriately trained scientists to take on careers in academia, industry, and government.

**Acknowledgments**

The author thanks the many teachers, colleagues, and trainees at Canadian institutions that have enriched his life in research and academia. This article is dedicated to the author’s outstanding doctoral and postdoctoral mentors, Profs. Gerald Marks and Allan Okey.

**Data Availability Statement**

The authors declare that all the data supporting the findings of this study are available within the paper and its Supplemental Data.

**Authorship Contributions**

*Participated in research design:* Riddick.

*Performed data analysis:* Riddick.

*Wrote or contributed to the writing of the manuscript:* Riddick.
References


Althurwi HN, Maayah ZH, Elshenawy OH, and El-Kadi AO (2015) Early changes in cytochrome P450s and their associated arachidonic acid metabolites play a crucial role in the initiation of cardiac hypertrophy induced by isoproterenol. *Drug Metab Dispos* **43**:1254-1266.


Beaubien AR and Pakuts AP (1979) Influence of dose on first-pass kinetics of $^{14}$C-imipramine in the isolated perfused rat liver. *Drug Metab Dispos* **7:**34-39.


Bélanger PM, Desgagne M, and Bruguerolle B (1991) Temporal variations in microsomal lipid peroxidation and in glutathione concentration of rat liver. *Drug Metab Dispos* **19:**241-244.

Bélanger PM and Grech-Bélanger O (1979) Metabolic reduction of 1-nitrosoadamantane by rabbit liver microsomes: properties of a C-nitroso reductase system. *Drug Metab Dispos* **7:**171-175.


Gamble JT, Nakatsu KJ, and Marks GS (2003) Comparison of the formation of N-alkylproto-
porphyrin IX after interaction of porphyrinogenic xenobiotics with single cDNA-
expressed human P450 enzymes in microsomes prepared from baculovirus-infected

oral administration of pure chemical and ACAPHA. *Drug Metab Dispos* **37**:884-891.

Gerges SH and El-Kadi AOS (2023) Sexual dimorphism in the expression of cytochrome P450
enzymes in rat heart, liver, kidney, lung, brain, and small intestine. *Drug Metab Dispos*
**51**:81-94.

Gharavi N and El-Kadi AOS (2005) t-Butylhydroquinone is a novel aryl hydrocarbon receptor


Ghosheh O and Hawes EM (2002a) Microsomal N-glucuronidation of nicotine and cotinine:
human hepatic interindividual, human intertissue, and interspecies hepatic variation.
*Drug Metab Dispos* **30**:1478-1483.

Ghosheh O and Hawes EM (2002b) N-Glucuronidation of nicotine and cotinine in human:
formation of cotinine glucuronide in liver microsomes and lack of catalysis by 10

Ghosheh O, Vashishtha SC, and Hawes EM (2001) Formation of the quaternary ammonium-
linked glucuronide of nicotine in human liver microsomes: identification and


Hasinoff BB (1990) The hydrolysis activation of the doxorubicin cardioprotective agent ICRF-187 [(+)-1,2-bis(3,5-dioxopiperazinyl-1-y1)propane]. *Drug Metab Dispos* **18**:344-349.


Identification of phase-I and phase-II metabolites of fluphenazine in rat bile: intact

Joly JG, Doyon C, and Peasant Y (1975) Cytochrome P-450 measurement in rat liver
homogenate and microsomes: its use for correction of microsomal losses incurred by

on the metabolism of 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone by hamster liver

metabolism of 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone by adult and fetal

Joshi M and Tyndale RF (2006) Induction and recovery time course of rat brain CYP2E1 after

Ju C and Uetrecht JP (1998) Oxidation of a metabolite of indomethacin (desmethyldeschloro-
benzoylindomethacin) to reactive intermediates by activated neutrophils, hypochlorous

Jurima M, Inaba T, and Kalow W (1985a) Mephenytoin hydroxylase activity in human liver:

*Drug Metab Dispos* **13**:151-155.


Lee RP and Forkert PG (1999) Inactivation of cytochrome P-450 (CYP2E1) and carboxylesterase (hydrolase A) enzymes by vinyl carbamate in murine pulmonary microsomes. *Drug Metab Dispos* **27**:233-239.


Lin L, Wright MR, Hop C, and Wong H (2022) Physiologically based pharmacokinetic models can be used to predict the unique nonlinear absorption profiles of vismodegib. *Drug Metab Dispos* **50**:1170-1181.


Riddick DS (2023) Fifty years of aryl hydrocarbon receptor research as reflected in the pages of *Drug Metabolism and Disposition*. *Drug Metab Dispos* **51**:657-671.


Taylor WG, Hall TW, and Vedres DD (1993) Metabolism of N,N-diethylbenzamide and N,N-diethyl-\(\alpha,\alpha\)-\(^{13}\)C-benzamide by rat liver microsomes. *Drug Metab Dispos* **21**:133-140.


Footnotes

**Funding:** This work received no external funding.

**Financial disclosure:** No author has an actual or perceived conflict of interest with the contents of this article.

**Address correspondence to:** Dr. David S. Riddick, Department of Pharmacology and Toxicology, Medical Sciences Building, University of Toronto, Toronto, ON, Canada M5S 1A8. E-mail: david.riddick@utoronto.ca
Figure Legends

**Fig. 1.** A primer on Canada’s vast geography. Superimposed on the map of Canada are the names of each province and territory, along with the official two-letter abbreviation and an estimate of the percentage of the country’s total population (40 million) accounted for by that specific province or territory. Also shown are the recognized grouping into Territories, Prairie Provinces, and Atlantic Provinces.

**Fig. 2.** A decade-by-decade depiction of the percent Canadian content of DMD publications. CAN CON % = DMD Papers of Canadian origin / Total DMD Papers x 100. The inset pie charts for each decade provide a visual representation of the proportion of DMD papers of Canadian origin coming from academia (A, blue), industry (I, gray), or government (G, green).
# TABLE 1

A decade-by-decade analysis of Canadian DMD publications by province

<table>
<thead>
<tr>
<th>Province</th>
<th>1970s</th>
<th>1980s</th>
<th>1990s</th>
<th>2000s</th>
<th>2010s</th>
<th>2020s</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>BC</td>
<td>2</td>
<td>5</td>
<td>19</td>
<td>25</td>
<td>6</td>
<td>1</td>
<td>58</td>
</tr>
<tr>
<td></td>
<td>(7.41%)</td>
<td>(8.20%)</td>
<td>(14.07%)</td>
<td>(17.12%)</td>
<td>(7.59%)</td>
<td>(12.50%)</td>
<td>(12.72%)</td>
</tr>
<tr>
<td>AB</td>
<td>5</td>
<td>9</td>
<td>14</td>
<td>6</td>
<td>11</td>
<td>2</td>
<td>47</td>
</tr>
<tr>
<td></td>
<td>(18.52%)</td>
<td>(14.75%)</td>
<td>(10.37%)</td>
<td>(4.11%)</td>
<td>(13.92%)</td>
<td>(25.00%)</td>
<td>(10.31%)</td>
</tr>
<tr>
<td>SK</td>
<td>0</td>
<td>3</td>
<td>11</td>
<td>9</td>
<td>0</td>
<td>0</td>
<td>23</td>
</tr>
<tr>
<td></td>
<td>(0%)</td>
<td>(4.92%)</td>
<td>(8.15%)</td>
<td>(6.16%)</td>
<td>(0%)</td>
<td>(0%)</td>
<td>(5.04%)</td>
</tr>
<tr>
<td>MB</td>
<td>2</td>
<td>0</td>
<td>4</td>
<td>6</td>
<td>0</td>
<td>0</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>(7.41%)</td>
<td>(0%)</td>
<td>(2.96%)</td>
<td>(4.11%)</td>
<td>(0%)</td>
<td>(0%)</td>
<td>(2.63%)</td>
</tr>
<tr>
<td>ON</td>
<td>13</td>
<td>28</td>
<td>52</td>
<td>65</td>
<td>43</td>
<td>3</td>
<td>204</td>
</tr>
<tr>
<td></td>
<td>(48.15%)</td>
<td>(45.90%)</td>
<td>(38.52%)</td>
<td>(44.52%)</td>
<td>(54.43%)</td>
<td>(37.50%)</td>
<td>(44.74%)</td>
</tr>
<tr>
<td>QC</td>
<td>4</td>
<td>14</td>
<td>29</td>
<td>32</td>
<td>16</td>
<td>1</td>
<td>96</td>
</tr>
<tr>
<td></td>
<td>(14.81%)</td>
<td>(22.95%)</td>
<td>(21.48%)</td>
<td>(21.92%)</td>
<td>(20.25%)</td>
<td>(12.50%)</td>
<td>(21.05%)</td>
</tr>
<tr>
<td>NS</td>
<td>1</td>
<td>1</td>
<td>5</td>
<td>3</td>
<td>3</td>
<td>1</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>(3.70%)</td>
<td>(1.64%)</td>
<td>(3.70%)</td>
<td>(2.05%)</td>
<td>(3.80%)</td>
<td>(12.50%)</td>
<td>(3.07%)</td>
</tr>
<tr>
<td>NL</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>(0%)</td>
<td>(1.64%)</td>
<td>(0.74%)</td>
<td>(0%)</td>
<td>(0%)</td>
<td>(0%)</td>
<td>(0.44%)</td>
</tr>
<tr>
<td>Total</td>
<td>27</td>
<td>61</td>
<td>135</td>
<td>146</td>
<td>79</td>
<td>8</td>
<td>456</td>
</tr>
<tr>
<td>Total DMD Papers</td>
<td>596</td>
<td>1261</td>
<td>1923</td>
<td>2569</td>
<td>2287</td>
<td>515</td>
<td>9151</td>
</tr>
</tbody>
</table>

CAN CON % = DMD Papers of Canadian origin / Total DMD Papers x 100.

---

a Data indicate the number of DMD papers contributed by a corresponding author from a Canadian institution located in the specified province for each decade.

b There have been no DMD papers contributed by a corresponding author from the Territories or from the provinces of New Brunswick or Prince Edward Island.

c Numbers in parentheses indicate the percentage of the Canadian total for a specified province for each decade.

d Analysis includes all DMD publication types except: announcements, editorials, letters and correspondence, erratum, book reviews, and highlights of current literature. Publications cover the history of DMD from Vol. 1, Issue 1 (January 1973) to Vol. 51, Issue 9 (September 2023), inclusive.

e The percent Canadian content, CAN CON % = DMD Papers of Canadian origin / Total DMD Papers x 100.
TABLE 2

The top ten most prolific DMD corresponding authors from Canadian institutions

<table>
<thead>
<tr>
<th>Rank</th>
<th>Name</th>
<th>Institution</th>
<th>Total DMD papers as corresponding author</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>K. Sandy Pang</td>
<td>University of Toronto</td>
<td>46</td>
</tr>
<tr>
<td>2.</td>
<td>Poh-Gek Forkert</td>
<td>Queen’s University</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>Chantal Guillemette</td>
<td>Université Laval</td>
<td>16</td>
</tr>
<tr>
<td>4.</td>
<td>Patrick du Souich</td>
<td>Université de Montréal</td>
<td>15</td>
</tr>
<tr>
<td>5.</td>
<td>Micheline Piquette-Miller</td>
<td>University of Toronto</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>Jack P. Uetrecht</td>
<td>University of Toronto</td>
<td>14</td>
</tr>
<tr>
<td>7.</td>
<td>Frank S. Abbott</td>
<td>University of British Columbia</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>Ayman O.S. El-Kadi</td>
<td>University of Alberta</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>David S. Riddick</td>
<td>University of Toronto</td>
<td>13</td>
</tr>
<tr>
<td>10.</td>
<td>Tadanobu (Ted) Inaba</td>
<td>University of Toronto</td>
<td>11</td>
</tr>
</tbody>
</table>

a Data indicate the number of DMD papers contributed by a corresponding author from a Canadian institution.
b Analysis includes all DMD publication types except: announcements, editorials, letters and correspondence, erratum, book reviews, and highlights of current literature. Publications cover the history of DMD from Vol. 1, Issue 1 (January 1973) to Vol. 51, Issue 9 (September 2023), inclusive.
### TABLE 3

A decade-by-decade analysis of Canadian DMD publications by research sector $^a$

<table>
<thead>
<tr>
<th>Sector</th>
<th>1970s</th>
<th>1980s</th>
<th>1990s</th>
<th>2000s</th>
<th>2010s</th>
<th>2020s</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Academia</td>
<td>20</td>
<td>54</td>
<td>119</td>
<td>139</td>
<td>79</td>
<td>8</td>
<td>419</td>
</tr>
<tr>
<td></td>
<td>(74.07%) $^b$</td>
<td>(88.52%) $^b$</td>
<td>(88.15%) $^b$</td>
<td>(95.21%) $^b$</td>
<td>(100%) $^b$</td>
<td>(100%) $^b$</td>
<td>(91.89%) $^b$</td>
</tr>
<tr>
<td>Industry</td>
<td>0</td>
<td>2</td>
<td>9</td>
<td>7</td>
<td>0</td>
<td>0</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>(0%)</td>
<td>(3.28%)</td>
<td>(6.67%)</td>
<td>(4.79%)</td>
<td>(0%)</td>
<td>(0%)</td>
<td>(3.95%)</td>
</tr>
<tr>
<td>Government</td>
<td>7</td>
<td>5</td>
<td>7</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td>(25.93%)</td>
<td>(8.20%)</td>
<td>(5.19%)</td>
<td>(0%)</td>
<td>(0%)</td>
<td>(0%)</td>
<td>(4.17%)</td>
</tr>
<tr>
<td>Total $^c$</td>
<td>27</td>
<td>61</td>
<td>135</td>
<td>146</td>
<td>79</td>
<td>8</td>
<td>456</td>
</tr>
</tbody>
</table>

$^a$ Data indicate the number of DMD papers contributed by a corresponding author from a Canadian institution based in the specified research sector for each decade.

$^b$ Numbers in parentheses indicate the percentage of the Canadian total for a specified research sector for each decade.

$^c$ Analysis includes all DMD publication types except: announcements, editorials, letters and correspondence, erratum, book reviews, and highlights of current literature. Publications cover the history of DMD from Vol. 1, Issue 1 (January 1973) to Vol. 51, Issue 9 (September 2023), inclusive.
TABLE 4

A decade-by-decade analysis of Canadian publications in *Drug Metabolism and Disposition* acknowledging operating grant support from MRC/CIHR

<table>
<thead>
<tr>
<th>Decade</th>
<th>1970s</th>
<th>1980s</th>
<th>1990s</th>
<th>2000s</th>
<th>2010s</th>
<th>2020s</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total DMD Papers (^a)</td>
<td>596</td>
<td>1261</td>
<td>1923</td>
<td>2569</td>
<td>2287</td>
<td>515</td>
<td>9151</td>
</tr>
<tr>
<td>Canadian DMD Papers</td>
<td>27</td>
<td>61</td>
<td>135</td>
<td>146</td>
<td>79</td>
<td>8</td>
<td>456</td>
</tr>
<tr>
<td>MRC/CIHR Funding</td>
<td>13</td>
<td>37</td>
<td>93</td>
<td>98</td>
<td>64</td>
<td>4</td>
<td>309</td>
</tr>
<tr>
<td>MRC/CIHR % (^b)</td>
<td>48.15</td>
<td>60.66</td>
<td>68.89</td>
<td>67.12</td>
<td>81.01</td>
<td>50.00</td>
<td>67.76</td>
</tr>
</tbody>
</table>

\(^a\) Analysis includes all DMD publication types except: announcements, editorials, letters and correspondence, erratum, book reviews, and highlights of current literature. Publications cover the history of DMD from Vol. 1, Issue 1 (January 1973) to Vol. 51, Issue 9 (September 2023), inclusive.

\(^b\) The percent MRC/CIHR-funded, MRC/CIHR % = MRC/CIHR-funded Papers of Canadian origin / Papers of Canadian origin x 100.
Figure 1

Total Population of Canada
≈ 40 Million

- Yukon (YT) ~ 0.1%
- Northwest Territories (NT) ~ 0.1%
- Nunavut (NU) ~ 0.1%
- British Columbia (BC) ~ 13.7%
- Alberta (AB) ~ 11.8%
- Manitoba (MB) ~ 3.6%
- Ontario (ON) ~ 39.0%
- Québec (QC) ~ 22.1%
- New Brunswick (NB) ~ 2.1%
- Nova Scotia (NS) ~ 2.6%
- Newfoundland & Labrador (NL) ~ 1.3%
- Prince Edward Island (PE) ~ 0.4%

Prairies

Atlantic