To the Editor:

From the beginning of time, we human beings have been exposed to potentially dangerous chemicals from the environment, in the air we breathe, and also in our search for food; nature’s toxins are plentiful in wild herbs, plants, and shrubs (1). Foreign chemicals that generally lack any nutritional value are referred to as xenobiotics from the Greek word xeno meaning “foreign.” It is widely accepted that the diversity of cytochrome P450 enzymes, mainly located in the liver and gut, evolved to protect the body from the actions of exogenous toxic substances (2,3).

Few men in the history of pharmacology and toxicology have made such a career-long contribution to knowledge about the disposition and fate of foreign substances in the body as Richard Tecwyn Williams (Figure 1). I hope the readers of Journal of Analytical Toxicology will enjoy this tribute to a veritable pioneer in the field of foreign compound metabolism. Richard Tecwyn Williams, or RT as he was known, was born as the first of five children in the small mining town of Abertillery in South Wales, United Kingdom (4). His parents came originally from North Wales, where they lived for some years after Tecwyn’s birth, which meant that he grew up speaking Welsh as his first language. He learnt English later when the family returned to live in Abertillery. After obtaining good grades in the sciences at secondary school, RT enrolled for studies at University College Cardiff with chemistry as his major subject (4). He obtained his BSc degree in 1928 and followed this with research for a PhD degree (awarded 1932) while working at the Physiology Institute (Newport Road, Cardiff) with the carbohydrate chemist Dr. John Pryde as his thesis supervisor.

Knowledge about the human metabolism of drugs owes much to the early pioneers in organic chemistry and pharmacology, mainly from German-speaking countries. The history of drug metabolism during the 19th century and the first half of the 20th century were reviewed in depth by Bachmann and Bickel (2) and Conti and Bickel (3), and these articles are highly recommended. The first metabolic pathway discovered was the biotransformation of benzoic acid into hippuric acid, which meant that an aromatic carboxylic acid group was conjugated with an endogenous amino acid (glycine). By the turn of the 20th century, other conjugation reactions were discovered including glucuronidation and sulfation (2). Soon afterwards, oxidation and reduction reactions were recognized as key processes in the detoxication of drugs and chemicals, making them less lipophilic and easier to eliminate from the bloodstream via the kidney (2,3). However, elucidation of the biochemical mechanisms involved in the biotransformation of drugs and pharmaceuticals was a long way into the future.

When Tecwyn Williams arrived on the scene the formation of glucoconic acid conjugates of drugs was already established, although the chemical structure of the “carbohydrate” metabolite was not. Large quantities of glucuronide conjugate were necessary for Williams’s doctorate research, and this was obtained by feeding borneol to dogs and isolating and purifying the excretion product from urine. Importantly, he also observed toxic effects on the animals after chronic dosing and warned about use of this substance in humans. A series of hydrolysis, methylation, and oxidation reactions allowed Williams to verify a pyranoid ring structure for glucuronic acid. The results of this work appeared in RT’s first scientific paper, co-authored with his supervisor Dr. John Pryde, which was published in the British journal Nature (5).

After completion of his doctorate degree (University of Wales 1932), Williams was appointed lecturer in biochemistry at the University of Birmingham. There he continued his work on drug metabolism under the influence of another British pioneer in biochemistry, namely Professor W.V. Thorpe (6). In 1939, with 22 published papers on his CV, Tecwyn Williams was awarded a senior doctorate degree (DSc). His next move was to the University of Liverpool, where he was appointed to a senior lectureship in biochemistry in 1942, and it was during this tenure that he made his name as one of the leaders in the field of foreign compound metabolism. His final academic appointment came in 1948 when RT Williams was appointed to the first chair of biochemistry at St. Mary’s Hospital Medical School in London where he remained until reaching retirement age in 1976 (4).
Before moving to the University of Liverpool, Williams realized the need for a textbook to bring together all that was known at the time on the subject of in-vivo drug metabolism (7). The preface to the first edition contained the following: “In writing this book, my object has been to gather together in orderly fashion the available information on the metabolic fate of organic compounds foreign to the body, so that working hypotheses can be advanced.”

The book’s publication was delayed because of special war-work that Williams was involved with such as research on the metabolism of 2,4,6-trinitrotoluene (TNT). Industrial workers were being exposed to this toxic chemical when making explosive shells, so TNT’s metabolism and fate in the body was important to know. The classic textbook (Figure 2) Detoxification Mechanisms: The Metabolism of Drugs and Allied Organic Compounds was published in 1947 by Chapman & Hall (8). This represented a landmark publication in the field of drug metabolism, and about 10 years later (1959) it was followed by a much expanded and highly acclaimed second edition, which is still widely used today (9).

A long series of papers on the metabolism of drugs and chemicals by Williams and his group were published in the Biochemical Journal under the title “Studies in Detoxication”, which reached part 86 (10). Thereafter, the editors changed their policy and stopped publishing numbered series of articles. Some biochemists and enzymologists at the time failed to appreciate the significance of research dealing with the metabolism of drugs and industrial chemicals. This type of research was considered something between organic chemistry and pharmacology and not at all related to biochemistry and intermediary metabolism. This prompted RT and his colleagues to look for more appropriate scientific journals to submit their papers, as exemplified by the formation of new periodicals such as Biochemical Pharmacology and Xenobiotica.

In the first edition of his famous book, Williams introduced the concept of phase I and phase II metabolism of drugs, although he was fully aware that there were exceptions and that instead of detoxication some drugs underwent bioactivation, especially following phase I reactions such as the CYP2E1 catalyzed oxidation of acetaminophen into its toxic metabolite. The products of phase 2 synthetic reactions are also sometimes pharmacologically active, as exemplified by morphine 6-glucuronide, a metabolite of heroin and morphine.

The established way of studying drug metabolism in animals (mainly chinchowa rabbits) involved administering the drug, collecting urine, and then the laborious task of isolating and identifying the metabolites by classic chemical methods, which represented a very time consuming process (11). The ready availability of radioisotopes after WWII simplified studies of drug metabolism and paved the way for elucidating metabolic pathways of many compounds by sidestepping the need for traditional chemical analysis of urinary excretion products (11). Williams and his collaborators were quick to capitalize on chromatographic separation methods, such as thin-layer and column chromatography as well as instrumental techniques, such as infrared and UV spectrophotometry for elucidation of chemical structure.

Under close scrutiny from the news media, Williams and his students made a systematic study of the toxicity of a new sedative-hypnotic drug marketed as thalidomide (2,6-dioxo-3-phthalimido-piperidine). The results were published in 1962–63 but came too late to avoid the devastating effects this teratogenic drug had on thousands of unborn children and their parents (12). Species and strain differences in drug metabolism were investigated by Williams and his group, which resulted in scores of publications with both domestic and wild animals (7,11). This interest led to a close collaboration and many exchanges with scientists from West Africa, especially Nigeria (University of Ibadan). In 1964, Williams received one of his four honorary doctorate degrees from this same university (4).

Systematic studies were made related to the metabolism of aromatic hydrocarbons, alkyl and halogenated derivatives of benzene tagged with radio-isotopes (14C), pharmaceutical products, food additives, pesticides, and drugs of abuse (4). Williams and his group also made major contributions to studies of microbial (gut) metabolism of drugs, biliary excretion and enterohepatic recirculation, as well as demonstrating the key role played by microsomal enzymes (7,11). Of particular interest to many of today’s forensic toxicologists is a seminal paper from 1953 documenting the non-oxidative metabolism of aliphatic alcohols including the formation of ethyl glucuronide (13). This minor metabolite of ethanol is now widely used as a biomarker to disclose recent drinking after ethanol is no longer measurable in the blood stream by standard methods (14).

During the 1970s, a lot of attention was given to the disposition and metabolism of dependence producing drugs, prompted by the wave of recreational drug use by young people worldwide (7). This led to studies of the metabolic fate of sympathomimetic amines, such as ephedrine, norephedrine, phenmetrazine, amphetamine, and methamphetamine in...
man and various animal species (15,16). One of the last of RT's publications dealt with the metabolic fate of lysergic acid diethylamide using 14C-radiolabelled LSD (17).

Although arriving rather late in his career (1967), RT Williams received a highly significant recognition of his many contributions to science by being elected to Fellowship of The Royal Society of London (equivalent to membership in the U.S. National Academy of Sciences). This entitled him to add the letters FRS after his name (4). No toxicologist before him or since has, to my knowledge, received this level of recognition. The biographical memoir published after his death contains the complete bibliography of Tecwyn Williams, which lists 392 major publications, making it clear that he was indeed a founding father of the drug metabolism field (4). Many graduate students who worked with Williams for their PhD training went on to become established scientists, some being appointed to university professorships in biochemical pharmacology or toxicology. Others made names for themselves in the pharmaceutical industry.

The name of Richard Tecwyn Williams is synonymous with xenobiotic metabolism, species differences in drug metabolism, and the concept of phase I and phase II metabolic pathways. His contributions to toxicology rank alongside those of pioneers such as Louis Lewin (1850–1929) from Germany, Bernard B. Brodie (1907–1989), and the husband and wife team James Miller (1915–2000) and Elisabeth Miller (1920–1987) from the U.S. These scientists made fundamental contributions to knowledge about the absorption, distribution, metabolism, and excretion of many drugs and toxic chemicals in the body. The overall body of work by these five pioneers is considered by some as being of Nobel class, but none were lucky enough to receive the ultimate scientific accolade (18).

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References