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Review Article

Isotopic chemistry at Eli Lilly and Company – a look back at the past fifty years†

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Abstract: This review will chronicle the genesis and the next fifty years or so of the Isotopic Chemistry effort at Eli Lilly and Company. It all began from a seed planted in Bob McMahon's mind while a post-doctoral fellow at MIT in 1949 and was later cultivated when he joined the Lilly Research Laboratories in 1954. From the humble beginnings of a few part-time radiochemists/part time metabolism scientists (Bob McMahon and Hugh Sullivan), the group has evolved to the eleven dedicated scientists that we have today. Copyright © 2007 John Wiley & Sons, Ltd.

Keywords: Eli Lilly; isotopic chemistry; fifty years

Robert E. McMahon was a man of vision. Working in the laboratories of S. M. McElvain, he received his PhD degree in organic chemistry from the University of Wisconsin in 1948 (he was an Eli Lilly and Company Fellow from 1947 to 1948). From Madison, he traveled east to Cambridge for a post-doctoral appointment in the laboratories of John D. Roberts at M.I.T. It was at M.I.T. that Bob began his foray into the synthesis and use of carbon-14-labeled compounds as tracers.[1–3] Bob continued the use of carbon-14-labeled compounds as tracers during a brief stint at Standard Oil Co. (Indiana)[4]; he joined Eli Lilly and Company in 1954 in the Chemical Research Division. Almost immediately, Bob realized that radiolabeled compounds would be useful in the study of drug metabolism. Bob was responsible for the formation of both the drug metabolism and radiosynthesis efforts at Eli Lilly and Company. At the 11th Annual Symposium on Tracer Methodology, Bob stated, 'In modern pharmaceutical research, an increasing emphasis is being placed on studies of drug dynamics (i.e. absorption, distribution, metabolism and elimination) of an administered drug. Radiocarbon labeling can be one of the most valuable tools for such studies, provided that the drug to be studied can be synthesized containing the radiocarbon label.[5] Throughout the next 25 or so years, until his untimely death from lung cancer in late 1980, Bob was intimately involved in not only the synthesis of radiolabeled (and stable-labeled) compounds, but also in their use in drug metabolism and disposition studies.

Flynn *et al.* reported that the reaction of erythromycin with ethyl chloroformate yielded the unexpected product *O*,*N*-dicarbethoxy-*des*-methylerythromycin (**1a**) in which one of the *N*-methyl groups in the desosamine had been displaced (Scheme 1).[6] In a subsequent paper, Ed Flynn, Hubert Murphy and Bob McMahon repeated the previous chemistry; reaction of erythromycin with benzyl chloroformate, followed by hydrogenolysis of the Cbz groups with H_2/Pd to afford *N-des*-methyl-erythromycin (**2**).[7] *N-des*-methyl-erythromycin (**2**) retained only 5% of the activity of erythromycin by bioassay. Welles *et al.* had reported the isolation of **2** from bile after oral administration to dogs.[8] In order to determine whether *N-des*-methylation was the only change affected by this series of reactions, **2** was re-methylated by reductive amination by reaction with CH_2O to yield a product that was identical to an authentic sample of erythromycin in all respects. Realizing the opportunity to prepare radiolabeled erythromycin, the reductive amination of **2** was repeated using $^{14}CH_2O/H_2$/EtOH to yield erythromycin-[*N*-methyl-^{14}C] (1.1 μCi/mg) which was identical to erythromycin in all respects (X-ray powder pattern, melting point and a bioassay of 980 μg/mg). Examination of the product by paper chromatography showed that 99% of the bioactivity was associated with

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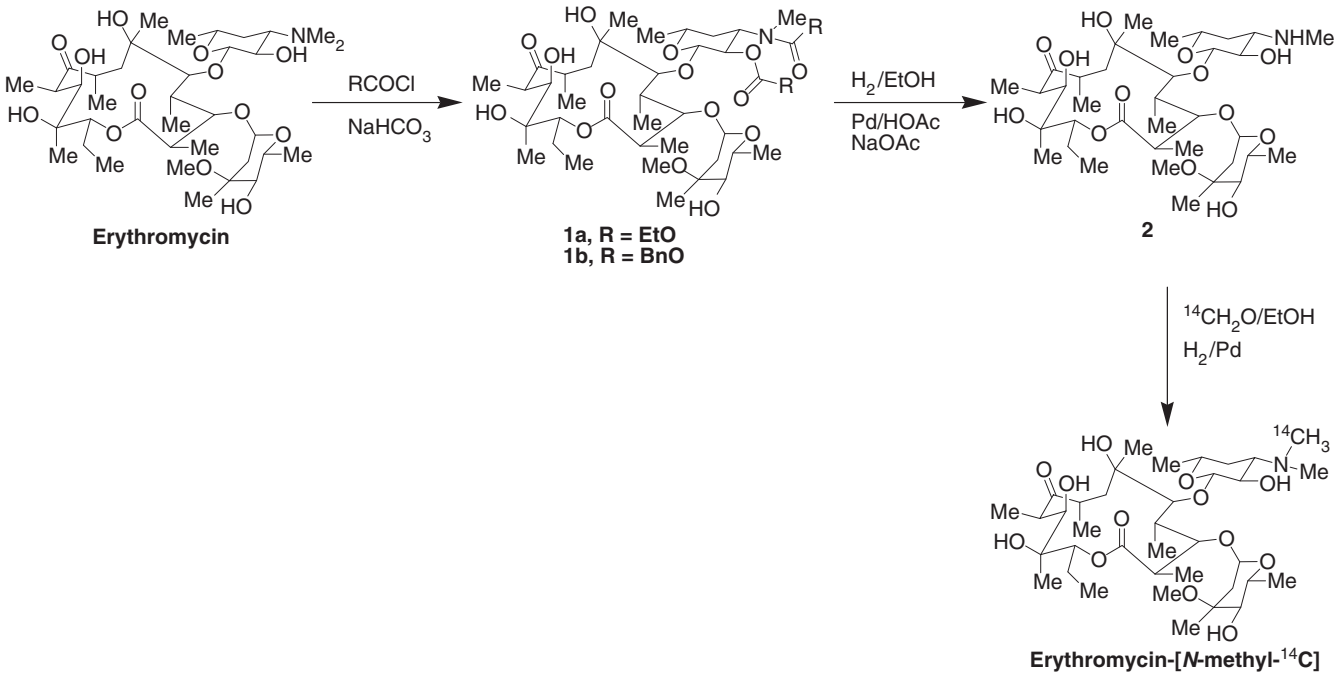

Scheme 1

erythromycin and the remainder with erythromycin B. Thus, the era of radiosynthesis at Lilly began with facilities in the basement of Research Building 28.

Over the next several years, Bob synthesized carbon-14 isotopomers of propoxyphene,[9,10] 1-ethynylcyclohexyl carbamate,[11] ethoxybutamoxane[12] and 2-(butylaminomethyl)-1,4-benzodioxane,[13] and used them in metabolism studies. Using $^{18}O_2$, Bob showed that molecular oxygen was the source of oxygen in the oxidative *N*-demethylation of amines by hepatic microsomes.[14] The results of these experiments provided support for the earlier proposed reaction pathway involving *N*-hydroxylation of amines as the initial step in microsomal dealkylation.

Hugh Sullivan another organic chemist joined the effort in the late 1950s. Hugh was responsible for the synthesis of many of the early carbon-14-labeled cephalosporin antibiotics (cephalothin,[15] cephaloridine,[15] cephaloglycin[16] and cephalexin[17]) as well as the study of their metabolism and disposition. In 1962, as Bob and Hugh began to concentrate more on the metabolism, Dr Frederick J. Marshall joined the group (from the Lilly Chemical Research Division) and assumed responsibility for most of the synthetic work, supporting radiochemistry requirements for human medicine as well as veterinary medicine and plant science. Bob and Fred collaborated on several early projects. In the late 1960s, they developed a strategy for the labeling amines based on a method published by Easton *et al.* in 1958.[18] Typical chemistry used to alkylate amines (i.e. Clarke–Eschweiler, alkylation with methyl iodide, etc.) suffered from the inability to stop the alkylation after the addition of one alkyl group. Easton's group envisioned the acylation of a primary amine with thyl chloroformate and subsequent reduction of the resulting carbamate with $LiAlH_4$ to yield the desired secondary amine. Finding a satisfactory method for the preparation of carbon-14-labeled ethyl chloroformate from labeled phosgene enabled the preparation of the C-14-labeled isotopomer of the antidepressant nortriptyline (Scheme 2)[19] using the Easton chemistry. The synthesis of the unlabeled carbamate followed by reduction either with $LiAl^3H_4$ or $LiAl^2H_4$ provided tritium- and deuterium-labeled nortriptyline.[20]

Hammar *et al.* published a paper in 1968 detailing the use of gas chromatography–mass spectrometry (GC–MS) for the qualitative identification of drugs and their metabolites in biological fluids.[21] In June 1970, these authors along with Gaffney and McMahon submitted a paper which proposed the use of isotopomers of the analyte as internal standards (SLIS) in the quantitative bioanalysis of drugs in biological matrices.[22] I am sure that at the time of their submission, they believed that they were the first to use this technique (which has since proved invaluable). Unfortunately, in May 1970, Samuelsson, Hamberg and Sweeley submitted a short communication detailing the use of a SLIS in the analysis of serum levels of PGE_1

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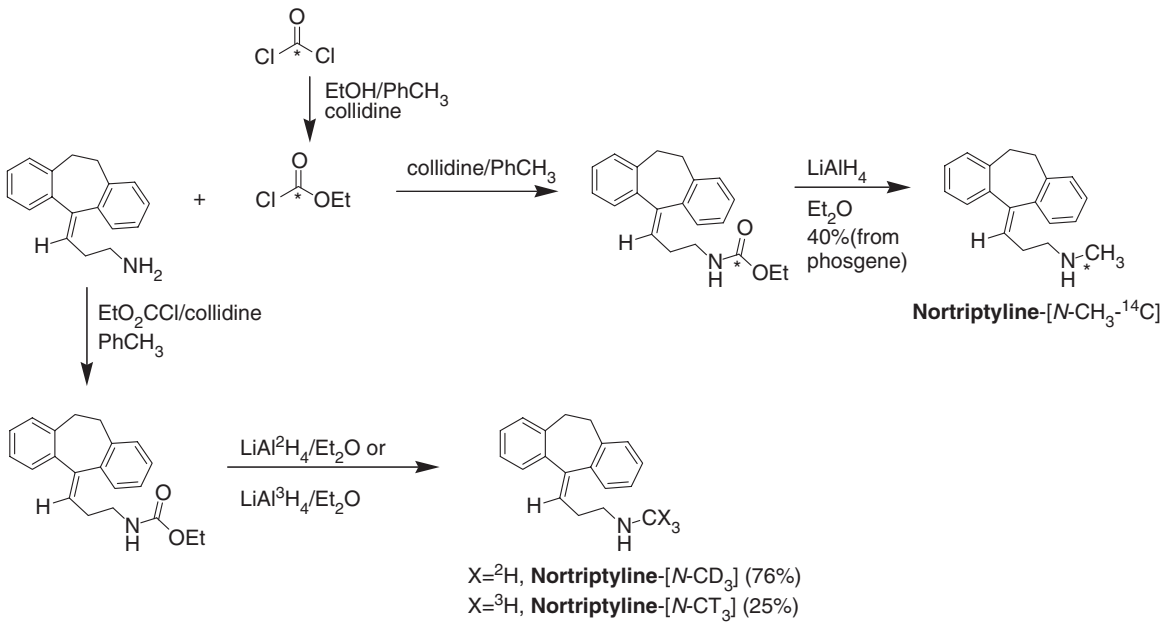
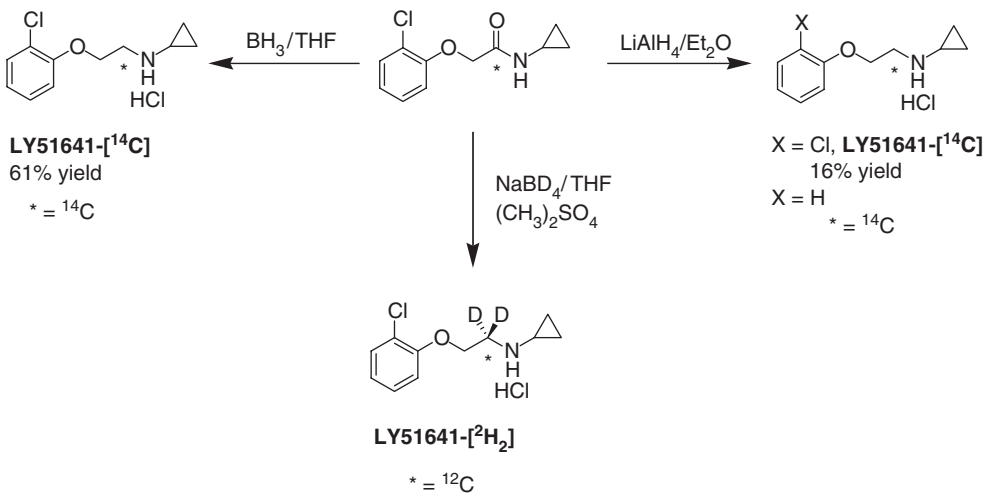
by GC–MS; this paper was published in November 1970 nearly 4 months prior to the Gaffney paper.[23] Gaffney *et al.* highlighted the comparison of results using two stable labeled isotopomers and an analog as internal standards in the bioanalysis of nortriptyline. The use of the deuterated isotopomer (M + 2 AMU) avoided interference from natural abundance of ^{13}C present in the unlabeled nortriptyline. In addition to the deuterium-labeled SLIS, a ^{15}N-, $^{2}H_2$-labeled isotopomer was used to further separate the SLIS from the parent ion of nortriptyline. Regardless of who was first, these papers were seminal in the introduction of a technique that has become routine today. Marshall *et al.* described the synthesis of these SLIS, by reduction of amide analogs using BD_3 (prepared *in situ* using the method of Bell *et al.* which described the reaction of $NaBD_4$ with $(CH_3)_2SO_4$[24]).[25] This method parallels the earlier method, but enabled the preparation of compounds where the reduction with $LiAl^2H_4$ (or $LiAlH_4$) was unsuccessful or in compounds containing aromatic chlorine substituents which are frequently partially lost during the reduction with $LiAl^2H_4$ (or $LiAlH_4$) (Scheme 3). In addition to the synthesis of LY51641-[^{14}C] and –[$^{2}H_2$], this paper also highlights the synthesis of carbon-14-labeled LY32391 (2-(2,4-dichloro-6-phenylphenoxy)ethylamine-[^{14}C] HCl and



Scheme 2



Scheme 3

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3-(amino-methyl)pyridine) by the borane reduction of the corresponding carbonyl-labeled amide and cyano-labeled nitrile.

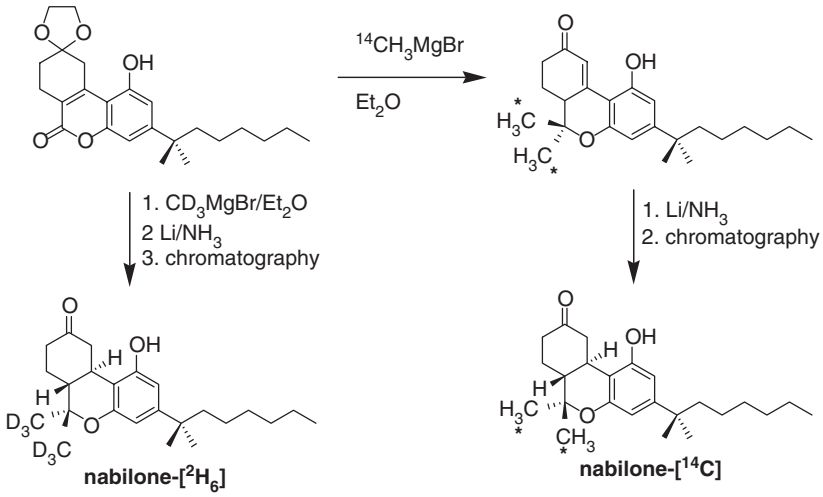
Fred published methods for the preparation of carbon-14-labeled acronine,[26] methadone[27] and acetohexamide.[28] Fred labeled trifluralin (Treflan, *N,N*, -dipropyl-2,6-dinitro-4-α,α,α-trifluoromethylaniline) in the trifluoromethyl moiety, the *N*-propyl moiety and in the ring (UL-[^{14}C]) so that all possible routes of metabolism could be followed.[29] In the late 1960s, Elanco was formed and moved to laboratories in Greenfield, Indiana, to drive the discovery of compounds for use in agriculture and Norman Terando began to provide radiochemical support for Elanco. Norm published on the synthesis of radiolabeled tilmicosin,[30] ractopamine[31] as well as a general method for the preparation of carbon-14-labeled perfluoroalkyl carboxanilides.[32]

The number of new compounds being studied increased and as the Drug Metabolism group added new members, there was an increased need for radiochemical support. In the mid-1970s, Bob offered me a position in the radiochemistry group (I had been part of the Chemical Research Division during 1965–1967). I had just returned to Eli Lilly in 1970 after graduate school and felt that I was unable to accept his offer and remained in the Pharmaceutical Research Department. Donald L. K. Kau, a former researcher in the Chemical Research Division and working at that time at Oak Ridge National Laboratories, accepted the position in 1971. Don's career in radiochemistry spanned over 23 years. Don was responsible for the synthesis of drugs from a wide range of structural types; he published on the syntheses of carbon-14- and tritium-labeled fluoxetine,[33] carbon-14-labeled cefamandole[34] and cefaclor (cephalosporin antibiotics),[35] the conjugate of tritium-labeled *des*-acetylvincablastine hydrazide with KS1/4 monoclonal antibody[36] as well as the conjugate of tritium-labeled *des*-acetylvincablastine hydrazide with ^{35}S-labeled KS1/4 monoclonal antibody.[37] He also published on the synthesis of carbon-14- and deuterium-labeled LY195115[38] and carbon-14- and ^{18}O-labeled LY175326.[39] Don prepared the d6 isotopomer of nabilone as outlined in Scheme 4[40]; this method also provided the basis for the preparation of carbon-14-labeled nabilone (Scheme 4).[41]

As one might imagine, Don and Fred were also responsible for the synthesis of a whole host of additional compounds for which the disposition and metabolism were reported, but the synthetic methods were never published (fenoprofen,[42] quinelorane,[43] quinpirole[44] and indecainide,[45] to name just a few).

In 1971, the radiochemistry group moved from Building 28 into new state-of-the-art facilities especially designed for radiochemistry in Building 88. The group continued with this level of support through the 1970s and on into the 1980s. After the untimely death of Bob McMahon in 1980, the Drug Metabolism group had grown significantly and became a department with Dr Patrick J. Murphy as its first head.

My first foray into radiosynthesis was in 1978, when I collaborated with Hugh Sullivan on the conversion of LY149541-[^{14}C] (synthesized by Don Kau) to its crystalline sodium salt. At the end of 1983, Fred Marshall retired after 35 years of service to Eli Lilly and Company. In 1984, Pat Murphy offered me the position in the radiochemistry group replacing Fred; this time I accepted and began my career as a radiochemist. After



Scheme 4

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spending the last 14 years synthesizing cephalosporin antibiotics, it was refreshing to begin to work on short-term projects involving a diverse range of organic molecules.[46–63] At this juncture, it was decided to decommission a laboratory dedicated to radiochemistry which was located at our Erl-Wood research facility in Windlesham in the United Kingdom. Thus, Don Kau and I provided global radiochemical support to the pharmaceutical part of our business. Late in 1986, Steven Gabriel,[64] fresh with a MS degree in organic chemistry from Indiana University joined our group. Early in 1988, a position for a radiochemist opened up at Burroughs-Wellcome. The lure of going home again to North Carolina was just too much to pass up and Steve left for Research Triangle Park to work with Dr John Hill. Soon after, Douglas O'Bannon joined our group from ChemSyn Science Laboratories in Lenexa, Kansas.

As Drug Disposition continued to grow, the need for radiochemical support grew as well, and in 1992, Dr Fengjiun Kuo joined our group.[65–70] With the addition of Fengjiun to our staff, we needed to expand our facility. At that time, Lilly had a laboratory for radioiodination that was a part of Biochemistry Research; this effort mainly supported our insulin and protein franchise. The work by Preston *et al.* demonstrated the utility of radioiodinated penicillin V (synthesized by W. E. (Ed) Legan in the radioiodination laboratory using the method described by Balszczak *et al.*[71]) for radiolabeling penicillin-binding proteins.[72] It was clear that other radioiodinated small molecules could be potentially useful probes for mechanistic studies. It was felt that there would be a useful synergy between Ed and the radiochemistry group and Ed joined our group in 1993. Half of Ed's space (which housed the Liquid Scintillation equipment which was re-located) was gutted and completely remodeled for use as a laboratory for carbon-14 synthesis.

Don Kau retired from Lilly in 1994 and Dr Boris Czeskis[73–79] joined our laboratory later that year after completing post-doctoral studies at Stanford University. When the plant science effort of Elanco was spun off into a joint venture with the plant science unit of Dow Chemical to form Dow–Elanco in Indianapolis in 1989, Norm Terrando moved as well. This left the remaining part of Elanco, which became Elanco Animal Health (EAH), without any radiochemical support for their discovery and development efforts. EAH hired Dr John Kennington in 1995 to fill that gap. Rather than locate John in Greenfield, it was decided that he would join our radiochemistry group in Indianapolis and for the first time, all of the global radiochemistry efforts were co-located. Of course, this required additional facilities and Dr Kuo's laboratory was duplicated in some newly acquired space.

Dr Barry Peterson (1997), Michael Spence (1998), Dr Frank White (1998) joined our group to meet the increasing demands for isotopically labeled compounds. In addition, Dean Clodfelter joined the Radiochemistry Group to provide radioanalytical support. To accommodate all of these new additions, a new radioiodination facility was built that allowed all operations from the synthesis of ^{125}I-labeled substrates to their purification and packaging to be conducted in fume hoods with leaded glass sashes. The old radioiodination laboratory was gutted and re-modeled as an analytical facility. In addition, two additional laboratories were built for carbon-14 synthesis and a tritiation facility was built. In anticipation of the need for stable-labeled compounds for use as internal standards (SLIS), Eli Stoddard (2000), Cheryl Mattingly (2000) and R. Aleks Davis (2002) joined our group; Tamara Priest (2002) joined us for added analytical support as well. Lennon McKendry joined us briefly (May 2001–July 2003) to conduct radiosyntheses, following his retirement from DowAgrosciences.

In addition to the preparation of carbon-14-labeled compounds for pre-clinical studies in laboratory animals, the Radiochemistry Group also had the responsibility for the preparation of the carbon-14-labeled APIs for studies in humans. There is an expectation that these APIs will be prepared under current good manufacturing procedures (cGMPs). I began having conversations with our Corporate Quality Assurance representatives soon after starting in 1984. Our procedures evolved from a document of a few pages to the whole range of SOPs that we have today. It soon became obvious that we needed a dedicated facility for the preparation of carbon-14-labeled API and we secured space and began plans for such a facility in 2002. After planning for some time, as we were about to send the plans out for bids, a decision was made that the building we occupied was sadly in need of renovation (the building was first occupied in 1971). Even though all of our laboratories (except the original two) were relatively new, we had to begin to plan for new space. After two years of planning and construction, in February of 2006, we moved to a beautiful new facility. For the first time, our radioactive facilities are completely separate from our other space. Our non-radioactive laboratory is a large space with 12 eight-foot fume hoods. The entry to the radiochemistry facility is by card-reader access through a clean area. There are five suites for carbon-14 syntheses (one houses the tritiation facility as well), a radioiodination suite, a scintillation laboratory and an analytical laboratory. In addition, there is a dedicated facility for cGMP

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syntheses (card-reader access as well) with two separate suites.

In 2004, after leading the effort for 20 years, my direct leadership role for the Radiochemistry Group ended as the group became a department (Isotopic Chemistry) as part of a re-organization within Drug Disposition. Dr John Kennington became the Head of Drug Disposition – Isotopic Chemistry and I concentrated on the new role which came as part of my promotion to Research Fellow in 2003.

We have come a long way in 50 years. From a seed planted in Bob McMahon while a post-doctoral fellow at MIT in 1949 and was later cultivated when he joined the Lilly Research Laboratories in 1954, we have moved from cramped quarters in the basement of Research Building 28 to what eventually became eight laboratories in Research Building 88 (4th floor) and finally to our elegant new home in Research Building 77 (3rd floor). We started from a few part-time radiochemists/part-time metabolism scientists (Bob McMahon and Hugh Sullivan) and evolved to the 11 dedicated scientists that we have today.

As I stated at the outset, Bob McMahon was truly a man of vision; I am proud to be a part of the fruition of that vision. This has been interesting taking the trip down the memory lane; I appreciate the invitation by Dr Jones which enabled me to do so. It was a wonderful opportunity to recall and chronicle our roots. In my career at Lilly which has now spanned well over 40 years, I have had the privilege to know and work with nearly all of the Lilly scientists mentioned in this paper. Obviously, I have had closer contact with members of Drug Disposition, of which Isotopic Chemistry is a part. I have referenced only papers published in peer-reviewed journals; as was mentioned for Don and Fred, each of the isotopic chemists listed herein was also responsible for the synthesis of a whole host of additional compounds for which the disposition and metabolism were reported but the synthetic methods were never published.

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