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Turtles All the Way: Reflections on myo-Inositol

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It has been said that retirement consists of going from "Who's who?" to "Who's he?" My invitation to contribute to the *Journal of Biological Chemistry* (*JBC*) Reflections is an honor and timely as well in that as an emeritus professor, I have the time and an opportunity to beat the clock to "Who was he?" In a Venn diagram of biological sciences in which circles representing biochemistry and neuroscience overlap, the lens-shaped area can be defined as neurochemistry or, more recently, as molecular neuroscience and best describes my research area. My career in neuroscience is summarized in an autobiographical series recently published under the auspices of the Society for Neuroscience (1). In it, I detail my research on neuroplasticity, the ability of the nervous system to undergo change as a result of external inputs. This includes interventive studies on the role of protein synthesis in memory formation and correlative studies on optic nerve regeneration, both in teleost fish (1). This *JBC* Reflections article encapsulates my biochemical career, with emphasis on the neurochemical significance of *myo*-inositol, one of nine positional isomers of hexahydroxycyclohexane, and its phosphates.

My early years are described in Ref. 1. Briefly, I was born in Detroit in 1926, graduated from Cass Technical High School in 1944, entered a Navy premedical officer training program at the University of Michigan, and received an M.D. from Wayne State Medical School. I cannot resist sharing a recollection. In 1946, as a 20-year-old freshman medical student, I found myself surrounded by returning World War II veterans who were not only older than I, but understandably a bit rustier in college chemistry. In our freshman biochemistry class, I volunteered to go to the blackboard to derive and discuss the Henderson-Hasselbach equation. I returned to my seat, satisfied that I had done a clear and concise job. The 30- or so year-old returning veteran sitting next to me whispered, "Are you going to end up as a biochemistry professor?" Fishing for a compliment, I said, "No, why?" He answered, "The way you got right up there and mumbled into the blackboard, you just can't fake that!" He became a psychiatrist, and I, a biochemist. I interned in Sayre, PA, and had a postdoctoral fellowship with F. O. Schmitt in the Department of Biology at the Massachusetts Institute of Technology, until I was recalled by the Navy for a 2-year stint at the National Naval Medical Center in Bethesda, after which I moved to the nearby National Institutes of Health (NIH) in 1952.

The "PI Effect"

Now a research scientist in the Section of Lipid Chemistry in the intramural program of the National Institute of Neurological Diseases and Blindness (NINDB, presently NINDS) and searching for a suitable research problem, I was influenced by the reports of Mabel and Lowell Hokin that $^{32}P_i$ incorporation into phospholipids in pigeon pancreas and guinea pig brain slices was stimulated by the presence of carbamylcholine and was blocked in the presence of atropine (2). The labeled lipids were identified as phosphatidic acid (PtdOH, PA) and phosphatidylinositol (PtdIns, PI). At the time, there was some question as to the relevance of the finding because maximal stimulation required excessively high (millimolar) concentrations of carbamylcholine. Neverthe-

less, 10 μM atropine was sufficient to block the effect. Another potential drawback was the then prevalent view that PA was an uninteresting lipid because it was best known as a degradation product of the action of cabbage phospholipase D on phospholipids. Even so, it had already been shown by this time that PA could be biosynthesized from long-chain acyl-CoA and *sn*-glycerol 3-phosphate (3). I was additionally drawn to the Hokins' findings of the involvement of PI by virtue of its phosphorylated homologs (4), later to be identified as PI(4)P and PI(4,5)P_2 (5, 6). Their prominence in brain suggested a possible relevance of the stimulated labeling to nerve function. Eugene Kennedy's laboratory had at that time discovered the critical role of cytidine nucleotide derivatives in the biosynthesis of phosphatidylcholine and phosphatidylethanolamine (7). The biosynthetic pathways for PI remained unknown. Could there be a CDP-inositol analogous to CDP-choline and CDP-ethanolamine that reacted with 1,2-diacylglycerol to form PI? Around this time, I learned that Roy Bradley, a former Navy laboratory technician, was now a civilian and looking for employment, and I succeeded in getting him hired as my technician. He was a superb associate, and we worked together for my remaining 4 years at NIH. I began to look for the appearance of radiolabeled acidic products of tissue slices and homogenates following incubation with ^{3}H-labeled inositol, searching for an acidic product that might be the predicted CDP-inositol. Guinea pig kidney homogenates produced a labeled acidic substance from ^{3}H-labeled inositol that looked promising. Just at that time, an abstract appeared in the upcoming FASEB (Federation of American Societies for Experimental Biology) meeting proceedings, eventually published in *JBC* (8), in which Frixos Charalampous reported the oxidation of *myo*-inositol into glucuronic acid in kidney preparations. Recognizing that I had been pursuing a dead end, I switched to seeking other products of [^{3}H]CMP. I soon found labeled lipid-soluble material in incubated guinea pig kidney preparations that did not accumulate in the presence of added inositol. The deacylation product of the labeled lipid co-migrated upon chromatography with known CDP-glycerol, and on that basis, I proposed the existence of a novel substance, CDP-diacylglycerol (CDP-DG), coined a "liponucleotide," as the precursor of PI (9).

I put the PI project on hold at this in order to spend a year in the laboratory of Feodor Lynen, at the Max Planck Institute for Cell Chemistry in Munich, to participate in his exciting search to unravel the biosynthesis of cholesterol (10, 11). It was truly a memorable and productive experience. I was able during the year to meet at the University of Geneva with Theodore Posternak, who was a recognized authority on cyclitols and whom I had known through his encyclopedic treatise (12). During that year, Paulus and Kennedy synthesized CDP-diacylglycerol chemically and confirmed the biosynthetic step in studies using a chicken liver microsomal preparation (13).

During my NIH years, I collaborated with Harry Eagle on inositol biosynthesis in cultured cell lines (14), with John Burns' laboratory on inositol conversion to L-gulonate in rat liver (15), and with Spivey Fox on competition between dietary inositol and choline in growing chicks (16).

Back to Ann Arbor

In 1960, I accepted an offer from the University of Michigan for a joint appointment in the Department of Biological Chemistry and the Mental Health Research Institute, where my laboratory space was located. There were a number of attractions to the new position, not least of which was the opportunity to retain my identity as a biochemist and at the same time to pursue a growing interest in biochemical aspects of brain function. Thus began a dual research career and an unwillingness to give up either of my interests. I have urged my students and postdoctoral students to avoid the situation in which unrelated projects coexist in one's laboratory. Nevertheless, I probably would do it over, unable to resist the lure of each of the two disparate research areas (1).

Together with biochemistry graduate students, we perfected a chemical synthesis of CDP-DG (17), demonstrated its biosynthesis in embryonic chick brain particulates from CTP and PA (18), and established in a guinea pig brain microsomal preparation an enzymatic preference for *myo*-inositol in PI synthesis over the other cyclitols (19). We returned to CDP-DG many years later to clone the human gene (20) for the synthase after it had been demonstrated in *Drosophila*. Thought to be a substrate-limiting step in the PI cycle in signal transmission, its formation remains a possible site for pharmaceutical intervention.

Our interest in inositol phosphates led to the development of a low-pH high-voltage paper electrophoretic (HVE) separation technique (21). We separated a partial hydrolysate of plant IP_6 (phytate) into multiple components using sodium oxalate buffer at pH 1.5, visualized with a phosphomolybdate spray. A slowly migrating band was seen for P_i as well as a rapid one for unhydrolyzed phytate. Between them were distinct regions for inositol monophosphate as well as for inositol di-, tri-, tetrakis-, and pentakisphosphates, within which could be seen partial separation of positional isomers. This later proved use-

ful for us in many ways, but at the time, the HVE method was picked up primarily by soil chemists, who have noted that the inositol esters likely comprise the major organophosphorus mass on Earth (22). Many years later, in working out a gas chromatographic technique for inositol phosphates with my technician Ed Seguin, I used an aqueous methanolysis product of PIP_2 that co-migrated upon HVE with one of the inositol 3-phosphate (Ins(3)P)) bands of the phytate hydrolysate and surmised it to be Ins(1,4,5)P_3 (23). The biological activity of this preparation was eventually confirmed (M. J. Berridge, personal communication). In examining $^{32}P_i$-labeled mitochondrial lipid hydrolysates by HVE, Amiya Hajra and I were led to a novel intermediate, acyldihydroxyacetone phosphate, providing an alternate biosynthetic pathway to PA formation that bypasses *sn*-3-glycerophosphate (25, 26). Hajra later demonstrated that acyldihydroxyacetone phosphate is the precursor of the alkenylacyl and alkylacyl phospholipids (27).

Much of our work in which the PI effect was studied in brain utilized an isolated nerve-ending preparation (synaptosomes). Using this preparation, we were able to identify the form of the muscarinic cholinergic receptor that coupled to increased phosphoinositide turnover in response to carbamylcholine (28). Unexpectedly, even though it had been widely assumed that the increases in inositol lipid turnover occurred within presynaptic structures, results from hippocampal nerve-lesioning experiments conducted by Steve Fisher and Kirk Frey demonstrated that dendrite-derived structures present in the preparation were likely responsible for the observed changes. Thus, in common with other non-neural tissues, the PI effect was shown to be associated predominantly with activation of receptors on postsynaptic structures (29). Although we had characterized the nature of the muscarinic receptor binding and its relationship with the PI effect, we had made little progress in unraveling a connection with cellular responses, such as secretion and neurotransmission. When we examined the effect of thrombin on ^{32}P-labeled platelets, we found a decrease in labeling of PIP_2 and an increase in the appearance of radiolabeled IP_3. Whereas more label was associated with IP_2, the largest increases in labeling following thrombin addition were observed for IP_3. We concluded that there was a labeling cycle and that stimulation by the thrombin occurred at the level of PIP_2 cleavage (30). Later that year and 30 years after the Hokins initiated their studies, Streb, Irvine, Berridge, and Schultz answered the question of the significance of the PI effect by demonstrating that I(1,4,5)P_3 is the second messenger that leads to intracellular Ca^{2+} release and to various physiological cell responses (31). During the long interim between the Hokins' identification of PA and PI as the lipids in the stimulated labeling (2) and elucidation of the inositol lipid-related signal transduction process (31), it can be seen through the "retroscope" that many investigators had solved bits and pieces of the PI cycle puzzle along the way, including the Hokins' work on diglyceride kinase, the work of our laboratory and Kennedy's on CDP-DG, and evidence of ligand-stimulated breakdown of PIP_2 (30, 33–35). Michell had long proposed the existence of a link between PI labeling and elevated cellular Ca^{2+} (36). The role in signal transduction for activation of protein kinases by diacylglycerol, which, like Ins(1,4,5)P_3, is produced in the cleavage of PI(4,5)P_2, had been demonstrated by the Nishizuka laboratory (37). An additional major chapter in the myriad roles of inositol phosphates arose from the discovery of PI(3)P (38) and eventually many additional phosphoinositides: PI(3,4)P_2, PI(4,5)P_2, PI(3,5)P_2, and PI(3,4,5)P_3 (39).

Inositol Phosphates and the Turtle

There are 63 possible phosphomonoesters of *myo*-inositol (6 each of IP_1 and IP_5, 15 each of IP_2 and IP_4, 20 of IP_3, and IP_6). About half have been identified thus far in eukaryotes. Confusion in numbering and in depicting the Haworth projections of the six hydroxyls is mitigated by use of a three-dimensional visual mnemonic (40) in the form of a turtle, in which the axial hydroxyl is its head, and the five equatorial hydroxyls serve as forelimbs, hind limbs, and the tail, as illustrated in the Fig. 1. Using the D numbering convention, one proceeds counterclockwise, from above. The hydroxyl of *myo*-inositol that is diesterified to diacylglycerol is at carbon D1, the right forelimb. The axial hydroxyl serves as the turtle's head at D2, and the left forelimb represents carbon D3, moving on to the left hind limb (D4), the tail (D5), and the right hind limb (D6). The less used L numbering system begins at the turtle's left forelimb (L1) and proceeds clockwise with the head at L2 and the right forelimb at L3, etc. The product of the action of inositol synthase on glucose 6-phosphate can thus be termed *myo*-inositol D3 monophosphate or *myo*-inositol L1 monophosphate.

IP_6 through IP_9

Phytate (IP_6), a major component of plant seeds, was named phytin in 1903 by S. Posternak, father of Theodore Posternak. Phytate was removed from grain flour in the 1920s on the basis that it was "rachitogenic," that is, by binding dietary calcium, could cause or aggravate rickets, a

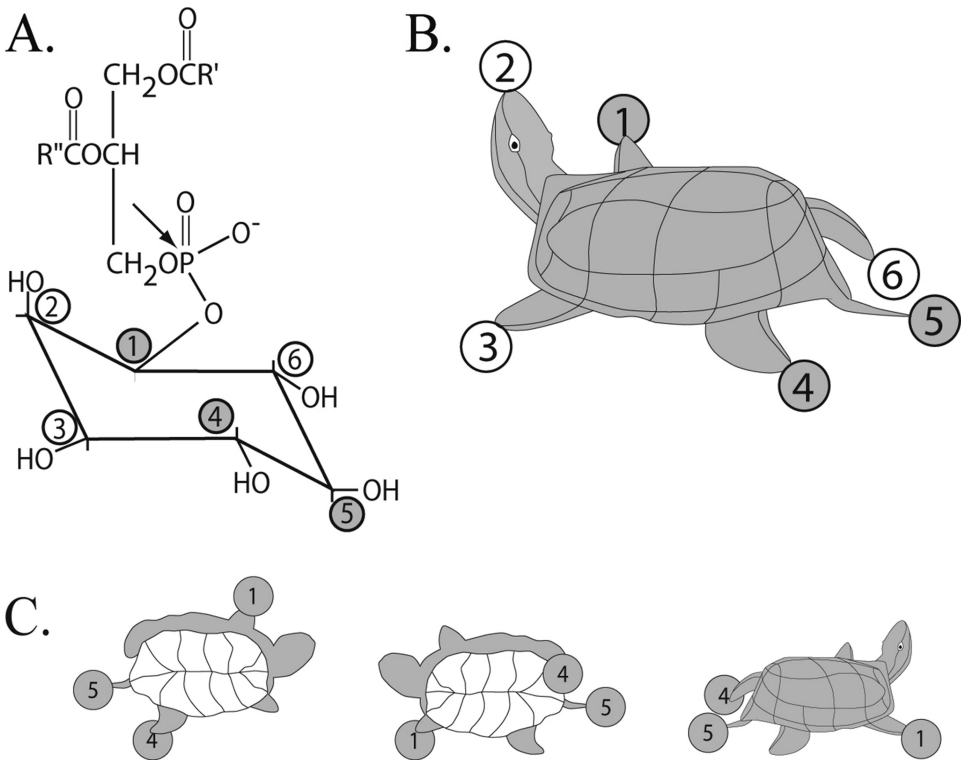

FIGURE 1. "**The turtle.**" *A*, PI(4,5)P_2 and its cleavage at hydroxyl D1 of inositol by phospholipase C; *B*, I(1,4,5)P_3 depicted as a turtle; *C*, views of the turtle from different vantage points (modified from Ref. 41). Use of the turtle is suggested by the International Union of Biochemistry Nomenclature Committee (42).

disease of bone malformation in growing children in the pre-vitamin D supplementation days. The disease is now rare, and there are some who now praise phytate's virtues; for example, it binds dietary iron and thereby acts as an antioxidant. Its multivalent ionic environment may affect its solubility and chelating ability (43). Phytate and I(1,3,4,5,6)P_5 that additionally have varying amounts of pyrophosphates on the D1, D3, or D5 position are referred to as IP_7 and IP_8, and there is even an IP_9. At present, 15 of these pyrophosphorylated inositol phosphates been identified as enzyme products (44). Some have been shown to phosphorylate protein, and their possible physiological significance is being actively explored (45, 46).

Brain Inositol and Lithium

Free inositol in mammalian brains is ~6 mM, serving as a non-ionic osmolyte (47). Scyllitol, with all six of its hydroxyls equatorial, is present in brain at a level about one-tenth that of the *myo*-isomer. Although enzymes can oxidize *myo*- and *scyllo*-inositol to the 2-inosose and interconvert them via reduction, the origin of scyllitol in brain is thought to be dietary. D-*myo*-Inositol 3-phosphate can be synthesized from glucose 6-phosphate by a synthase and cleaved to free inositol in the meningeal chorioid bodies (48), but inositol enters the brain principally via an active transport system. The enzyme is blocked by Li^+, and this proved to be very useful in the experiments that helped define the phosphoinositide cycle (32). Lithium (LiCl or Li_2CO_3) is widely prescribed for the treatment of bipolar psychiatric disease, even though it is not a profitable pharmaceutical, and its mechanism(s) of therapeutic action is not well understood (49). The possibility that the therapeutic action of Li^+ is related to its block of inositol monophosphatase led to the search for an effective drug that, like lithium, would block the monophosphatase but lack some of the side effects of Li^+. These efforts have not proven successful thus far (50).

Inositol, a Prebiotic Molecule?

Taking advantage of the disinhibiting effect of an invitation to reflect, I offer a speculation: that terrestrial inositol preceded the existence of living organisms. A number of investigators who study the origin of living matter have addressed the question as to when inositol and relevant enzymes for its synthesis and utilization appeared during evolution (51, 52). I propose that cyclitols, as has been proposed for amino acids (53), be considered prebiotic "Ur" molecules (in the sense that they may have preceded the existence of living matter, not that they are self-replicating). My hypothesis harks back to the formose reaction, reported by Butlerow in 1861 (54), in which formaldehyde in the presence of aqueous calcium hydroxide produced a high yield of a syrupy sugar-like material, rich in DL-ketohexoses. Emil Fischer's source of reducing sugars for his famous crystallization of their phenylhydrazine osazones was formose reaction products. The possibility that photosynthesis was mediated by reduction of carbon dioxide to formaldehyde was later investigated and abandoned, as were many unsuccessful attempts over the years to produce nutritional products from formaldehyde or glycolaldehyde (55). The possible role of carbohydrates arising from formose, specifically ribose, as a prebiotic molecule

has been proposed (56) and criticized based on the conclusion that it would not be sufficiently stable over long time periods thought to be required for the emergence of living matter (57). Unlike reducing sugars or acyclic polyols, *myo*-inositol is remarkably stable to degradation by temperature or oxidation. Its stability was in fact the basis of a chemical method for determination of inositol in tissue, in which other polyols such as glycerol were oxidized by periodate, whereas inositol oxidation required a much higher pH and temperature (9). Could then inositol, a most stable carbohydrate, have sat by, waiting patiently over the aeons, as a prebiotic energy source and/or building block? Cyclitols have not been reported as products of the formose reaction, but the presence of polyols including inositols has been reported in meteorites (58), lending credence to this hypothesis. In addition, it has been proposed that inositol lipid harks back to early beginnings in the origin of life (52). Pyrophosphates must certainly have been present prebiotically as well (24), and hexose phosphoesterification could have facilitated cyclization to cyclitol phosphates. The prebiotic existence of inositol phosphates thus could have preceded that of free inositols. It may have been "turtles all the way": up (alluding to an ancient cosmological belief that the world rests on a giant turtle that in turn rests on a still larger turtle, that "it's turtles all the way down"; folk lore cited by William James, Thomas Huxley, Bertrand Russell, and more recently by Stephen Hawking (59)).

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