Polyamines have a long history in biochemistry and physiology, dating back to 1678 when Leeuwenhoek first reported crystals that were composed of spermine phosphate in seminal fluid. Their quantification and biosynthetic pathway were first described by Herb and Celia Tabor in collaboration with Sanford Rosenthal in the late 1950s. This work led to immense interest in their physiological functions. The 11 Minireviews in this collection illustrate many of the wide-ranging biochemical effects of the polyamines. This series provides a fitting tribute to Herb Tabor on the occasion of his 100th birthday, demonstrating clearly the importance and growth of the research field that he pioneered in the late 1950s and has contributed to for many years. His studies of the synthesis, function, and toxicity of polyamines have yielded multiple insights into fundamental biochemical processes and formed the basis of successful and continuing drug development. This Minireview series reviews the highly diverse properties of polyamines in bacteria, protozoa, and mammals, highlighting the importance of these molecules in growth, development, and response to the environment, and their involvement in diseases, including cancer, and those caused by parasitic protozoans.

It is a pleasure and privilege to write a prologue to the Minireviews on polyamine research in this issue of Journal of Biological Chemistry. Herb Tabor’s contributions to this field cover more than 60 years. His early papers with his wife Celia (Fig. 1) and with Stanford Rosenthal had an enormous impact on the field (1–5). Their experiments published in 1958 in JBC (3) identifying the biochemical pathway by which spermidine (H₂N(CH)₄NH(CH)₃NH₂) is formed from putrescine (H₂N(CH)₂NH₂) in Escherichia coli formed the basis for many subsequent investigations into the highly regulated synthesis and maintenance of polyamine content in mammals, plants, pathogenic parasites, and many other species. This paper (and a subsequent investigation of the enzymology and genetics involved (6) which is described below) was featured in the series of papers celebrating the JBC centennial (Fig. 2) (7).

Their descriptions of the enzymology of this pathway in E. coli and in Saccharomyces cerevisiae (8–11) led to studies in many other laboratories showing that these enzymes were essential for proliferation and were important therapeutic targets. Their identification of the genes for these enzymes and their elegant use of the microbial mutants lacking these genes (Fig. 3) led to a general appreciation of the critical roles played by these simple molecules in growth and development (12–18).

Many of these functions are described in the articles making up the 11 Minireviews in this issue of Journal of Biological Chemistry (19–29). These Minireviews cover many but by no means all of the important biological functions of polyamines.

Some indication of the explosive growth of the polyamine area during Herb’s career is given by the exponential rise of papers mentioning putrescine, spermidine, or spermine (H₂N(CH)₄NH(CH)₃NH(CH)₃NH₂) in PubMed. From 1920 to 1958, there were 55 publications; from 1959 to 1970 this rose to 359 publications; in the next decade there were 1833 publications; and in each subsequent decade there were more than 3500 publications.

Polyamines have a long history in biochemistry/physiology that is quite easy to summarize prior to work by the Tabors, because the entire field has less than 100 publications. It is well-known (and indeed referenced in several of the Minireviews) that the first publication describing them dates to 1678 when, in a letter to the Royal Society describing spermatozoa, Leeuwenhoek reported crystals that appeared with time in seminal fluid (30). These crystals are spermine phosphate, which is relatively insoluble and precipitates as the phosphate level rises as a result of phosphatase action. A detailed historical account of multiple studies describing these crystals and their formation is given by Williams-Ashman (31). In 1865, Boettcher mistakenly suggested they were made of protein and was corrected by Schreiner, who showed that they were the phosphate salt of an organic base. Similar salts were obtained from other tissues and named spermine by Abel in 1878. Early analyses of their chemical composition were incorrect. The Russian researcher von Poehl obtained the correct empirical formula but also published unfounded and improbable claims for the therapeutic value of spermine. In the 1920s, Otto Rosenheim and Wrede independently established the correct structure and verified it by chemical synthesis (32, 33). Except for studies on the production of amines, including putrescine and agmatine by bacteria, which were known to be due to amino acid decarboxyl-
ases by the work of Gale (34, 35), little was known about polyamine synthesis and functions until the pioneering studies of Herb and Celia Tabor, who together with Sanford Rosenthal introduced analytical methods for measuring polyamine content, as well as understanding their pharmacology, toxicology, and biosynthesis (2).
The Tabors’ work over many years is wonderfully summarized in an autobiographical article published in 1999 (36). Herb has worked at National Institutes of Health (NIH) since 1943. He initially worked with Rosenthal on electrolyte changes after traumatic shock and then on the metabolism of histamine. This led him to purify diamine oxidase (histaminase), which also acts on putrescine. He and his wife Celia then commenced their groundbreaking studies on the analysis, distribution, pharmacology, and toxicology of the polyamines spermidine and spermine. In the late 1950s when this work was started, the NIH was an extremely fertile ground for interactions between scientists moving biochemistry forward with fundamental discoveries. One of these was the discovery of spermidine (AdoMet) (37), which the Tabors showed was not only the source of methyl groups but also the precursor of the aminopropyl groups of the polyamines.

On a personal note, in 1966, I joined the laboratory of Guy Williams-Ashman at The Johns Hopkins University, and he suggested that I investigate the synthesis and endocrine regulation of polyamines in the prostate. Guy said there was not much known on the topic, and indeed I found fewer than 250 research papers, more than half of which were chemistry, on the whole field of polyamines. However, these included the seminal contributions of the Tabors on methods for their analysis and the mechanism of spermidine synthesis from putrescine in *E. coli*. The pathway for spermidine synthesis in rat prostate was easily determined because the reactions were identical to those described by the Tabors. Spermine, which is not formed in *E. coli*, is produced by spermine synthase that catalyzes a very similar reaction to spermidine synthase (38). One minor but important difference is that the only route to putrescine in mammals is via ornithine decarboxylase (ODC), whereas, as described at that time by Morris and Pardee (39), *E. coli* has two routes to putrescine: the direct decarboxylation of ornithine and the decarboxylation of arginine followed by conversion of agmatine by agmatine ureohydrolase. The content of polyamines and the activities of two key enzymes, ODC and SAM decarboxylase (AdoMetDC), were greatly increased by androgens in the prostate (40, 41).

Studies by multiple investigators of the effects of many other hormones and growth-promoting stimuli in numerous other tissues also described large and rapid increases in the enzymes of polyamine synthesis and increased polyamine content (reviewed in Ref. 42). These observations led a drug company research institute (Merrell in France, later Merrell Dow, which relocated to the United States) directed by Al Sjoerdsma, previously of NIH, to undertake an extensive program of the production of inhibitors of polyamine synthesis (43). However, at that time, no structural information was available on the enzymes; potent and specific inhibitors of ODC and AdoMetDC were synthesized based on known enzyme mechanisms and shown to be powerful anti proliferative agents (44–47).

One of these, 2-difluoromethylornithine (DFMO; eflornithine), is a mechanism-based inactivator of ODC first described in 1978 (44). DFMO acts a substrate for ODC, but its decarboxylation generates a highly-reactive intermediate that irreversibly inactivates the enzyme. Studies using cells in culture showed that DFMO was profoundly antiproliferative, and there were hopes that it would be a viable drug for treatment of malignant diseases. Unfortunately, initial clinical trials for this purpose were not sufficiently promising to justify the costs of developing antitumor drugs that, even at that time, were substantial. However, studies on the possible use of these compounds to treat parasitic diseases revealed that DFMO had considerable potential for the cure of trypanosomiasis caused by *Trypanosoma brucei gambiense* (48, 49). After the donation to charity of both large amounts of the drug and the relevant patents by the company, therapeutic use for trypanosomiasis was developed by the World Health Organization. This has led to a successful combination therapy when used with nifurtimox, which increases oxidative damage (43, 50). The history of synthesis and development of DFMO, its use for trypanosomiasis, and the influence of Herb and Celia Tabor on this work are described in detail in the biography of Sjoerdsma (43). The
mechanism of DFMO as an antiparasitic agent and the unique biochemical features of polyamine pathways and functions in protozoan parasites that could lead to the production of additional drugs are described in the Minireview by Phillips (25).

For many years, the Tabor laboratory continued to make major findings on the enzymology, synthesis, and function of polyamines in *E. coli* and budding yeast. Their characterization of the enzymes in the pathway included the first purifications of bacterial spermidine synthase (9) and a series of studies using purified and cloned AdoMetDC. In these experiments, they showed that AdoMetDC belongs to a class of decarboxylases that use a covalently bound pyruvate as a cofactor (8, 51, 52) and that this pyruvate is generated from an internal serine residue via an autocatalytic post-translational modification (6, 7, 53). There are significant differences in the primary and subunit structures and activators of AdoMetDCs between different species, but all use a pyruvate prosthetic group, which is generated from a precursor in this way (54). Structural studies of these enzymes and their mutants that cannot cleave due to mutation of the serine to an alanine, as carried out by Ealick and co-workers (55, 56), have provided a detailed picture of this process (Fig. 4).

**Figure 3. Genetics of biosynthetic pathway of polyamines.** The upper section shows the pathway and genes in *E. coli*, and the lower section shows the pathway and genes in *S. cerevisiae*. From Ref. 36, based on Refs. 3, 8 – 14. These data were originally published in the Annual Review of Biochemistry. Tabor, C. W., and Tabor, H. It All Started on a Streetcar in Boston. Annu. Rev. Biochem. 1999; 68:1 – 32. © Annual Reviews.
After elucidating the biochemical pathways of their synthesis, they used genetic techniques to investigate function by isolating mutants inactivating the key enzymes in *E. coli* \(^{(12–15)}\) and in *S. cerevisiae* \(^{(14, 16–18)}\). These strains and genetic analyses were used to identify possible polyamine-responsive target proteins and to show that polyamines provide protection from oxidative damage \(^{(15, 57, 58)}\), paraquat \(^{(59)}\), paromomycin \(^{(60)}\), and elevated temperatures \(^{(61)}\).

Their studies on growth of *E. coli* showed that it can grow aerobically, albeit at a reduced rate, in the absence of polyamines \(^{(15)}\), but it had an absolute requirement for spermidine to grow under anaerobic conditions. Polyamines were essential for the induction of the genes making up the glutamate-dependent acid resistance system that is important for the survival in the acid environment of the stomach \(^{(62)}\). Recently, Herb’s group has determined that this effect is mediated via the alternative \(\sigma\) factor RpoS, which stimulates gadE expression, which in turn induces the glutamate-dependent acid resistance system (see Fig. 5) \(^{(63)}\).

Another unique feature of polyamine metabolism was reported in early work by the Tabors when they showed that *E. coli* is able to convert a large proportion of its spermidine into a glutathionylspermidine conjugate at the end of logarithmic growth \(^{(64)}\). More recently, Herb’s group has found that this unique synthesis is limited to kinetoplastids and certain bacteria but is found in all enterobacteria \(^{(65)}\). Using strains with deletions of glutathionyl synthetase/amidase, genetic analysis showed major effects on the expression of more than 100 genes. The function of glutathionylspermidine remains unproven, but a plausible explanation consistent with the genetic analysis is that it is important for survival in the crowded anaerobic intestinal lumen \(^{(65)}\).

Studies with yeast mutants lacking AdoMetDC or spermidine synthase indicated that spermidine was essential for growth \(^{(18, 66)}\) and that this was due to its role as a precursor of hypusine \(^{(67)}\). Spermine was not essential for growth in yeast \(^{(17)}\), but it could replace spermidine by virtue of its oxidative conversion to spermidine \(^{(18)}\). Microarray studies in which individual polyamines were added to yeast lacking spermidine synthase grown with the minimal amount of spermidine to allow hypusine formation showed that there were profound changes in gene expression with more than 200 genes up-regulated and a similar number down-regulated \(^{(68)}\). Spermine was much less effective with alterations in only 18 genes.

The 11 Minireviews \(^{(19–29)}\) describe some of the highly diverse properties of polyamines in bacteria, protozoa, and mammals. They illustrate the importance of polyamines in nor-

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**Figure 4. AdoMetDC processing and structures.** A and B show ribbon topology diagrams of the *Thermotoga maritima* AdoMetDC dimer (left) and the human AdoMetDC dimer (right). Helices are represented by circles; \(\beta\)-strands are represented by triangles. The breaks between the \(\alpha\) and \(\beta\) chains are indicated by gold stars. C shows a stereo view of the cleavage/pyruvate formation site. The three key active-site residues (Ser-55, His-68, and Cys-83) in the *T. maritima* AdoMetDC, which are involved in substrate binding, catalysis, and proenzyme, are structurally conserved in mammalian, plant, and microbial AdoMetDCs despite very limited primary sequence identity. They correspond to residues Ser-77, His-117, and Cys-140 in *E. coli* AdoMetDC. Data are from Ref. \(^{(56)}\). The original papers describing the pyruvate prosthetic group in *E. coli* and yeast AdoMetDC and the processing to generate it were published by the Tabor group \(^{(6, 8, 51–53)}\).

**Figure 5. Polyamine-mediated induction of glutamate decarboxylase-dependent acid-response system.** A shows the GAD box sequences identified, and B shows the RpoS-binding sites upstream in these genes. C shows the proposed pathway for polyamine action. Data are from Ref. \(^{(63)}\).
mal growth and development and response to the environment and in the development of pathologies. They also provide some outlines of how the polyamine pathway may be used for therapeutics.

A comprehensive overview of the importance of polyamines in bacteria and archaea is provided by Michael (19). He describes how spermidine goes back much further than 1678, having been identified as a component of the last common ancestor of life, which encoded a spermidine synthase. His article provides an excellent overview of the diversity of polyamines that are by no means limited to putrescine, spermidine, and spermine and of the multiple functions of polyamines in a wide range of microbes, including important pathogens. He describes many other polyamines that are critical cell components, their synthetic pathways, and their importance in the growth of the organism. Noteworthy are the long chain and branched polyamines that are essential for thermophilic organisms to survive and multiply at extreme temperatures. He also discusses the importance of agmatine (decarboxylated arginine), which, in addition to serving as a precursor of spermidine in some organisms, is needed in many archaea for the formation of 2-agonagmatine-cytidine in a tRNA\textsuperscript{AGN} that discriminates isoleucine and methionine codons and is essential for growth. Among the important roles of microbial polyamines are cell wall peptidoglycan synthesis and biofilm development in pathogens such as Vibrio cholerae and Yersinia pestis.

The article by Igarashi and Kashiwagi (20) describes detailed studies of the abilities of putrescine and spermidine to influence protein synthesis in E. coli. These polyamines stimulate protein synthesis via general effects on the synthesis and structure of ribosomes and by specific effects at the level of transition. They describe a polyamine "modulon" consisting of a number of proteins whose synthesis is stimulated by polyamines using one of three mechanisms. These include stimulation of certain Shine-Delgarno sequences, enhanced recognition of weak initiation codons, and stimulation of amber codon read-through. The latter influences RpoS, which, as described above, was identified in the Tabor laboratory as an important target for polyamines (62, 63). The Minireview (20) also describes multiple other functions of polyamines in E. coli, including their antioxidiant effects and allowing growth at acid pH. It also describes the importance of spermidine uptake systems in maintaining optimal polyamine levels.

A function of spermidine, which is essential for the growth of many organisms, including archaea, budding yeast, trypanosomatids, and mammals, is its ability to act as a precursor of hypusine, a post-translational modification of the eukaryotic translation factor eIF5A. The importance, mechanism of synthesis, and function of hypusine are described in the Minireview by Park and Wolff (21). Hypusine is produced by the sequential action of two enzymes. Deoxyhypusine synthase catalyzes the conversion of a specific lysine residue in eIF5A to deoxyhypusine (N\textsuperscript{4}-aminobutyllysine), which is subsequently hydroxylated to hypusine (N\textsuperscript{4}-amino-2-hydroxybutyllysine). The hypussinated form of eIF5A is needed for continued translation elongation at ribosome pausing sites, including those involving polyproline stretches. It also allows translation termination by stimulating peptide release. There are associations of eIF5A alterations with neurodevelopmental disorders. This Minireview also describes studies in collaboration with Dr. Tabor using mutants defective in polyamine synthesis, in which it was found that hypusine formation was the critical function for polyamines in S. cerevisiae (67). Other requirements for polyamines for protein synthesis particularly at the level of translation initiation can be fulfilled by Mg\textsuperscript{2+} in yeast where it can accumulate very high levels. This accumulation cannot occur in mammalian cells providing an additional requirement for polyamines.

The abilities of polyamines to influence protein synthesis at both the general and specific levels are elegantly described in the Minireview by Dever and Ivanov (22). Polyamine content can affect initiation, elongation, and termination in a variety of ways. These include the following: general effects on ribosomal RNA, tRNA, and mRNA structure; the hypusine modification in eIF5A, which affects proteins with certain amino acid sequences; the ability to influence frameshifting; the effects on the use of alternative translation start sites; and the effects on ribosome stalling at small open reading frames. As they point out, several of the original observations leading to the investigation and understanding of these effects originated in the Tabor laboratory (69–71). They also explain several of the ways in which some of these effects of polyamines are used to regulate the synthesis and hence content of the polyamines themselves.

One of the most interesting and intricate components of the regulation of polyamine content in eukaryotes is the control of ODC content via effects of a family of proteins termed antizyme. This system is described in the Minireview by Kahana (23). The ODC enzyme is very highly regulated, and its activity can be changed rapidly by many stimuli, including growth factors, oncogenes, and tumor promoters. Physiological changes in its activity are brought about solely by changes in the amount of enzyme protein. Regulation of this content occurs at multiple levels, including transcription, translation, and protein turnover. Mammalian ODC has a very short half-life (72). An intricate pattern of control of ODC degradation occurs via the action of the antizyme family. Antizyme binds to the ODC monomer inactivating the enzyme and targeting it to the proteasome for degradation without the need for ubiquitination. Kahana describes how antizyme synthesis requires a polyamine-mediated frameshift. Antizyme is, in turn, regulated by another protein termed antizyme inhibitor that resembles ODC but lacks its enzymatic activity. Antizyme inhibitor binds more tightly than ODC to antizyme thus preserving ODC activity. There is a family of antizyme proteins for which the relative importance and individual roles are still under active investigation. Antizyme proteins regulating ODC are found in many species, including yeast. An early indication that this was the case was published by Herb’s laboratory (73). In 2001, they showed spermidine caused reduction in ODC content in yeast implying the presence of an antizyme-like regulator, which was later identified and characterized by Dohmen and co-workers (74, 75).

Polyamines have an important function in protecting against oxidative damage. This aspect of their physiology in microorganisms was demonstrated in the Tabor laboratory for both yeast and E. coli (58, 66). However, polyamine catabolism can
also lead to significant oxidative damage. The complex role of the polyamines and their metabolic products in oxidative homeostasis is described in detail in the Minireview by Casero and co-workers (24). Many oxidases that degrade polyamines are known throughout the spectrum of living organisms. The Tabor laboratory performed pioneering studies on these oxidases (1, 76). Polyamine oxidation can generate hydrogen peroxide and reactive aldehydes, including acrolein. The presence of extracellular amine oxidases in serum from many mammals, including bovine sources, accounts for the toxicity of spermidine or spermine when administered intravenously or when added to cell cultures. Although this is well documented, there are numerous erroneous reports in the literature describing experiments in which polyamines are added to cell cultures without the use of amine oxidase inhibitors to prevent the generation of such toxic products. Physiological serum polyamine content is very low, and this type of toxicity does not occur normally. As described in detail in this Minireview, mammalian polyamine catabolism occurs inside the cell and involves highly inducible pathways (24). Both spermidine and spermine can be acetylated and then degraded by acetyl polyamine oxidase. Spermine can be degraded directly by spermine oxidase. Although both pathways can generate toxic products, including hydrogen peroxide, the latter oxidation has a greater potential to cause damage because spermine oxidase is present in the nucleus and cytoplasm, whereas acetyl polyamine oxidase is peroxisomal. Abnormal alterations in polyamine catabolism are, however, clearly associated with some diseases, including cancer. Spermine oxidase induction has been implicated in the toxic effects of pathogenic organisms such as Helicobacter pylori and Bacteroides fragilis and in inflammatory diseases.

The Minireview by Phillips (25) contains a comprehensive summary of the current state of understanding of the role of polyamines in trypanosomatids and other protozoan pathogens. Although there are common features in polyamine biochemistry with hosts such as the requirement for hypusine, there are unique aspects in the usage, synthesis, and uptake of spermidine in these pathogens, which are causative agents in important diseases (e.g. malaria, leishmaniasis, Chagas disease, cryptosporidiosis, and trichomoniasis) for which there are limited therapeutic remedies. As indicated by the success of DFMO for West African sleeping sickness caused by T. brucei gambiense, these differences may provide the basis of additional drugs. Factors contributing to this success may include the following: (i) mammalian ODC turns over much more rapidly than the trypanosomal equivalent; (ii) spermidine is needed in trypanosomes as the precursor of trypanothione, which counteracts oxidative damage; and (iii) reduced polyamine content may limit the ability of the parasite to escape the immune system. Another important factor is the extracellular location of the parasite, which limits its opportunities to take up polyamines from the host. It is likely that some means of interfering with uptake of host or dietary polyamines will be needed for parasites whose life cycle includes intracellular locations. A particularly exciting recent discovery made in the Phillips laboratory is that the trypanosomatid AdoMetDC and deoxyhypusine synthase both have significant structural differences from their host equivalents. These arise from gene duplications that have generated an inactive subunit needed to form an active heterodimer with a very weakly active paralog. (In mammals, the enzyme is a dimer or tetramer with identical pairs forming two active sites.) These differences may allow for the design of inhibitors based on unique interactions at the active sites rather than the mechanism-based inhibitors currently available. Such compounds could have much greater species specificity. Similar opportunities may exist in Plasmodium, which uses a remarkable fusion protein possessing both ODC and AdoMetDC domains for polyamine synthesis.

Two of the Minireviews describe the importance of polyamines in mediating tumor promotion and the effects of oncogenes that have led to continued attempts to use the polyamine biosynthetic pathway as a target for anticancer interventions (26, 27). As described above, initial attempts to use the battery of mechanism-based inhibitors of the enzymes in the polyamine biosynthetic pathway did not lead to approved therapies, although there were some encouraging preliminary results. More recently, there has been renewed interest in this field leading to further testing of inhibitors of biosynthesis alone and in combinations with other drugs, as well as trials of polyamine analogs that block growth-stimulatory actions and, in some cases, induce the biosynthetic degradation pathways. There are multiple studies using animal models showing that such interventions can be effective. This work has produced several promising developments and ongoing clinical trials (reviewed in Ref. 77).

Bachmann and Geerts (26) review the work showing that the ability of MYC proteins to stimulate polyamine synthesis is important in the development of tumors in response to this oncogene, which is overexpressed in many different tumor types. Production of drugs to target the MYC family directly has not yet been successful perhaps due to the wide variety of critical genes influenced by them. Studies by Cleveland and co-workers using transgenic mouse models and DFMO have shown that ODC is a key downstream target of MYC in both lymphoma (78) and neuroblastoma (79). The ongoing attempts to improve therapy for pediatric neuroblastoma in which MYCN gene amplification is a common event by using DFMO are described in detail in this article (26). The Minireview by Gerner et al. (27) outlines experimental and clinical studies on the importance of polyamines in the development of gastrointestinal cancer. Several lines of evidence attest to their key role in this major cause of human disease. Elevation of polyamine synthesis and content occurs in familial adenomatous polyposis. Mutations of the APC tumor suppressor cause up-regulation of ODC and other polyamine biosynthetic enzymes in humans and in the murine ApcMin/+ model of colon cancer. DFMO treatment also decreases tumor incidence in this model. These considerations have led to clinical trials of DFMO to lower cancer incidence in high-risk groups. The lack of serious toxicity upon prolonged treatments with DFMO renders it potentially suitable for such a long-term treatment in patients with risk but without current disease. Combinations with nonsteroidal anti-inflammatory drugs (NSAIDs), such as sulindac or celecoxib, have produced significant reductions in tumor burden in both ApcMin/+ mouse models and in human trials. NSAIDs may act not only...
via effects on prostaglandin metabolism but also by influencing polyamine-mediated pathways, because they repress ODC and stimulate polyamine catabolism.

It is now recognized that an important function of polyamines in humans is in the regulation of ion channels. Two of the Minireviews cover this important area. Nichols and Lee describe their effects on inward-rectifying potassium (Kir) channels (28). This action of polyamines was first described by Nichols’ laboratory in 1994 (80). The inward rectification is essential for the functioning of these channels, which control multiple critical cellular functions. Detailed structural analysis and experimental studies with mutations at key residues have provided a clear understanding of the importance of polyamines in their mechanism of action. The exact positioning of the polyamines needed for the block in the channel is still not fully established, but a plausible cavity-trapping model that is capable of experimental verification is proposed. Polyamines also regulate ionotropic glutamate receptors, and this phenomenon is reviewed by Bowie (29). Polyamines bind in the internal channels of these receptors blocking ion transport. Numerous channels are affected, including α-amino-3-hydroxy-5-methyl-4-isoxazole propionate (AMPA), N-methyl-D-aspartic acid (NMDA), kainate, and some orphan receptors. The magnitude of effect is dictated by both the polyamine bound and the subunit composition of the receptor as well as auxiliary regulatory proteins that can modulate the receptors. Thus, physiological effects on ion flow and function are complex. Structural analyses reveal the binding sites of polyamines, and experimental studies show that polyamines can pass into the cell through these channels. It is an interesting speculation that permeation of polyamines through these channels may be a mechanism of polyamine transport into the brain.

Both Minireviews on ion channels describe some clinical correlations with alterations in polyamine regulation. They also mention the possibility that some of the dysfunctions in patients with the inherited condition Snyder-Robinson syndrome may be related to altered functions in these channels. Snyder-Robinson syndrome is due to an X-linked inheritance of mutations in spermine synthase (81). This leads to a marked increase in the spermidine/spermine ratio and an increase in total polyamine content. Potential alterations in oxidative damage as mentioned in the Minireview by Casero and co-workers (24) could also be involved in the complex phenotype of Snyder-Robinson syndrome. The phenotype of patients with Snyder-Robinson syndrome shows clearly that spermine is need for normal development in humans. This is confirmed by animal studies because Gy mice, which have a deletion of the part of the X chromosome that contains spermine synthase, have multiple defects, including a short life span which is at least partially due to arrhythmias that are consistent with altered ion channel function. All of these defects are corrected by transgenic expression of spermine synthase (82). There are quite striking differences in individual disabilities in Snyder-Robinson syndrome patients that do not correlate with the degree of reduction in spermine synthase. This suggests that there are other gene products that influence the response to polyamine imbalance and are consistent with the finding that a complete inactivation of spermine synthase in mice is compatible with viability only on the mixed B6C3H background (82).

The 11 Minireviews contained in this issue contain summaries of many but by no means all of the important roles of polyamines in biology. Several other areas that should be mentioned include the following: the importance of polyamine interactions with DNA; polyamine biochemistry in plants; the critical interactions between the polyamine pathway and sulfur metabolism; and the mechanisms and importance of polyamine transport. Tabor’s research has had major influences on all of these areas that are summarized briefly below.

The binding of polyamines to DNA can affect its structure, transcription, and stability (83). This is one of the reasons why they are essential for the replication of many viruses (84). The ability of polyamines to condense DNA is not only important in viral packaging but also in the production of nanometric particles for gene therapy (85). Their importance in protecting DNA from damage at high temperature is described by Michael (19). Their ability to protect DNA from depurination may be a significant factor in this effect (86).

Polyamines perform many of the functions described above in plants where they are also used as structural scaffolds in the production of many diverse plant-specialized metabolites (87). Plant polyamine biosynthesis differs from other eukaryotes due to the presence of both an additional pathway to synthesize putrescine from arginine via agmatine and N-carbamoylputrescine and the presence of thermospermine synthase that produces a structural isomer of spermine (88). These pathways were acquired from the cyan bacterial ancestor of the chloroplast via end symbiotic gene transfer (87). The model plant Arabidopsis thaliana differs from most plants in having lost the ODC route for putrescine biosynthesis (89). Experimental deletion of its arginine decarboxylase or spermidine synthase results in embryo lethality (90, 91) demonstrating the essentiality of polyamines for plant growth. Deletion of Arabidopsis thermospermine synthase results in severe stunting due to greatly reduced stem elongation (92). Spermine synthase is not essential for its normal growth and development, but its deletion does render Arabidopsis more sensitive to salt and drought stress (93).

Another important topic with multiple facets is the close inter-relationship between the polyamine pathways and methionine and one-carbon metabolism. A significant proportion of the methionine usage outside of protein synthesis occurs via its conversion into polyamines (68). AdoMetDC irreversibly directs methionine to polyamine synthesis because decarboxylated SAM (dcSAM) is not used by methyltransferases and has no significant further metabolism except for polyamine synthesis (54). An underappreciated effect of ODC inhibition (94) or the loss of spermidine synthesis in Tabor’s yeast mutants is that dcSAM accumulates dramatically (95). Its content, which is normally only a few percent of SAM itself (96), can exceed that of SAM. This has important consequences for sulfur metabolism and cell growth and may contribute to the antiproliferative effects of ODC inhibitors. A by-product of the spermidine and spermidine synthase reactions is 5′-methylthioadenosine (MTA). This is recycled by a pathway that salvages both the adenine and the methylthio moiety and is commenced by a
hydrolase in bacteria, mammals, and yeast by a phosphorylase (MTAP) that generates adenine and methylthioribose 1-phosphate (97). MTA accumulates in the absence of this recycling pathway. This accumulation can occur due to inhibition of MTAP by drugs, loss of the MTAP gene expression, which occurs frequently in tumors or, as shown by the Tabor group, in yeast mutants with experimental deletion of the MTAP gene (68). The increase is limited by the ability of MTA to diffuse through the cell membrane but can lead to a loss of methionine and ATP content. MTA metabolism is also important to allow normal polyamine synthesis because both aminopropyltransferases are product-inhibited by MTA with spermine synethase being more sensitive (98, 99). Many tumors lack MTAP. The MTAP gene is adjacent to the CDKN2A/ARF tumor suppressor locus and may be co-deleted. It may also be inactivated by aberrant methylation. Absence of MTAP may contribute to the well-documented requirement of many tumors for methionine, and exploitation of the MTAP deficiency for cancer therapy is an ongoing research area (24).

Several of the Minireviews describe investigations of the mechanisms by which the polyamines, which are largely protonated at physiological pH, pass through membranes. Polyamine uptake by an E. coli transport system was first reported by the Tabors in 1966 (100). Transporters from E. coli, other bacteria, and yeast have now been fully characterized (101). Transport from the host has been shown to be important in the supply of polyamines to intracellular parasites (25). In mammals, there is good evidence for energy-dependent saturable transport processes, which, as described by Kahana (23), are inhibited by antizyme. Three models of transport have been proposed with some supporting evidence for each (102). One model involves a membrane permease followed by processing polyamines through a series of endosomes; in the second model, polyamines are bound to heparin sulfate moieties in glypicans-1 at the cell surface and are then internalized by endocytosis; in the third model uptake occurs by caveolar endocytosis in gastrointestinal cells. The exact details of these systems and their relative importance in affecting the content of each of the polyamines are still unclear. Because there are abundant polyamines in dietary sources, their potential to influence the effectiveness of polyamine inhibitors as drugs and for interventions in patients with Snyder-Robinson syndrome is obvious.

The breadth of the polyamine field and their roles in so many aspects of biochemistry are evidence of the remarkable insight of Herb Tabor in choosing many years ago to pursue their biochemistry and genetics. All of the authors of these Minireviews and others currently working in the field have benefitted greatly from his seminal contributions and send their thanks and congratulations on his birthday.

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