

Cytochrome P450 research and *The Journal of Biological Chemistry*

DOI 10.1074/jbc.TM118.004144

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In honor of the 100th birthday of Dr. Herbert Tabor, JBC's Editor-in-Chief for 40 years, I will review here JBC's extensive coverage of the field of cytochrome P450 (P450) research. Research on the reactions catalyzed by these enzymes was published in JBC before it was even realized that they were P450s, *i.e.* they have a "pigment" with an absorption maximum at 450 nm. After the P450 pigment discovery, reported in JBC in 1962, the journal proceeded to publish the methods for measuring P450 activities and many seminal findings. Since then, the P450 field has grown extensively, with significant progress in characterizing these enzymes, including structural features, catalytic mechanisms, regulation, and many other aspects of P450 biochemistry. JBC has been the most influential journal in the P450 field. As with many other research areas, Dr. Tabor deserves a great deal of the credit for significantly advancing this burgeoning and important topic of research.

It is a pleasure to contribute this article on the occasion of Dr. Herbert Tabor's 100th birthday. I have indeed counted it as a special privilege to work with him for a number of years at *The Journal of Biological Chemistry*. His leadership at JBC has benefited many research communities, including that of cytochrome P450 (P450), a field that I have worked in since 1973. I have tried to highlight some of the more seminal advances in the P450 field that were published in JBC. In my opinion, P450 is a classic example of how good biochemistry moved a field to its current place, with all of the translational applications it now has.

With limitation of space and number of references, it is impossible to mention all of the P450 research published in JBC. A Clarivate "topic" search yielded 1437 "P450" or "P-450" papers in JBC, but many were probably missed if they did not actually use this term. In 2009, a Special Meeting Collection on P450 was done, and it includes 63 "classic" JBC papers published since 1962 (available at <http://www.jbc.org/site/collections/p450/classics/60s70s.xhtml>). In addition to a number of Minireviews on P450, the reader is also referred to several Classics and Reflections (1–7) and a Thematic Series

that appeared in 2013 (8). I apologize for not being able to include more papers and authors, but we have had a historic limit of ~100 for JBC Minireviews, the model for this Collection. There is no question that JBC has been the single most influential journal in P450 research.

Early work and the discovery of P450

P450 research was published in JBC before anyone realized it was P450. The field had its roots in the studies of the metabolism of drugs (9), steroids (10, 11), and chemical carcinogens (Fig. 1) (12, 13). These studies were done when pyridine nucleotide-dependent activation of molecular oxygen (O₂) was a new concept (16).

The term "P450" was used to describe a "pigment" with an absorption maximum at 450 nm seen with the ferrous-carbon monoxide complex of P450 in rat liver microsomes, published in JBC in 1962 (17). Tsuneo Omura and Ryo Sato published two more classic papers in 1964 (1, 18, 19), the first of which describes the spectrophotometric assay of P450 still ubiquitously used today.

An independent line of investigation by Irwin Gunsalus on a bacterial system that oxidized camphor also led to a P450, termed P450_{cam} (now named P450 101A1) (2, 20, 21). Because of its soluble nature and ease of large-scale purification, P450_{cam} has served as a very useful model in structural and biophysical studies for many years (22–24).

The mammalian P450s are all membrane-bound (mostly in the endoplasmic reticulum, some in mitochondria) and were difficult to work with in the 1960s. However, Minor Coon and Anthony Lu were able to use detergents and glycerol to successfully separate the P450, NADPH-P450 reductase, and phospholipid components from rabbit liver microsomes and then reconstitute fatty acid ω -hydroxylation activity by recombining the three components. Two classic papers published in 1968 and 1969 reported these milestones (3, 25, 26).

Purification of mammalian P450s

In today's world of recombinant heterologous expression systems and artificial affinity tags, it is sometimes hard to convey to students the difficulties of (i) purifying enzymes from tissues and (ii) evaluating criteria to determine whether a purified protein is homogeneous. However, there were several notable successes of purification of P450s from rabbit and rat liver microsomes in the 1970s (27–30). The significance of these purifications should be appreciated, because work beginning in the 1960s suggested that there were at least two forms of P450

This JBC Review is part of a collection honoring Herbert Tabor on the occasion of his 100th birthday. The author declares that he has no conflicts of interest with the contents of this article.

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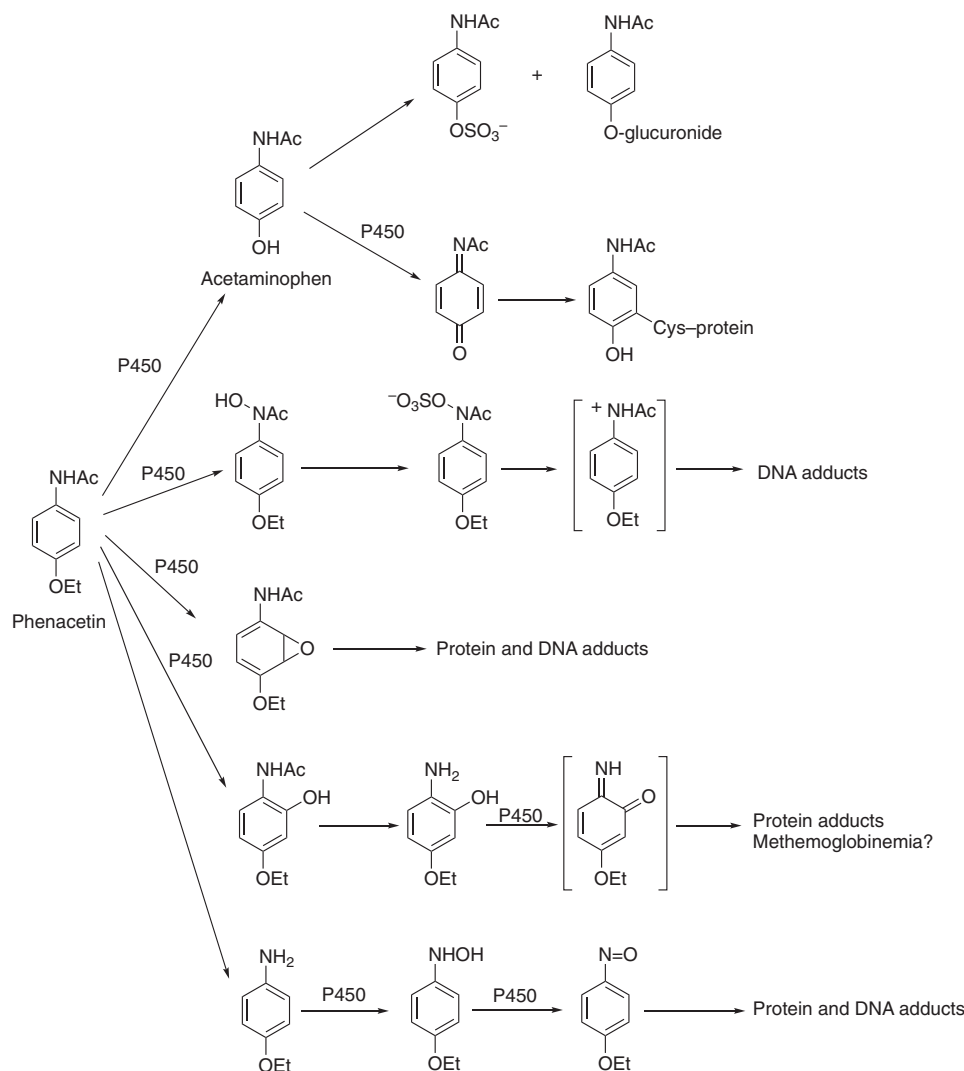


Figure 1. Roles of P450s in the bioactivation and detoxication of chemicals: The complex example of phenacetin. Acetaminophen (paracetamol, Tylenol®) is widely used as an analgesic, safe at low doses and hepatotoxic at high levels (15). Phenacetin has been classified as a carcinogen and withdrawn from use. Only in a few cases are the structures of the protein and DNA adducts known. Some of the indicated P450s have been identified in different species, including humans (14, 15).

in liver microsomes, although this proposal was not accepted by all. The 1970s saw a shift to biochemistry as a means of answering many of the fundamental questions about P450s. Indeed, proposals that there were as many as four or five P450s were met with skepticism. Today, we know, from genomic analysis, that there are 57 human P450 genes plus 88 in rats and 103 in mice.

Other important developments involved the accessory flavo-protein, NADPH-P450 reductase. One JBC paper by Bettie Sue Masters described an affinity column-based purification (31), still used today in my own laboratory. Another pair of papers by Janice Vermilion, working with Minor Coon and Vincent Massey, characterized electron flow through NADPH-P450 reductase (32, 33) and it is still generally accepted following more work by others.

Mitochondrial and microsomal P450s involved in steroid metabolism, including bile acids

Most of the mammalian work described thus far was with the microsomal P450s (now known to be 50 of the 57 human

P450s). However, it was already recognized that several important steroid oxidations occur in mitochondria, including those catalyzed by the cholesterol side-chain cleavage enzyme (now known as P450 11A1), which begins the whole process of steroidogenesis (Fig. 2).

The (seven) mitochondrial P450s are synthesized on ribosomes and then enter mitochondria following proteolytic processing. Instead of the microsomal NADPH-P450 reductase, these P450s receive electrons from a mitochondrial electron transport system consisting of a flavoprotein and a ferredoxin, NADPH-adrenodoxin reductase and adrenodoxin, respectively. Seminal early contributions toward understanding these systems were made by the groups of David Cooper, Ronald Estabrook, Otto Rosenthal, Michael Waterman, Henry Kamin, Peter Hall, and others (34–37). Other work by Narayan Avadhani has shown that fractions of some microsomal P450s are also partially localized in mitochondria (38) due to processing and other phenomena. I would be remiss not to mention the seminal work that David Russell (a for-

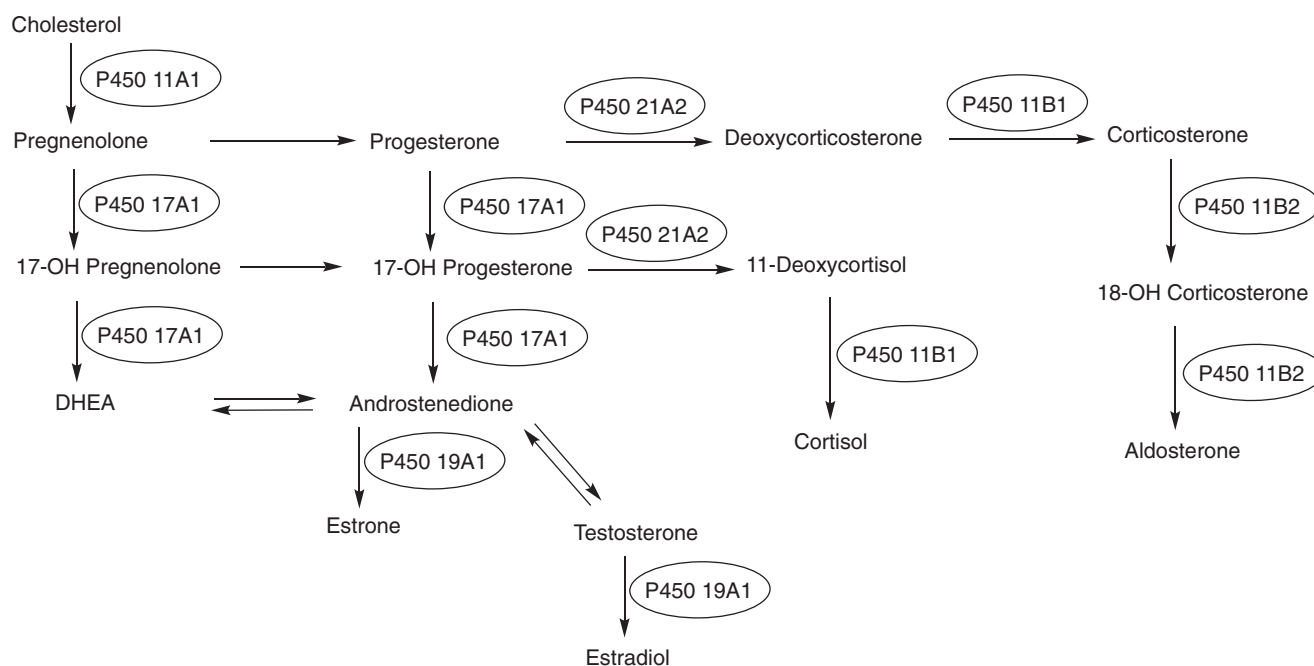


Figure 2. P450s involved in steroid metabolism. The pathways are dominated by P450s, with the only other major players being dehydrogenases.

mer JBC Associate Editor) did by applying techniques of recombinant DNA technology to solving problems with several P450s involved in the metabolism of sterols and vitamins (39–41). A number of other seminal papers in this area were published in JBC (42–51).

Human P450s

Experimental animals are used extensively in many areas of research, including drug discovery and development. In our early work with rabbit and rat liver P450s, we (and others) noted a number of differences, and we realized that ultimately the biochemistry of the human P450s would have to be studied directly in order to understand them. However, obtaining human tissue samples needed for purification and other studies was not easy.

Important observations about the influence of genetic variation by Robert Smith led me to the view that a single P450 could have a dominant role in the metabolism of a drug and that using such assays could guide productive purification. In the 1980s, we were successful in purifying what we now recognize to be several of the major human P450s (4, 14, 52, 53); other laboratories also contributed (54). One could argue that this work would have been done eventually by cloning and recombinant expression studies, but this early work shaped several concepts and was applied in the pharmaceutical industry. For instance, a limited number of P450s (~5) dominate drug metabolism. Induction and inhibition of these are major issues in drug–drug interactions. Genetic deficiencies are important. Today, it is possible to use *in vitro* methods to predict not only drug clearance for new compounds but also drug–drug interactions, pharmacogenetic issues, and other drug effects before proceeding with clinical trials; attrition of drug candidates due to human pharmacokinetic problems is no longer the major issue.

Metabolism of vitamins and eicosanoids

Although much of the interest in P450 came from studies on drugs, steroids, and carcinogens, these enzymes make major contributions in the metabolism of a number of other physiological compounds. Hector DeLuca had demonstrated that P450-catalyzed hydroxylation of vitamin D₃ was important in generating the most active forms (49, 50), and subsequent work has shown the importance of several P450s in the activation and catabolism of vitamin D (55–57). Deficiency in P450 27B1 is a cause of rickets disease (58, 59).

Retinoid metabolism involves several P450s, and maintaining the appropriate balance of proper levels of the signal retinoic acid is important. Several P450s oxidize retinoic acid (60, 61). More recent work from our own laboratory (in collaboration with Joseph Corbo) has shown the role of P450 27C1-catalyzed 3,4-desaturation of retinol in the eye of fish and amphibians, adjusting their visual spectra; however, in humans it is a skin enzyme (62) whose desaturation function is not yet known.

Prostaglandin H₂ is converted to thromboxane and prostacyclin by two P450s (5A1 and 8A1), as shown by Volker Ullrich and co-workers (63, 64). These are unusual P450 reactions in that they do not need electrons or O₂; they rearrange the endoperoxide function of prostaglandin H₂ (65). The balance between their two reactions has important health consequences in several disease contexts. Leukotrienes are also substrates for P450 hydroxylation (66).

Even some simple oxidation products of arachidonic acid have surprisingly potent biological activities (Fig. 3), as reported in a number of papers published in JBC by Jorge Capdevila and others (67–72). The epoxides and ω -hydroxy products of arachidonic acid have vasodilatory and vasoconstrictive activities, respectively, and are being considered in the context of cardiovascular and renal diseases.

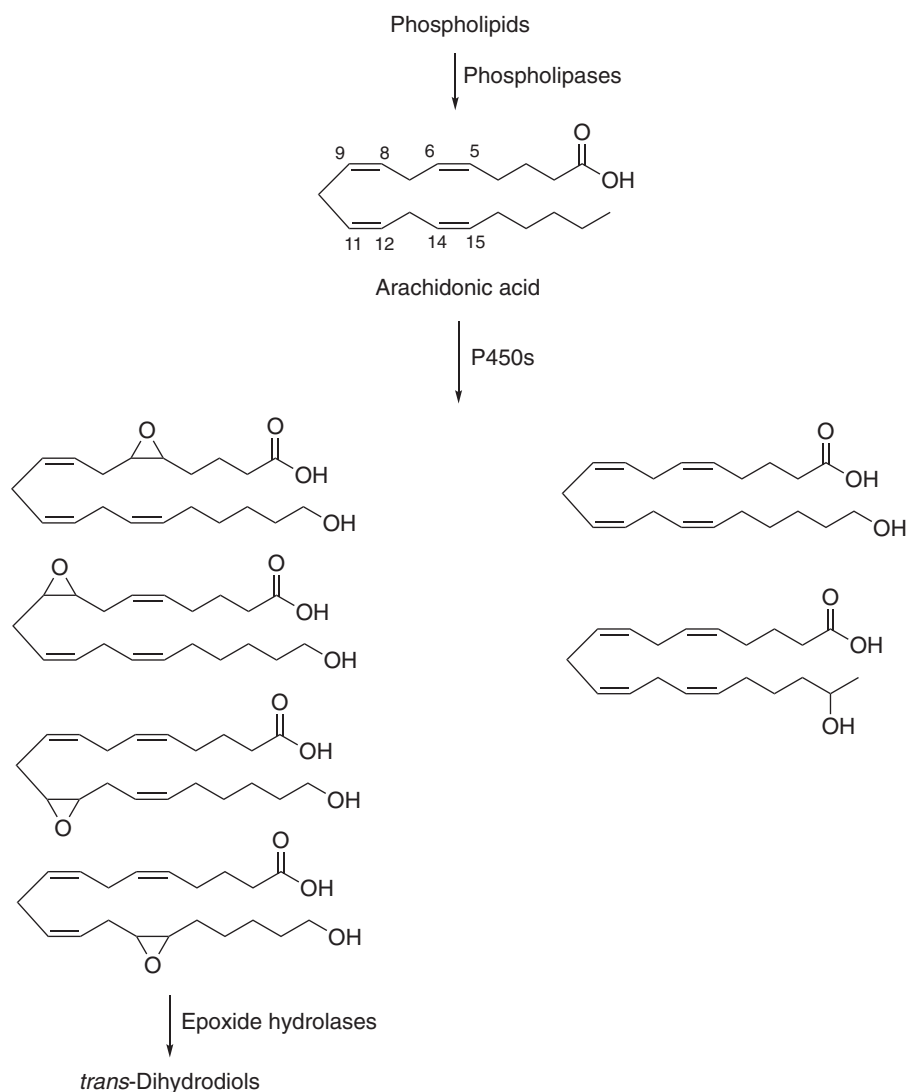


Figure 3. Oxidations of arachidonic acid catalyzed by P450s (67–72). The four epoxides (epoxytrieneic acids or EETs) are formed primarily by P450 Family 2C and 2J enzymes, and the ω -hydroxylation product (20-hydroxyeicosatetraenoic acid or 20-HETE) is formed primarily by human Family 4A and 4F enzymes. The epoxides have roles as vasodilators. 20-Hydroxyeicosatetraenoic acid can exert both pro-hypertensive (vasoconstriction) and anti-hypertensive (natriuresis) effects, depending on its site of synthesis.

Catalytic mechanisms of P450 catalysis

A number of the most important publications in this area have appeared in JBC. Paul Hollenberg and Lowell Hager's discovery (73) that chloroperoxidase is spectrally like P450s was a major driver in terms of "Compound I" chemistry, which was originally described in peroxidases and is now widely accepted in the P450 field. Paul Ortiz de Montellano and associates demonstrated the 1-electron oxidation of amines (74). Other important papers in a variety of areas include many kinetic and other mechanistic studies (23, 24, 75–77).

Regulation of P450s

The development of recombinant DNA methods in the 1980s greatly facilitated the study of the regulation of P450 genes, as with all other systems, and many of the pioneering studies were published in JBC. Although demonstrating enhanced mRNA transcription, isolating cDNAs, and obtaining nucleotide sequences (on home-made gels!) may seem trivial today, it was not 30 years ago. Many of the studies on both

P450s involved in the metabolism of both drugs and endogenous compounds were first published in JBC (78–85). Some of the first complete nucleotide sequences of cDNAs encoding P450s (an important milestone at the time) were first published by Yoshiaki Fujii-Kuriyama in JBC (86, 87). It is also noteworthy that the seminal papers by Alan Poland and Christopher Bradford on the biochemistry of the Ah receptor were published in JBC (88–90).

P450 structure and function

The first P450 X-ray crystal structure was of bacterial P450_{cam} (91). For several years, this was the only P450 structure available. An early effort at modeling, based on this structure, was made by Osamu Gotoh (92) in a JBC paper. The model has actually proven to have held up well.

One of the challenges in P450 research had been the ability to achieve high yields of heterologously expressed proteins. Work in 1991 from the laboratories of Minor Coon (93) and John Chiang (94) showed that expression of active enzymes was pos-

sible in *Escherichia coli*. The 1990s saw the publication of many site-directed mutagenesis studies on P450s in JBC, which are too numerous to discuss (95, 96).

The membrane-bound P450s had been difficult to crystallize, and work at the turn of the millennium by Eric Johnson paved the way. Many of these structures were published in JBC (97, 98), and JBC has been a leader in demanding rigor for crystal structures (*i.e.* Protein Data Bank validation requirements). A recent count in the Protein Data Bank showed at least 850 P450 X-ray crystal structures, 179 of which are human P450s. JBC continues to publish many P450 structures. At this time, crystal structures of 21 of the 57 human P450s have been reported, plus two animal orthologs. Several of these structures have revealed important mechanistic inferences, *e.g.* the recent work of Eric Johnson and Allan Rettie on P450 4B1 (99).

More microbial P450s

P450_{cam} was the first but by no means the last bacterial P450 of interest. Armand Fulco's work on P450_{BM-3} (now termed P450 102A1) was first published in JBC (100). P450_{BM-3} was the second P450 X-ray structure to be determined and became a popular platform for biotechnology applications.

Microbial P450s are not only useful models but have important metabolic roles (*e.g.* in antibiotic synthesis) and are also drug targets in some diseases (*e.g.* tuberculosis). A few of the many microbial P450 papers in JBC include studies on the enzymes from *Mycobacterium tuberculosis* (101, 102), *Streptomyces coelicolor* (103), and *Candida albicans* (104).

Plant P450s

Plants have far more P450-encoding genes than mammals, and *Arabidopsis thaliana* has 249 and wheat has 1476 (drnelson.uthsc.edu/cytochromeP450.html). Plant P450s are configured in complex metabolic pathways, and a number of studies on plant P450s have been published in JBC (105, 106).

P450s and disease

With more knowledge about P450s, there is now an enhanced appreciation of their contributions to disease (59). The role of P450 2E1, an ethanol-inducible enzyme, in acetaminophen-induced liver toxicity was convincingly demonstrated by Frank Gonzalez in a transgenic mouse model (Fig. 1) (15). The molecular basis for deficiencies of several P450s has been demonstrated in several inherited diseases, particularly in endocrine dysfunction (107, 108). JBC has also published many of the studies on the relationship of arachidonic acid oxidation products and hypertension (Fig. 3) (67–71), including a transgenic mouse study demonstrating a role for P450 4A11 (72). Interesting transgenic models with P450s having potential implications in understanding other human diseases have also been published in JBC (109, 110).

Relevance of P450 research

Today, the P450 field can be considered to be mature. That does not mean that all questions have been answered. However, 56 years after the “discovery” of this protein superfamily (17), it is reasonable to ask what benefits have accrued from the invest-

ment in its study. Indeed, there have been many practical outcomes, mainly in human medicine but now also in other areas.

We now understand the molecular basis of many diseases, perhaps most notably in endocrine diseases (59). For instance, many clinical cases of congenital adrenal hyperplasia are now understood to result from amino acid substitutions in the *CYP21A2* gene (108).

Knowledge about the human P450s involved in drug metabolism has led to the rapid characterization of substrates, inhibitors, and inducers with new drug candidates and has enabled rapid *in vitro* prediction of human (*in vivo*) pharmacokinetics and drug–drug interactions. Concepts developed from our knowledge of human P450s have led to better design by medicinal chemists, directing chemical synthesis to avoid rapid metabolism and bioactivation to toxic products (15). In the realm of drug development, it is now possible to understand metabolism and sometimes the toxicity of drugs in animal models through their interactions with P450s, in terms of similarities and differences with human models. Furthermore, it is possible to avoid many issues with genetic polymorphisms in drug metabolism and extreme pharmacokinetic variations. Moreover, potential inhibitors (*e.g.* drugs such as ritonavir for P450 3A4) can be managed effectively.

Future research needs for the P450 field

Basic research

Every aspect of basic P450 research would benefit from deeper knowledge. The following list is driven in part by some of my own interests and is not intended to be comprehensive.

One area of need is more information about the “orphan” P450s, not only in plants and microorganisms (*i.e.* comprising most P450s) but also humans. There are true orphans (*e.g.* P450 20A1), about which almost nothing is known, and also the “xenobiotic-metabolizing” enzymes. Is the role of the xenobiotic-metabolizing P450s (*e.g.* human P450 Families 1–3) limited to protection from foreign chemicals, or are their demonstrated interactions with endogenous substrates (*e.g.* fatty acids, steroids) relevant?

We have more to learn about three-dimensional structures and their relationships to P450 function. Currently, 21 of the human P450s have structures in addition to two animal orthologs (4B1 and 24A1). This leaves 36 human P450s that need structural characterization.

Although much has been written about allosteric regulation, we have few details beyond some X-ray crystal structures with multiple ligands bound. The matter of the auxiliary accessory protein cytochrome *b₅* is still devoid of many details. There are only two crystal structures of P450s with auxiliary partners (ferredoxins) but none for microsomal P450s with NADPH-P450 reductase or cytochrome *b₅*.

Finally, are we finished with learning about the chemistry or is there more to learn? Are there really alternatives to the Compound I mechanism or not? There are also kinetic questions about the degree of processivity of multistep P450 oxidations (111), and there is very limited information about the kinetics of individual steps in the reactions involving the mitochondrial P450s (62, 112).



Figure 4. Dr. Herbert Tabor (*left*) and the author at lunch at Dr. Tabor's home in 2016.

Applied research

Although we have a considerable amount of structural information about P450s (at least 850 Protein Data Bank entries, including 179 for humans), the question can be raised as to how we can better use it. For instance, can we really understand inherited P450 deficiencies seen in the clinic at a molecular level? Are WT structures really that predictive of problems due to a single base change (108, 113)?

Chemical carcinogenesis had long been a driver in the P450 field, but now we need to learn more about the roles of P450s (and their variants) in diseases, particularly nonendocrine diseases. What does the association between P450 4A11 variants and hypertension mean (114)? What are the prospects for gaining more insight into the association between P450 differences in humans and the incidence of certain cancers?

Although we have a large and developing database on single nucleotide variations (SNVs) in P450s, are we really getting any closer to applying it in clinical practice? Despite the excitement 20 years ago, can P450 research drive “personalized medicine” more than in a few cases as with P450s 2C9 and 2D6 (*e.g.* warfarin and iloperidone)?

Lastly, there are new research applications that are not discussed above such as the targeting of human P450s with drugs. For instance, inhibition of P450 19A1, the steroid aromatase, is now a popular strategy for treating breast cancer, and research is in progress to inhibit several other P450s in diseases, *e.g.* P450s 11B2, and 17A1. Another area of opportunity is to target fungal and bacterial P450s that are critical to membrane synthesis and viability (101, 102, 104, 115).

Finally, there are many opportunities for practical applications of P450 knowledge to veterinary and agricultural problems. Many of the applications described in human medicine can also be applied in the veterinary arena. There is great unrealized opportunity for understanding the plant P450s and their interactions with the P450s in insects and other plants. This information can in turn be used for the effective application of genetic modifications and pesticides in agriculture.

My role at JBC and relationship with Dr. Tabor

I began doing research on P450s in 1973, as a postdoctoral fellow with Minor Coon at the University of Michigan. In 1975, I started my own laboratory as a Biochemistry Faculty Member at Vanderbilt University. I have continued working with P450 since then, which means that I have spent 45 years in the field. My first P450 paper was published in JBC in 1975, and I have continued to publish much of my own research in the journal. By my count, I have authored or co-authored 117 primary articles in JBC (not all on P450), plus a number of reviews, and JBC remains a favorite journal for our papers.

In 1984, I was asked to join the JBC Editorial Board. When I was in the middle of my fourth term, I was invited to become an Associate Editor in 2006. Since that time, I have worked with Herb Tabor in several aspects of JBC work, and I have come to truly admire him as a person and appreciate what he has done for JBC (Fig. 4). Herb Tabor was Editor-in-Chief for 40 years. After I served in that capacity for 1 year (2015–2016) I can better appreciate all that he did, particularly in the pre-electronic era when paper manuscripts arrived at his home doorstep every evening for assignment. I also understand the effort required in dealing with problem manuscripts, author complaints, and the other issues that come with the job. Herb Tabor managed JBC very effectively during his long tenure as Editor-in-Chief, allowing Associate Editors to drive the journal activities and making critical decisions based on their input. He also reviewed manuscripts himself and has a genuine appreciation of what Associate Editors and Editorial Board Members do.

Dr. Tabor is an amazing man—he graduated from Harvard University at the age of 18 and from Harvard Medical School at 22. To this day he still assigns some of the new manuscripts and has gladly filled in when I am unavailable for this task. He is really a brilliant man but is also one of the most humble people I know. His focus was always on what was good for JBC and what was good for science, not for himself.

I rank being able to interact with Herb Tabor among the true privileges of my career. It has been a pleasure to work with him.

I wish there were more people like Herb Tabor in science, but I think we can all benefit from trying to emulate him.

Finally, Herb, I wish you all the best on this occasion of your 100th birthday. Thanks for the things you taught me about being an editor and a person.

Acknowledgments—I thank Prof. Michael Waterman for reviewing this article and adding some historical points. I also thank my long-time helper and JBC Editorial Assistant Kathy Trisler for her assistance in preparing the article and Barbara Gordon for the photograph (Fig. 4). Finally, I thank the many individual scientists in the P450 field who have served on the JBC Editorial Board over the years. Without their efforts, none of this would be possible.

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