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A Trail of Research on Cofactors: An Odyssey with Friends[1]

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Abstract

Over the span of 40 y and with the participation of over 60 students and postdoctoral colleagues, my laboratory has been able to elucidate numerous aspects of cofactor metabolism and function. Findings have been on the absorption, transport, utilization and excretion of vitamin B-6, riboflavin, biotin, lipoate and ascorbate. Specificity studies on those trace but essential enzymes that catalyze conversion of such vitamins as B-6 and riboflavin to their functional coenzymes led to our development of "biochemically specific absorbents" that prototypically exemplified what later was called "affinity chromatography." Characterization of the purified kinases for B-6 and riboflavin revealed preference for Zn^{2+} with the eucaryotic enzymes and delimited effects of inhibitors that relate to drug action. Flavin adenine dinucleotide synthetase, separable from flavokinase in mammals, prefers Mg^{2+}. Specifics for binding and function of flavocoenzymes were delineated for several flavoproteins. The flavin mononucleotide-dependent oxidase that converts the 5′-phosphates of pyridoxine and of pyridoxamine to pyridoxal phosphate is a connection between riboflavin and B-6 that we characterized in mechanistic detail and found to be the primary control point for conversion of B-6 to its coenzyme. Sequencing and cloning of a side-chain oxidase for riboflavin was achieved. Isolation and identification of metabolites of biotin and of lipoic acid, first from bacteria obtained by enrichment culture and then from mammals, provided seminal information on catabolic pathways involved, as have our other studies with flavin catabolites isolated from milk and urine.

Although it is relatively easy to summarize one's own research accomplishments, it is difficult to present them without the use of first person and seeming to be self-serving. Yet this whole exercise should be to emphasize the partnerships that make science. Hence, I have attempted to list within each of the following subdivisions of my research topics the names of colleagues who worked with me, and to use sufficient citations to literature to document our experimental findings.

My doctoral dissertation research, mentored by Professor Oscar Touster at Vanderbilt, was on pentose and pentitol metabolism. Studies on isotopically labeled pentitols and pentoses helped establish the metabolic interrelationships of xylitol/xylulose to glucose/glucuronate (Touster et al. 1957) and further to the pentose phosphate pathway (McCormick and Touster 1957). The general interdigitations of pentitol metabolism were extended (McCormick and Touster 1961) and the genetic defect of essential pentosuria clarified. Because one extension of glucuronate metabolism is toward ascorbate (vitamin C) as well as xylulose, and there was a strong interest in nutritional biochemistry within the Vanderbilt department when Bill Darby was chairman, my polarized interests were to head west where there were strong elements of vitamin/coenzyme research at the University of California–Berkeley.

Vitamin B-6 metabolism

Pyridoxal (pyridoxine, pyridoxamine) kinase—*M. Gregory, E. Snell.*

During postdoctoral research with Professor Esmond Snell at Berkeley, I began work initiated by M. Gregory. Isolation and comparative studies on both pro- and eucaryotic forms of pyridoxal kinase delineated general properties, including the first substantiated role of Zn^{2+} in preference to Mg^{2+} as the cosubstrate ATP complex for the mammalian phosphokinase (McCormick et al. 1961), and led to circumscription of inhibitory aspects (McCormick and Snell 1961), including the potent action of carbonyl reagents (McCormick 1959, McCormick et al. 1960, McCormick and Snell 1959) and such drugs as are known to bind to the kinase (McCormick and Chen 1999).

Pyridoxine (pyridoxamine) 5′-phosphate oxidase—*P. Barsa, D. Bowers-Komro, H. Chen, J. Choi, M. Davis, M. DePecol, D. Edmondson, K. Horiike, S. Kasai, M. Kazarinoff, W. Korytnyk, K. Matsui, A. Merrill, K. Ohashi, K. Rasmussen, D. Roe, H. Tsuge, K. Watanabe.*

As a faculty member at Cornell and Emory with the help of graduate and postdoctoral coworkers, we succeeded in the first complete purification of pyridoxine (pyridoxamine) 5′-phosphate oxidase, the flavin mononucleotide (FMN)[2]-dependent enzyme responsible for conversion of the kinase-derived phosphovitamin B-6 to coenzymic pyridoxal 5′-phosphate (Kazarinoff and McCormick 1975). More facile affinity purifications (Bowers-Komro et al. 1986, Tsuge and McCormick 1980) and assays (DePecol and McCormick 1980) were developed and circumscription of substrate (DePecol and McCormick 1980, Bowers-Komro and McCormick 1987, Kazarinoff and McCormick 1973, Kazarinoff and McCormick 1975, Merrill et al. 1980) and coenzyme specificities (Kazarinoff and McCormick 1974, Merrill et al. 1979b) accomplished. Systematic elucidation of the dimeric subunit association (Horiike et al. 1979a, Tsuge and McCormick 1980), active-site amino acid residues (Bowers-Komro et al. 1986, Choi and McCormick 1981, Horiike et al. 1979b, McCormick et al. 1976, Tsuge and McCormick 1980), kinetics (Choi et al. 1982, Choi et al. 1983), and ultimately mechanistic delineation of stereochemical aspects (Bowers-Komro and McCormick 1984b, Bowers-Komro and McCormick 1985a, McCormick and Bowers-Komro 1986) have provided definitive information on the way this essential flavoprotein operates (Bowers-Komro and McCormick 1984a), depends upon flavin status of an organism (Rasmussen et al. 1979, Rasmussen et al. 1980), and participates in the regulation of B-6 metabolism (McCormick and Merrill 1980, Merrill et al. 1978b). The sequences for

this essential oxidase from several organisms have been determined (McCormick and Chen 1999). An important interface between vitamins B-2 and B-6 is now clear.

The scheme given in **Figure 1** outlines the sequential roles of kinase and oxidase in the interconversions of B-6 vitamers toward the coenzyme pyridoxal 5′ phosphate.

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FIGURE 1

Interconversions of pyridoxine (PN), pyridoxal (PL) and pyridoxamine (PM) with their 5′-phosphates (PNP, PLP, PMP) as catalyzed by pyridoxal kinase (K), phosphatase (P) and pyridoxine (pyridoxamine) 5′-phosphate oxidase (O).

Flavin metabolism

Flavokinase—*C. Arsenis, R. Butler, B. Chassey, P. Hemmerich, S. Lee, A. Merrill, H. Nakano, Y. Yamada, Z. Zak.*

The first significant purification of flavokinase, shown by us to be another Zn^{2+} preferring enzyme (McCormick 1962, Merrill and McCormick 1980, Nakano and McCormick 1991b) responsible for catalyzing phosphorylation of riboflavin to yield FMN, was accomplished with classic techniques (McCormick 1962) and completely purified from mammalian tissues by "affinity techniques" (Arsenis and McCormick 1964a, Merrill and McCormick 1980, Nakano and McCormick 1991a) before the term and practice became commonplace. Detailed studies on the specificity of this enzyme (Chassy et al. 1965, McCormick and Butler 1962, McCormick et al. 1963, McCormick et al. 1964,, Yang et al. 1964) helped clarify the biological activities of flavin analogs. Investigations of substrate induction (Lee and McCormick 1983, Merrill et al. 1978a) and thyroid hormone stimulation (Lee and McCormick 1985, McCormick et al. 1984) have led to recognition of the "active" and "inactive" forms which are poised at the regulation site of flavocoenzyme biosynthesis.

FAD synthetase—*D. Bowers-Komro, B. Gomes, H. Hartmann, S. Lee, A. Merrill, H. Nakano, Y. Yamada, Z. Zak.*

We elaborated the substrate specificity of mammalian FAD synthetase (Bowers-Komro et al. 1989, McCormick 1964a, McCormick 1964b, McCormick et al. 1997) and accomplished its partial (Gomes and McCormick 1983) and then complete purification, again using affinity (FMN-agarose) methods (Oka and McCormick 1987). Further work led to more detailed characterization of the cooperatively interactive kinase/synthetase system and to their kinetic mechanisms (Yamada et al. 1990).

FMN phosphatase and FAD pyrophosphatase—*S. Lee, M. Russell.*

The interfering, nonspecific actions of alkaline and acid FMN phosphatases (McCormick 1961, McCormick and Russell 1962) and FAD pyrophosphatase have been separated and generally characterized as degradative hydrolases responsible for breakdown of flavocoenzymes (Lee and McCormick 1983).

Riboflavin side-chain oxidases—*H. Chen, D. Edmondson, T. Kekelidze, C. Yang.*

A bacterial side-chain oxidizing enzyme that had been called a "hydrolase" was found by us to have relative specificity (Yang and McCormick 1967a), whereas another enzyme narrowly specific for riboflavin (Kekelidze et al. 1994, Kekelidze et al. 1995) has been molecularly cloned and sequenced by us from a fungal organism (Chen and McCormick 1997a) and found able to form both aldehyde and acid products at the 5′-terminus (Chen and McCormick 1997b).

Flavin metabolites and analogs—*R. Addison, C. Chia, J. Chastain, J. Galloway, G. Kimmich, B. Ogunmodede, M. Oka, P. Preusch, F. Roughead, S. Tu, C. Yang, J. Zempleni.*

We have helped detail the overall metabolic fate of riboflavin (Chastain and McCormick 1987a, Chastain and McCormick 1987b, Chastain and McCormick 1988, Foley et al. 1967, Oka and McCormick 1985, McCormick 1975b, McCormick 1976a, McCormick et al. 1984, McCormick et al. 1988, Roughead and McCormick 1991, Yang and McCormick 1967b), 8α-amino acid flavins derived from covalent forms (Addison and McCormick 1978, Chia et al. 1978), and flavin analogs (Ogunmodede and McCormick 1966, Tu and McCormick 1969) in the mammal and in milk from cows (Roughead and McCormick 1990a) and humans (Roughead and McCormick 1990b). The finding that an 8α-sulfonyl-riboflavin appears in human urine as a result of catabolite turnover of monoamine oxidase is noteworthy (Chastain and McCormick 1987b). The predominant catabolite of riboflavin to appear in plasma following ingestion of riboflavin is the 7α-hydroxy compound (Zempleni et al. 1996a, Zempleni et al. 1996b). The in vivo kinetics of riboflavin absorption and disposition have been quantitated in the normal human (Zempleni et al. 1996a) and in women with liver cirrhosis (Zempleni et al. 1996c).

Flavocoenzyme function

Inter- and intramolecular complexes of flavins—*A. Bell, B. Chassy, W. Föry, H. Li, R. MacKenzie, F. Rizzuto, J. Roth, K. Shiga, G. Tollin, J. Tsibris, L. Wright, F. Wu.*

Our studies on the nature of inter- and intramolecular complexes of flavins with purines and pyrimidines (Chassy and McCormick 1965a, McCormick 1968a, Roth and McCormick 1967, Tsibris et al. 1965) including synthetic analogs of FAD helped elucidate the strength and types of interactions involved, particularly within FAD. Extension of such studies to flavin-aromatic amino acid systems (Föry et al. 1968, Föry et al. 1970, Getoff et al. 1978, Johnson and McCormick 1973, Johnson et al.

1975, MacKenzie et al. 1969, McCormick 1970, McCormick 1973, McCormick et al. 1975, McCormick 1977b, Wu and McCormick 1971a, Wu and McCormick 1971b) and ultimately to flavoproteins (McCormick 1970, McCormick 1977a, McCormick 1977a, McCormick and Tu 1970, Merrill et al. 1981b, Shiga et al. 1975, Tu and McCormick 1973, Tu and McCormick 1974, Wu et al. 1970) secured the expectation that such interactions are common, particularly with tryptophanyl and tyrosyl residues, and often account for part of the facilitated binding of flavins to proteins.

Flavin-dependent enzymes—*C. Arsenis, B. Chassy, S. Edelstein, P. Johnson, J. Koster, J. Roth, J. Tsibris, S. Tu, C. Veeger, J. Visser, F. Wu.*

The specificity of coenzyme binding and function (Arsenis and McCormick 1964b, Chassy and McCormick 1965b, McCormick et al. 1964, Merrill et al. 1979b, Roth et al. 1966, Tsibris et al. 1966, Visser et al. 1968), nature of active-site residues (Choi and McCormick 1981, Falk et al. 1976, Falk and McCormick 1976, Horiike et al. 1979b, Koster et al. 1968, McCormick et al. 1967, McCormick 1970, Tu and McCormick 1973, Tu and McCormick 1974, Wu et al. 1970), and physical properties of several flavin-dependent enzymes have been elucidated. One common feature is the binding of the pyrimidinoid portion of the isoalloxazine system of FMN within a cleft which often allows projection of the dimethylbenzenoid edge toward solvent. A prototypic example of using a coenzyme as a photochemical probe for the active site of an enzyme was provided by our work with FAD in D-amino acid oxidase, wherein a tyrosyl as well as lysyl and cysteinyl residues were proven critical (Tu and McCormick 1973). The spectrochemical effects of 8α-flavin linkage to a cysteinyl residue with monoamine oxidase were confirmed and quantitated by our synthesis of the active-site portion of this enzyme (Falk et al. 1976, Falk and McCormick 1976).

The scheme given in **Figure 2**outlines central aspects of riboflavin transport, metabolism, utilization and excretion.

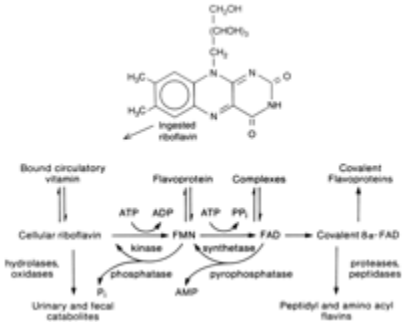

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FIGURE 2

Metabolic fate and utilization of flavins in mammals.

Biotin metabolism

Biosynthesis—*H. Li, J. Tepper, L. Wright.*

We secured direct proof that biotin is biosynthesized via dethiobiotin by use of the labeled precursor (Li et al. 1968a, Tepper et al. 1966).

Metabolism—*R. Brady, J. Chastain, W. Im, S. Iwahara, M. Kazarinoff, H. Lee, H. Li, L. Li, N. McCall, D. Mock, J. Roth, H. Ruis, J. Westendorf, L. Wright, J. Zempleni.*

The catabolic fate of this vitamin and analogs as wholly degraded in a pseudomonad (Brady et al. 1965, Brady et al. 1966, Im et al. 1970, Im et al. 1973, Iwahara et al. 1969, Kazarinoff et al. 1972, Roth et al. 1970, Ruis et al. 1968, Westendorf and McCormick 1980) and partly degraded in a fungus (Li et al. 1968b) and the rat (Lee et al. 1972, Lee et al. 1973a) was elaborated in our laboratory. Present knowledge of the metabolism of biotin is based on these detailed studies (McCormick 1975a, McCormick 1976b, McCormick and Olson 1984, McCormick and Wright 1970). The identification of such metabolites in humans has now been secured (Zempleni et al. 1996d). A discriminating colorimetric reaction for biotin and analogs was developed (McCormick and Roth 1970).

Based on the numerous catabolites we have isolated and structurally identified, an overview of events is illustrated in **Figure 3.**Whereas a soil pseudomonad forced to use biotin as the sole source of C, N, S, and energy can effect extensive degradation, including the bicyclic ring system, mammals operate more sparingly, mainly on side-chain β-oxidation and oxidation of the ring sulfur.

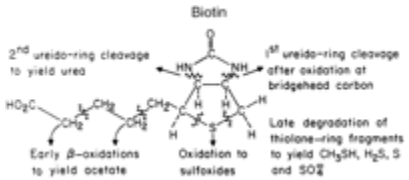

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FIGURE 3

Primary events and their general sequence in the degradation of biotin.

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Lipoate metabolism

Catabolite isolation and synthesis—*H. Chang, H. Furr, E. Harrison, S. Howard, M. Rozo, J. Shih, J. Spence, P. Williams.*

Similar studies on the catabolic fate of lipoate were conducted. We detailed total degradation in a pseudomonad (Chang et al. 1975, Furr et al. 1978, Furr and McCormick 1978, Shih et al. 1972, Shih et al. 1975) and in the rat (Harrison and McCormick 1974, Spence and McCormick 1976). Synthesis and delineation of the properties of critical side-chain shortened metabolites were also accomplished (Shih et al. 1974) as were HPLC chromatographic separations of metabolites (Howard and McCormick 1981).

The routes for oxidation of side-chain and of ring sulfurs of lipoate are shown in **Figure 4.**More extensive ring degradation may occur in bacterial than mammalian systems.

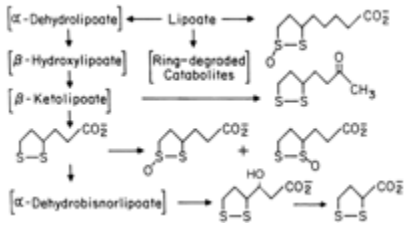

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FIGURE 4

Lipoate catabolism based on compounds isolated (structures) as well as inferred (names in brackets)

Transport and uptake of water-soluble vitamins

Transport—*C. Clagett, J. Choi, B. Foley, J. Froehlich, J. Gregory, W. Innis, T. Joseph, A. Kosik, R. MacKenzie, A. Merrill, D. Murray, D. Nixon, G. Shapira.*

Our studies on the means by which animals transport riboflavin have led to detailed knowledge on selective affinity purification (Merrill and McCormick 1978) and properties of the avian carrier/storage proteins (Froehlich et al. 1980) including its flavin-binding specificity (Choi and McCormick 1980), the first recognition of pregnancy-induced plasma riboflavin-carrier protein in a mammal (Merrill et al. 1979b), and the occurrence of other cytosolic binding proteins (Merrill et al. 1982). Further work has led to the identification of immunoglobulin carriers in the human (Innis et al. 1985, Innis et al. 1986, Merrill et al. 1981a). Both physical (Pritchard et al. 1967) and biological (Lee et al. 1973b) interactions of biotin with avidin were investigated, as was specificity of avidin (Zempleni et al. 1996e) and biocytinase (McCormick 1969).

Uptake—*T. Aw, B. Bowman, D. Bowers-Komro, J. Gregory, T. Joseph, A. Kosik, Y. Suzuki, H. Tsuge, Z. Zhang.*

Hepatocyte uptake of riboflavin, which is carrier-mediated but not Na^+-dependent and involves metabolic trapping by flavokinase-catalyzed phosphorylation (Aw et al. 1983), has been contrasted

with gut (enterocyte) absorption and with uptake by proximal tubular renal cells (Bowman et al. 1989). The entry of pyridoxine into liver cells is similarly insensitive to Na^+ (and hence Na^+/K^+ ATPase) and dependent on metabolic trapping by pyridoxal kinase (Kozik and McCormick 1984), whereas uptake by renal proximal tubular cells is similar but may involve Na^+/H^+ exchange and/or pH gradient effects (Bowman and McCormick 1987, Bowman and McCormick 1989, McCormick 1989). Disposition of B-6 glucosides was shown to depend upon uptake as well as subsequent metabolic events (Joseph et al. 1996, Zhang et al. 1993a). Biotin entry depends on ligandin (glutathione S-transferase) as typical for organic acid anions (Bowers-Komro and McCormick 1985b). Information from these studies coupled with our knowledge of the enzymic events that occur upon entry led to the design of vitamin analog models that exemplify transporter-enhanced delivery of bioactive compounds (McCormick 1994, Zhang et al. 1993b, Zhang and McCormick 1991, Zhang and McCormick 1992a, Zhang and McCormick 1992b).

A means by which some less-transportable compounds of therapeutic use can be imported into cells is exemplified in **Figure 5.**A specific example we have documented is the chemical attachment of bioactive amines to Vitamin B-6 such as to be "piggybacked" through the B-6 transporter to be released inside of liver or kidney cells as free amine plus coenzyme B-6.

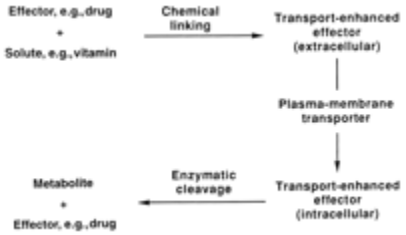

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FIGURE 5

Principle for delivery of a pharmacologically active compound by using transporters for vitamins and other solutes.

Metal ions

Coordination with biochemicals—*K. Becker, R. Griesser, M. (Joiner) Hayes, C. Neumann, B. Prijs, G. Sander, H. Sigel, F. Walker, L. Wright.*

Not only have we shown the involvement of certain metal ions, e.g., Zn^{2+}, for specific enzymes (McCormick et al. 1961, McCormick 1962, Sander et al. 1965), but the general liganding properties of several important functional groups (Griessen et al. 1971) including amino acids (Griesser et al. 1969, McCormick et al. 1969, McCormick et al. 1974, Sigel et al. 1969a, Sigel et al. 1969b, Sigel et al. 1970, Sigel et al. 1972, Sigel et al. 1977, Sigel and McCormick 1971, Sigel and McCormick 1974,

Walker et al. 1972), nucleotides (Sigel et al. 1967, Sigel and McCormick 1974), and such vitamins as biotin (Griesser et al. 1970, Griesser et al. 1973, Sigel et al. 1969c, Sigel et al. 1978a, Sigel and McCormick 1974) and lipoate (Sigel et al. 1978a, Sigel et al. 1978b) have been delineated for important cations of the Irving-Williams series. These latter studies extend our knowledge of the possible interactions within biological metal ion-containing systems.

Other

To be certain to credit some colleagues who joined with me in yet other categories of interest, I would mention work on amino acid metabolism with C. Crispen, L. Uhler (Uhler et al. 1971), and M. Woods (McCormick et al. 1965, Woods and McCormick 1964); dihydroorotase with G. Sander and L. Wright (Sander et al. 1965); carbohydrate and lipid with J. Coniglio (Coniglio et al. 1956); steroids with J. Feher (Feher et al. 1974); vitamin C and D. Bowers-Komro, G. Iacobucci, G. King, and J. Sweeney (Bowers-Komro et al. 1982).

In summary, my associates and I have unraveled details in the absorption, transport, cellular uptake, metabolism and function of several water-soluble vitamins and coenzymes and have provided additional information on metal-ion coordination. During the course of these studies, we have pioneered in affinity chromatography (Arsenis and McCormick 1964, Arsenis and McCormick 1966, Bowers-Komro et al. 1986, Froehlich et al. 1980, Kazarinoff et al. 1975, McCormick 1965, McCormick et al. 1991, McCormick et al. 1997, Merrill et al. 1979a, Merrill and McCormick 1978, Merrill and McCormick 1980, Nakano and McCormick 1991a, Oka and McCormick 1987, Sander et al. 1966) and immobilized enzymes (Merrill and McCormick 1979, Tu and McCormick 1972), established theoretical (Horiike and McCormick 1979, Horiike and McCormick 1980) and experimental protocols for chemical (Choi and McCormick 1981, Horiike et al. 1979a, Horiike et al. 1979b, McCormick 1970, Nakano et al. 1992, Nakano and McCormick 1992, Tsuge and McCormick 1980) and photochemical (Koster et al. 1968, McCormick et al. 1967, McCormick 1968b, McCormick 1970, Tu and McCormick 1973) modifications of enzymes, and successfully bridged information from chemical models (spectroscopic and metal coordination compounds) to biochemical complexes and functional systems.

Together we have followed a trail of research on cofactors which many of you and others who follow will still find rewarding.

Footnotes

Presented as part of the symposium "Mechanistic Aspects of Vitamin and Coenzyme Utilization and Function: A Symposium in Recognition of the Distinguished Career of Donald B. McCormick" as part of the Experimental Biology 99 meeting held April 17-21 in Washington, D.C. This symposium was sponsored by the American Society for Nutritional Sciences. The proceedings of this symposium are published as a supplement to Guest editors for this supplement publication were Alfred H. Merrill, Jr., Emory University School of Medicine, Atlanta, GA; Barbara B. Bowman, U.S. Centers for Disease Control and Prevention, Atlanta, GA; and Peter C. Preusch, National Institutes of General Medical Sciences, Bethesda, MD.

Abbreviations used: FMN, flavin mononucleotide; FAD, flavin adenine dinucleotide.

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