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Applications of chemically defined diets to the solution of nutrition problems*

Review Article

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Summary. Chemically defined amino acid diets have been developed for most laboratory and meat-producing animal species as well as for humans. In many cases, growth performance of animals fed these diets equals that obtained with standard intact-protein diets. The pattern of both essential and nonessential amino acids is critical to obtaining excellent voluntary food intake. Other factors such as carbohydrate and fat type and level, acid-base balance (i.e., cation-anion ratio), and texture are important to the success of purified diets. Chemically defined diets provide amino acids, mineral elements and vitamins in forms that are maximally bioavailable. Also, virtually any nutrient can be manipulated at will for studies of a) requirements, b) bioavailability, c) factors affecting requirements and bioavailability, d) nutrient-nutrient interrelationships, e) nutrient-drug or nutrient-toxin interrelationships, f) absorption phenomena and g) efficiency and priority aspects of nutrient utilization. Requirements for essential nutrients are generally lower with purified diets than for practical diets because the nutrients in the former are more bioavailable, but also because purified diets generally lack antagonizing factors such as phytate and soluble fiber. That chemically defined diets for pigs, rats and dogs yield such excellent rates of growth suggests that a specific peptide requirement many not exist for these species. Also, this suggests that all known nutrients necessary for maximal growth must be present in the diet. Whether additional nutrients, or different levels, may be necessary for optimal health and immunocompetency, or for maximal life span, needs further study.

Keywords: Amino acids – Purified diets – Minerals – Vitamins

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Introduction

Because chemically defined diets are such a valuable tool in biological research, our laboratory at the University of Illinois has been active in developing efficacious purified amino acid diets for several animal species: chicks (Dean and Scott, 1965; Baker, 1977a; Baker et al., 1979), rats and mice (Hirakawa et al., 1984), cats (Anderson et al., 1980; Baker and Czarnecki-Maulden, 1991), dogs (Hirakawa and Baker, 1988; Baker and Czarnecki-Maulden, 1991) and pigs (Baker et al., 1966; Easter and Baker, 1976; Chung and Baker, 1991a). There are a multitude of nutritional and biochemical problems that can be solved only with a chemically defined diet; an even greater number can be solved more precisely and more definitively with defined diets. The discussion that follows will focus on many of these problems and of our experiences in dealing with them.

Nutrient requirements

The scientific literature contains a plethora of papers dealing with nutrient requirements. Many, indeed most, of these papers are difficult to interpret, and much of the confusion stems from problems with diets. When a nutrient is supplemented into a diet deficient in that nutrient, one must know several things in order to properly interpret the results: What is the nature of the population being sampled? What is the caloric density of the diet? Is the diet, when properly supplemented with the nutrient under study, fully efficacious? Are the subjects consuming set amounts of diet, or is *ad libitum* intake assumed? What is the feeding interval? How bioavailable is the nutrient being supplemented? How bioavailable is the test nutrient in the basal diet? Are there factors in the basal diet that might either enhance or antagonize utilization of the test nutrient? What criterion of response should be used to assess adequacy — maximal growth or nitrogen retention, maximal lifespan, minimal disease susceptibility? Should the requirement satisfy a need for the mean of the population being sampled or should a safety factor be applied such that nearly 100% of a given population is satisfied? Should economic considerations be applied to the selection of a requirement?

Few papers on nutrient requirements deal with all, or even most, of these important considerations (Baker, 1986a). Is it therefore any wonder that the public sector has become highly skeptical, and sometimes cynical, about the many and varied efforts on the part of government-sponsored agencies that develop publications on nutrient requirements.

If a given requirement can be determined with a chemically defined diet that has been proven through research to be as efficacious as a conventional diet, many of the problems inherent in nutrient estimation can be dealt with. Using a defined population with regards to age, sex, weight and body composition, one can manipulate a purified diet to be (at least) adequate in all known essential nutrients except the nutrient under study. It helps later interpretation if the diet also is designed to contain the same caloric density (ME, i.e., metabolizable energy) and nitrogen as that generally consumed in practice by the population in

question. Subjects, be they humans or animal models, should be fed at intervals and in quantities that simulate those used in practice.

The requirement ultimately can be defined as that necessary under idealized conditions, i.e., under conditions promoting maximal gut absorption and subsequent utilization. Thus, a lysine requirement for chicks might be defined as 1.00% of the diet (for maximal feed efficiency), 2.5 mg/kcal or 800 mg/day. This requirement estimate, however, cannot be applied to practice where instead of being 100% absorbed, as crystalline lysine is (Izquierdo et al., 1988), corn-soy lysine is only about 80% bioavailable. Thus, the lysine required in conventional diets would be 1.25% of a diet containing 23% protein and 3,200 kcal ME/kg. If diets are used that contain both intact-protein lysine and crystalline lysine, suitable adjustments should be made, taking account of the different bioavailabilities of lysine in L-lysine · HCl and lysine in a corn-soy blend. Likewise, if the requirement assay employed dietary energy and protein levels different from those used in practice, or if the birds in practice are fed energy and/or protein levels different from those generally fed, adjustments need to be made. Also, birds whose lean:fat ratio differs from those used in the requirement assay may require more or less lysine. Clearly, increases in body leanness, energy density and protein level result in increases in amino acid requirements, expressed in terms of dietary concentration (Baker, 1977a; 1986a; 1987; 1989).

Estimation of vitamin requirements, conceptually, is not unlike estimation of amino acid requirements in that one can generally assume that vitamins in crystalline (synthetic) form are almost 100% utilized while those in intact foods and feeds are present as coenzymes or otherwise bound in some manner (requiring gut enzymatic activity for release), thereby being less than 100% utilized. Of course, as with amino acids, isomeric configuration and Maillard-type binding (thiamin, folacin) must be considered when dealing with many of the vitamins. Also, oxidative losses, precursor situations (β-carotene $\rightarrow$ vitamin A, tryptophan $\rightarrow$ nicotinic acid, methionine methyl $\rightarrow$ choline, cobalt $\rightarrow$ vitamin B-12) and stability of the vitamins in a stored premix cannot be ignored.

Mineral requirement estimation represents a different and more complex situation in that many essential mineral elements, even in their most bioavailable inorganic forms, are poorly absorbed from the gut. Also, diet components such as phytate and soluble fiber can reduce absorption still further. Thus, taking zinc (Zn) as an example, the minimal requirement of chicks is about 10 mg/kg diet (purified) but the requirement increases at least 3-fold when dealing with a corn-soy type diet. Another factor, however, must be considered — that of the particular Zn salt that is used to supplement the diets. Zinc sulfate provides bioavailable Zn twice as efficiently as ZnO (Wedekind and Baker, 1990). Hence, while the minimal Zn requirement may be only 10 mg/kg with $ZnSO_4$ in a phytate and soluble fiber-free purified (amino acid or egg white) diet, the requirement may be as high as 20 mg/kg (purified diet) or 60 mg/kg (conventional diet) when ZnO is the supplement being used. By using a purified diet that is devoid of soluble fiber and phytate, one can estimate the "minimal" requirement under idealized conditions. Then, suitable adjustments can be made for the myriad of factors that influence the requirement such that a realistic estimate can be made

of the total level of dietary Zn that is necessary in the more practical diet that is actually intended for consumption.

Efficacy of nutrients and nutrient precursors

Purified diets are indispensable tools in assessing nutrient utilization. Requirements for all nutrients depend on the efficiency with which they are used, given the dietary and environmental factors that exist in the practical setting. The discovery of which nutrients were essential for life, or for maximal growth, necessitated feeding a purified diet that was devoid of the nutrient in question (cf. Rose et al., 1935). This has been extended to nutrient precursors and to sources of the nutrient other than the intact crystalline nutrient, the latter generally used to represent a standard and often assumed to represent 100%. The 100% *relative* value, however, should not be assumed to mean that the nutrient is really 100% utilized by the body. Thus, even with free amino acids that are consumed at levels at or below the minimal dietary requirement for the physiological function being studied (maintenance, growth, lactation, pregnancy), gut absorption is indeed 100% (Baker et al., 1966; Izquierdo et al., 1988; Han et al., 1990; Chung and Baker, 1991b) but body retention is probably no greater than 80% (Baker, 1991).

There are obligatory losses of amino acids from body pools. One should always keep in mind that up to 80% of the amino acid needs for protein synthesis come from protein degradation, with the remainder needed from dietary sources. Also, because oxidative losses of amino acids from tissue pools are greater for fast-turnover amino acids like methionine and isoleucine than for slow-turnover amino acids like lysine, the efficiency of utilizing (retaining) absorbed lysine is greater than the efficiency of utilizing absorbed methionine or isoleucine (Baker, 1991). This helps explain why growth and nitrogen retention are more negative with a methionine or isoleucine-free diet than with a lysine-free diet (Ousterhout, 1960; Okumura et al., 1985; Kino and Okumura, 1986; 1987). It also helps one understand why methionine, alone, produces a nitrogen retention response when it is supplemented into a nitrogen-free diet (Muramatsu et al., 1986).

To properly study utilization (i.e., quantitative efficacy) of any nutrient, diets must be designed to be deficient in the nutrient under study. The same can be said for determinations of quantitative efficacy of a precursor of a given nutrient. With amino acids, the portion of the growth or nitrogen retention response curve where utilization is constant (i.e., change in dependent variable as a function of change in independent variable) is the best place to make comparisons. Because weight gain as a function of amino acid intake in a growing animal is a sigmoidal response, the linear response surface for the amino acid under investigation should be determined *prior to* conducting the quantitative efficacy study (Baker, 1986a). Generally, the linear response area of an amino acid response curve occurs at intakes that are between 30 and 70% of the quantity that will yield maximal response. Outside of this area, responses are curvilinear. The ratio of slopes (at least three doses per compound evaluated) in the linear response area of the growth curve is probably the best means of establishing quantitative

efficacy values for precursors of L-amino acids (i.e., D-isomers, keto or hydroxy analogs, oxidized amino acid products, N-acetylated amino acids, heat damaged amino acid products, peptide-bound amino acids). In bioassays of this type, the reference standard is taken to be the pure crystalline form of the amino acid under study, and 100% gut absorption is assumed (the amino acids in casein, too are essentially 100% absorbed, cf. Izquierdo et al., 1988; Chung and Baker, 1991b). Absorption efficiency of 100% for free amino acids is probably a valid assumption based upon true absorption values recently determined for free amino acids in a purified diet administered to pigs fitted with ileal canulae or given to cecectomized cockerels (Chung and Baker, l991b). However, one should keep in mind that free amino acids, even though 100% absorbed, are not 100% retained. Thus, using D-methionine for the young rat as an example, it is proper to say that the oral activity of D-methionine *relative to L-methionine* is 88.5% (Funk et al., 1990).

There are numerous examples in the literature where erroneous conclusions have been drawn because not only was the nutrient assessed outside the linear response area, but, also, the nutrient in question may, in fact, not even have been deficient in the diet employed. One cannot assume 100% molar efficacy for a nutrient precursor if the nutrient being replaced is present in the diet at a level that is in excess of the requirement (Baker, 1976). Other examples where erroneous conclusions have been drawn have involved efficacy comparisons in model animals in which growth or nitrogen retention was assessed as a function of nutrient (or precursor) *concentration* rather than on the basis of *absolute intake* (Baker, 1984). Clearly, voluntary food intake must be measured accurately in efficacy bioassays in that the efficacy of any nutrient or nutrient precursor is a function of not only dietary concentration, but also of voluntary food intake.

There have been many discoveries in nutritional biochemistry that could not have been made without the aid of a well-defined purified diet. Some of these which have been studied in our laboratory and elsewhere are itemized below.

1. Relative to glutamate or diammonium citrate, indispensable amino acids (the classical 10) are inefficient precursors of the amino nitrogen required for synthesis of dispensable amino acids (Stucki and Harper, 1961; Allen and Baker, 1974).
2. Rats, mice and cats require the full array of dispensable amino acids to grow maximally, but pigs and chicks grow maximally when fed diets containing glutamate, alone, as the supplier of dispensable amino nitrogen (Rogers and Harper, 1965; Baker et al., 1979; Anderson et al., 1980; Hirakawa et al., 1984; Chung and Baker, 1991a).
3. Through gut (including bacteria) and/or body processes, animals can derive usable nitrogen for dispensable amino acid biosynthesis from urea (gut urease) and from certain purines (adenine) and pyrimidines (uracil) provided either from the diet or from body turnover (Rose et al., 1949; Featherston et al., 1962; Grimson et al., 1971; Baker and Molitoris, 1974).
4. Dietary or endogenous glutathione (GSH) can spare the dietary or physiological need for cysteine (Dyer and du Vigneaud, 1936; Harter and Baker, 1977; Boebel and Baker, 1983; Cho et al., 1984; Chung et al., 1990); methi-

onine, through transsulfuration, is 100% efficient (molar basis) in providing cysteine (Graber and Baker, 1971); inorganic sulfate but not taurine can spare up to 15% of the dietary need for cysteine (Smith, 1973; Sasse and Baker, 1974a; 1974b); L-2-oxothiazolidine-4-carboxylate is an efficient precursor of intracellular cysteine (Williamson and Meister, 1981; Chung and Baker, 1990); D-methionine, but not N-acetyl D-methionine is an efficient precursor of L-methionine, except in humans (Stegink et al., 1971; Katz and Baker, 1975; Kies et al., 1975; Zezulka and Calloway, 1976; Rotruck and Boggs, 1975; Baker, 1979; Baker et al., 1984; Funk et al., 1990); N-acetyl-L-methionine is protected from Maillard destruction and is fully effective as an L-methionine precursor (Baker, 1979; Baker et al., 1984); sulfur amino acids that through food processing have undergone oxidation (methionine sulfone or sulfoxide, cysteic acid) or crosslinking (cysteine → lanthionine) lose all, or most, of their capacity to furnish bioavailable methionine or cysteine (Anderson et al., 1975; 1976; Robbins et al., 1980); the DL-isomer of methionine hydroxy analog is a good precursor of L-methionine, but lack of 100% molar efficiency results from D-OH-methionine being more bioactive than L-OH-methionine (Baker and Boebel, 1980; Boebel and Baker, 1982a); excess methionine can eliminate the dietary need for choline (methionine methyl used for choline biosyntheses), except in avian species where choline biosynthesis is inefficient (du Vigneaud et al., 1940; Jukes et al., 1945; Anderson et al., 1979b; Czarnecki et al., 1983; Baker et al., 1983); a dietary source of taurine is definitely required by felids — for vision and cardiac function (Knopf et al., 1978; Anderson et al., 1979a; Pion et al., 1989) and exogenous taurine may be needed by neonates of many species (Chesney, 1988); L-homocysteine has a methionine-sparing value of 60 to 70% and a cysteine-sparing value of 100% for chicks and rats, but D-homocysteine has a methionine-sparing value of only 7% while its cysteine-sparing value is 68% (Harter and Baker, 1978; Baker and Czarnecki, 1985).

5. As precursors of L-isoleucine, L-KMV (ketomethylvaleric acid) is an efficient precursor, D-alloisoleucine has 60% activity, and L-alloisoleucine, D-isoleucine and D-KMV are devoid of activity (Baker 1986b; Izquierdo and Baker, 1987; Funk et al., 1987; Funk and Baker, 1989).
6. Among the precursors of L-phenylalanine, D-phenylalanine, L-phenyllactic acid and phenylpyruvic acid are efficient precursors, but D-phenyllactic acid is devoid of activity (Boebel and Baker, 1982b; Baker, 1986b).
7. Keto analogs of valine and leucine, though not 100% bioactive, can be used as nonnitrogen precursors of L-valine and L-leucine (Robbins and Baker, 1977; Boebel and Baker, 1982c; Baker, 1986b; Funk et al., 1987; Funk and Baker, 1989).
8. D-isomers of lysine, arginine, threonine, histidine and cysteine are devoid of biological activity (Baker and Harter, 1978; Baker and Boebel, 1981; Baker, 1986b).
9. D-tryptophan is well utilized as an L-tryptophan precursor by rats and swine, but it is an inefficient precursor of L-tryptophan in mice, avians and dogs (Baker et al., 1971; Ohara et al., 1980; Czarnecki and Baker, 1982; Baker, 1986b).

10. With tryptophan as perhaps the sole exception, avians use D-amino acids and keto or hydroxy analogs of amino acids more efficiently than rats (Baker, 1986b).
11. Consumption of an arginine-free diet by cats results in rapid and devastating consequences within hours — hyperammonemia, coma and death (Morris and Rogers, 1978); felid species have limited pyriline-5-carboxylate synthase activity in the intestinal mucosa and therefore can synthesize only minimal quantities of ornithine *de novo* (Rogers and Phang, 1985); dietary ornithine will keep cats (and other species) alive, but unlike citrulline, will not allow felids to growth (Morris et al., 1979); citrulline is poorly taken up by liver tissue (Windmueller et al., 1981) but is efficiently taken up by kidney tissue (where arginase activity is low), and this explains why citrulline but not ornithine (taken up efficiently by liver where ornithine transcarbamoylase as well as arginase activities are high) is an efficient precursor of arginine (no ornithine transcarbamoylase activity in kidney), cf. Tamir and Ratner (1963), Szepsi et al. (1970), Rogers et al. (1972), Czarnecki and Baker (1984), Edmonds et al. (1987).
12. In addition to depressed nitrogen retention, orotic aciduria is a biochemical marker of arginine deficiency; dogs and rats may experience 50 to 100-fold elevations in urinary orotate when arginine is deficient (Milner and Visek, 1975; Czarnecki and Baker, 1984), but most other species (eg., cats, pigs) show only modest elevations in urinary orotic acid output when arginine is deficient (Costello et al., 1980; Southern and Baker, 1983; Edmonds et al., 1987).
13. Healthy adult humans, and adult gravid or nongravid swine, do not exhibit a dietary requirement for arginine (Easter et al., 1974; Easter and Baker, 1976; Carey et al., 1987).
14. Food products that contain glutathione (Wierzbicker et al., 1989) help satisfy the sulfur amino acid requirement, and those that contain carnosine (Crush, 1970) help satisfy the dietary need for histidine (du Vigneaud et al., 1937; Robbins et al., 1977).
15. To grow maximally, avian species require a dietary source of both proline and glycine; serine, however, is fully efficacious in replacing the dietary need for glycine (Almquist and Grau, 1941; Baker et al., 1968; Akrabawi and Kratzer, 1968; Graber and Baker, 1973).
16. Among the nutritional idiosyncrasies of felids, tryptophan cannot spare or replace niacin (DaSilva et al., 1952), β-carotene cannot be converted to vitamin A (Gershoff et al., 1957; Lakshmanan et al., 1972), and preformed arachidonic acid is a dietary necessity (McLean and Monger, 1989).
17. Biological activity is lost when lysine in intact proteins (or in free form) is bound in Maillard linkages or when it is converted via food processing to lysionalanine (Carpenter, 1973; Adrian, 1974; Robbins and Baker, 1980; Robbins et al., 1980).
18. The molar efficiency of using (excess dietary) tryptophan as a precursor of nicotinic acid is about 4% (Krehl et al., 1946; Goldsmith et al., 1961; Baker et al., 1973; Baker, 1977a), but the molar efficiency of methionine

sulfur → cysteine sulfur and phenylalanine → tyrosine is 100% (Graber and Baker, 1971; Sasse and Baker, 1972).

19. The efficiency of converting β-carotene to vitamin A is considerably greater in rats than in most other species (Braude et al., 1941) and the gut absorption of intact β-carotene is more efficient in humans, felids and preruminant calves than in rats and many other species (Brown et al., 1989; Poor et al., 1991).
20. Vitamin D_2 is poorly utilized by avians, and only the D-isomer of pantothenic acid and biotin, and the L-isomer of ascorbic acid, are utilized by animals (Hoffmann-LaRoche, 1989).
21. Food processing involving heat can result in considerable destruction of thiamin and folacin as a result of Maillard binding, i.e., both vitamins have reactive free amino groups (Hoffmann-LaRoche, 1989).
22. Most mammalian neonates, due to lack of enzymatic capacity, can not utilize either sucrose or fructose; adults of most species (including lactose-intolerant humans) do not hydrolyze lactose efficiently, and other animals regardless of age (avians, pacific pinepeds) have limited capacity to hydrolyze lactose (Rutter et al., 1953; Becker et al., 1954a,b; Becker and Terrill, 1954; Baker et al., 1967; Aherne et al., 1969; Kretchmer, 1972).
23. Xylose is poorly utilized by most animals (Wise et al., 1954; Wagh and Waibel, 1966; Baker, 1977b).
24. Purified diets based upon either amino acids or casein are more conducive to trace element or heavy metal toxicity as well as chemotherapeutic agent (e.g., methotrexate) toxicity than diets based upon natural ingredients or soy (Kehoe et al., 1986; McAnena et al., 1987; Funk and Baker, 1991a,b).
25. Under most circumstances, the most limiting amino acids at the gut absorption sites (i.e., duodenum, jejunum) in ruminant animals are methionine and lysine (Nimrick et al., 1970).

The discovery and synthesis of the last essential amino acid, threonine, in 1935 (Rose et al., 1935) was instrumental in future attempts to develop palatable and efficacious chemically defined diets. Still, for many years subsequent to 1935, crystalline L-amino acids were not readily available in forms that were either economical or pure. Much of the research work done with amino acid diets between 1935 and 1965 involved use of DL-isomers and in some cases, particularly with DL-threonine and DL-isoleucine (four separate isomers of each amino acid), one could not be sure of the exact ratio of isomers present. Also, based upon current knowledge, one can question some of the early purified diets because they were either marginal or deficient in vitamin B-12 (synthesized in 1948, cf. Rickes et al., 1948; Smith, 1948) or selenium (discovered to be a dietary essential in 1957 and a component of glutathione peroxidase in 1973, cf. Schwarz and Foltz, 1957; Rotruck et al., 1973). Given these and many other unknowns, it is indeed remarkable that investigators like W. C. Rose and V. du Vigneaud in the area of amino acids and a host of scientists working in the area of B-vitamins made such impressive discoveries. Their contributions set the stage for the improved chemically defined diets that are in use today.

Purified diets have been important, indeed indispensable, in bringing nutritional science to the modern era of protein quality assessment (using a casein standard), enteral and parenteral feeding of hospitalized patients (Talbot, 1991; Mobarhan and Trumbore, 1991), low bulk diets for space travel (Winitz et al., 1965), the description of physiological roles for ultratrace elements (Nielson, 1988), the design of diets for specific disease states as well as for heritable inborn errors in metabolism, studies of the role of glutamine in nutrition and disease (Windmueller and Spaeth, 1974; Lacey and Wilmore, 1991), and many other areas of endeavor. We are now approaching an era where attempts are being made to establish the efficiency with which absorbed amino acids are utilized (i.e., retained). Likewise, attention is being focused on partitioning of amino acids for their various metabolic functions and how biologically active growth factors, both endogenous and exogenous, may affect amino acid partitioning as well as rates of protein synthesis and degradation. Advances are occurring regularly in tissue and cell culture; this together with the newer techniques in molecular biology offer promise that the future of nutritional physiology and biochemistry will be exciting – and fruitful.

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