Hypertension
Nutritional Factors

Human Nutrition and Blood Pressure Regulation: An Integrated Approach

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SUMMARY This review highlights the complex interactions that constitute the disciplines of nutrition and cardiovascular physiology. Nutritional factors have long been considered as critical in the pathogenesis of human hypertension. Theoretical and established contributions of various nutrients to blood pressure regulation are presented. A brief historical perspective of sodium's dominance in this area is provided. "Accepted" principles of nutrient interaction are then applied to cardiovascular research. First, the interrelationships among all macronutrients and diet composition, nutrient absorption, renal elimination, and ultimate bioavailability to the vascular tissue are assessed. An analysis of dietary recall data from human studies is provided to illustrate such nutrient interaction. Second, associated factors that influence nutrition are considered in relation to both human and animal investigations of blood pressure regulation. Finally, the development and interpretation of future studies are assessed in light of these principles. Examples from both the human and animal literature are provided to show why it is necessary to incorporate fully the established principles of nutrition into our current concepts of the pathogenesis of hypertension. Future progress in terms of nutrition, food, and health will be dependent upon such an integrated approach.

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KEY WORDS • human nutrition • blood pressure research • diet and hypertension • macronutrients • cardiovascular research

ALMOST 40 years after Kempner’s first description of the control of hypertension by means of extreme dietary restriction, the biomedical research community and the public sector are confronted with many unresolved questions concerning the relative contribution of various constituents of the human diet to the regulation of blood pressure. Given the complexities of both human nutrition and cardiovascular physiology, it is remarkable that the research efforts of nutritionists, epidemiologists, basic investigators, and clinicians alike have been focused primarily on one nutrient — sodium.

Normal control of blood pressure involves many organs that either directly contribute to determining cardiac output and/or vascular resistance or indirectly modify the response of the end-organ involved via neural or humoral inputs. At a cellular level, complex interactions among membrane receptors, ion transport mechanisms, enzyme-dependent processes, and energy-dependent metabolic responses ultimately dictate a cell type’s or organ system’s contribution to normal or abnormal cardiovascular physiology. Some of the physiologic components of blood pressure regulation are listed below:

1. Organ Systems
   Central nervous system
   Heart
   Kidney
   Adrenal — cortex/medulla
   Thyroid
   Parathyroid
   Vascular tissue — arterial/venous

2. Vasoactive Hormones/Compounds
   Norepinephrine
   Epinephrine
   Angiotensin II
   Mineralocorticoids
   Insulin
   Parathyroid hormone
   Vasopressin
   Endorphins
   Prostaglandins
   Kinins
3. Ions
   
   Cations
   Ca^{2+}  
   Mg^{2+}  
   K^{+}  
   Na^{+}  
   Zn^{2+}  
   Vn^{2+}  

   Anions
   Cl⁻  
   PO_{4}^{3-}  
   SO_{4}^{2-}  
   HCO_{3}⁻  

4. Vascular Smooth Muscle
   Membrane-associated factor
   Receptors
   Ion channels
   Ion transport systems
   Membrane metabolism

   Cytosol-associated events
   Ion fluxes
   Ca^{2+}-calmodulin interaction
   Enzyme induction
   Contractile protein response

   The process of acquiring the macronutrients that provide the substrates for these physiologic events is equally as complex as the cardiovascular mechanisms that are contingent upon them. It encompasses selection of a diet, preparation of food, and the net effect of digestion, absorption, metabolism, and elimination of the nutrients.

   This symposium has brought together investigators with diverse interests in macronutrients and cardiovascular pathophysiology, basic mechanisms of blood pressure regulation, genetic and cultural factors contributing to the pathogenesis of hypertension, and the role of governmental and public interest groups in the future delineation and integration of nutrition and high blood pressure research. The intent of this review is to present an objective and balanced rationale as to why all macronutrients must be considered when one assesses the influence of nutrition on the pathogenesis and therapy of hypertension, and to provide a more comprehensive means by which past data can be better evaluated and the design of future studies in both humans and animals can be improved.

Nutritional Factors and Cardiovascular Physiology

Representative mechanisms whereby various macronutrients may contribute to normal cardiovascular physiology are listed below:

1. Total Calories
   Diet composition
   Energy generation
   Metabolic requirements

2. Carbohydrates
   Energy metabolism
   Membrane synthesis
   Insulin regulation — Na⁺ excretion
   Catecholamine regulation — vascular tone

3. Proteins
   Protein/peptide synthesis
   Control of cellular function
   Membrane transport systems

4. Lipids
   Energy source
   Cell membrane components
   Prostaglandin synthesis

5. Sodium
   Intravascular volume
   Hormone regulation
   Membrane potential

6. Potassium
   Vascular tone
   Hormone regulation
   Cation transport

7. Calcium
   Receptor-ligand binding
   Hormone synthesis/release
   Vascular tone
   Contractile protein interactions

8. Magnesium
   Regulation Ca^{2+} channels
   ATP production
   Contractile protein interaction

9. Phosphorus
   Membrane structure
   ATP — energy metabolism
   cAMP component

10. Trace Metals
    Cu²⁺ — vascular integrity
       Mn²⁺ — energy metabolism
       Cr²⁺ — CHO/lipid metabolism
       Vn²⁺ — Na⁺/K⁺ ATPase

11. Vitamins
    Vitamin E — prostaglandin synthesis
    Vitamin D — Ca^{2+} balance
    Vitamin B₆ — enzyme cofactor

   With fats, carbohydrates are prerequisites in the generation of cellular energy. Through their modulation of insulin and catecholamine synthesis and release, carbohydrates may influence both intravascular volume³ and vascular resistance.⁴ Protein synthesis is critical in the metabolic cycle of all tissues. The requirement for L-tyrosine as the precursor of catecholamine biosynthesis is a specific example.⁵ Both plasma membrane receptors and the ion channels that mediate their actions are protein-dependent.⁶ Lipids are also a principal constituent of cell membranes that link the extra- and intra-cellular spaces. Mobilization of essential fatty acids in the membrane and their conversion through arachidonic acid to prostaglandins may modify both vascular tone and renal regulation of volume.⁷
Besides being a major contributor to extracellular volume, sodium has other specific actions modifying both vascular cells' cytosolic calcium and/or potassium concentrations, and sensitivity to hormones. Potassium is essential as a primary determinant of cell membrane potential. Alterations in potassium balance can modify both excitability of vascular tissue and mineralocorticoid metabolism. Calcium is a cofactor, along with calmodulin, in the regulation of diverse intracellular events in most tissue. For vascular smooth muscle, the cation modulates receptor-ligand binding, internal translocation of the membrane-stimulation signal, and activation (in association with calmodulin) of the enzymatic sequences that lead to the cells' contraction via the interaction of contractile proteins, actin and myosin. An example of calcium's effects on nonvascular tissue is its regulation of the synthesis and release of renin by the juxtaglomerular cells of the kidney.

Magnesium is a necessary cofactor in a variety of metabolic pathways. In vascular tissue, the cation regulates plasma membrane-associated interactions between receptors and ligands. Intracellularly, magnesium is important in the contractile process directly and, in part, through its influence on the uptake and distribution of calcium in vascular tissue. Phosphorus is a cofactor in the metabolism of carbohydrates, proteins, lipids, and in the generation of high energy, phosphate-containing metabolites. Through its incorporation into cAMP, phosphorus participates in the translation of the signal that is initiated by hormones' binding to membrane receptors, and results in the stimulation of many intracellular events.

Trace elements include chromium, copper, cobalt, manganese, vanadium, molybdenum, selenium, and zinc. They serve as cofactors in various enzymatic processes important to cardiovascular physiology. Manganese is required in the metabolism of carbohydrates and in the generation of ATP. Zn is a cofactor in the enzymatic reaction that generates angiotensin II, while V inhibits Na-K ATPase. Vitamins, like the trace elements, are essential to a variety of metabolic pathways that serve to regulate the balance of the macronutrients. Some are also substrates in metabolic pathways that generate compounds such as steroids and cell membrane constituents.

Macronutrients in the Pathophysiology of Hypertension

Our knowledge of the relationship between most of the macronutrients and the clinical and experimental condition of high blood pressure is limited. This void reflects, in part, the primary emphasis placed on one nutrient-sodium. This research imbalance has its roots in several historical and technical facts. First, the recognition over 40 years ago that structural and vascular modification of the kidney would produce hypertension in animals suggested a link between sodium balance and hypertension. Second, Kempner's demonstration that accelerated hypertension could be treated by extreme dietary sodium restriction provided clinical evidence. Third, Tobian and Binion's report of an accumulation of sodium in vascular tissue implicated a cellular defect. Fourth, the development of thiazide diuretics — drugs that both facilitate renal sodium excretion and lower blood pressure — furthered the notion that an abnormality of sodium balance existed in hypertension. Fifth, Dahl et al.'s hypertensive animal model of sodium sensitivity provided a possible genetic link in the story. Last, the assertions of Dahl and Page et al. that variations in blood pressure among human populations were correlated with sodium intake appeared to be the most compelling evidence.

Several important technical factors also contributed: 1) sodium is easily measured in biological fluids; 2) in contrast to most other nutrients, sodium balance is readily determined by assessing urinary excretion; 3) the accessibility in laboratory animals of the kidney and its vascular supply provided a technical advantage; and 4) the ability to measure and/or synthesize peptide and steroid hormones involved in sodium balance facilitated laboratory investigations in this area. Recent technological advances, though, now extend our research capabilities to the other macronutrients.

The following discussion briefly summarizes some of the established and postulated contributions of all the macronutrients to the pathogenesis of hypertension. Caloric intake may be the single most important nutritional consideration in the pathogenesis of hypertension. Previously, the association among caloric intake, obesity, and hypertension was felt to reflect excessive sodium ingestion. The recent demonstration that weight reduction, without a change in average sodium intake, may lower blood pressure suggests an independent effect of total calories on blood pressure control. The clinical observation that cardiovascular conditioning without weight loss may lower blood pressure in obese subjects suggests even more complex interaction. Carbohydrate intake has not been shown to differ between humans with and those without high blood pressure. Normalization of carbohydrate metabolism during weight loss has been associated with reductions in insulin levels and in sympathetic nervous system activity that parallel the improvement in blood pressure. The type of carbohydrate (simple versus complex) may be an additional factor, as the fiber content of the diet is typically higher in less industrialized societies where the prevalence of hypertension is lower.

Dietary protein has not been extensively studied in either human or experimental hypertension. Where assessed, reductions in protein intake have been associated with lower blood pressures. Furthermore, protein malnutrition during infancy induces a reduction in both alpha and beta adrenergic receptor-binding in the brain of experimental animals, and protein intake in humans will modify both calcium and potassium balance. Since differences in protein nutrition exist both among and within societies, the possible contribution...
of this macronutrient to the development of hypertension requires further investigation.

The source and type of lipids in the diet do vary among populations. Industrialized societies often shift to a higher percentage of saturated fats, at the same time increasing polyunsaturated fats derived from vegetable oils. A protective effect of the essential fatty acids (linoleate, arachidonate, linolenate) derived from either vegetable or fish sources has been suggested by human and animal studies. The lipids from these sources may either increase the synthesis of vasodilating prostaglandins or alter long-term vascular changes associated with hypertension.

It is beyond the scope of this manuscript to review the literature that has addressed the relationship between sodium intake and hypertension. Data from population surveys have been frequently cited by investigators who believe that there is an association between sodium intake and mean arterial pressure. There is substantial disagreement, though, both as to how strong this relationship is, and whether the data support an interpretation. The interpopulation studies often cited represent a heterogeneous collection of research designs and measurement techniques, as well as populations that differ in a multitude of ways in addition to sodium consumption. Therefore, the statistical validity of using these surveys in an attempt to correlate sodium intake with hypertension remains doubtful.

Data from 30 population surveys are depicted in figure 1 (Appendix A1-A31). The mean daily sodium intake (as estimated by dietary recall, dietary analysis, or measurement of 24-hour urinary excretion of sodium) is plotted against mean arterial pressure. Studies included in this graphic analysis involved adult subjects for whom blood pressure data and estimated sodium intake were provided. While this graph suggests that a society’s mean arterial pressure may increase if sodium intake is increased, it is evident that there are societies that do not fit such a relationship; i.e., they have high mean pressures but relatively low sodium intakes, or they have high sodium intakes, but normal pressures. A majority of the populations have sodium intakes that exceed 125 mEq/day (shaded area), and mean arterial pressures of 88 to 106 mm Hg. Within those ranges, there is no predictable relationship between sodium intake and blood pressure. Furthermore, within the range (darkly shaded area) of 125 to 175 mEq of sodium intake (the average exposure in the American diet), the cited populations vary dramatically in their mean arterial pressures. With a few notable exceptions, intrapopulation studies have generally failed to document a relationship between sodium intake and blood pressure. Several investigations have found a positive correlation, while others have demonstrated negative correlations.

The acute effects of sodium loading on the blood pressure of humans are minimal. In the chronic study of Luft et al., in which humans consumed up to 1500 mEq (or 10 times the normal amount of sodium in the diet), blood pressure did not rise until dietary sodium reached 800 mEq/day. Interestingly, when the study was repeated and potassium balance was maintained, blood pressure did not change. Investigations in which sodium has been restricted chronically have not uniformly demonstrated a reduction in blood pressure, though recent studies have shown that blood pressure will decrease by approximately 7 mm Hg when sodium intake is reduced by 50% in hypertensive individuals. It is apparent from intervention studies that the vast majority of normotensive subjects’ blood pressures are resistant to the influence of sodium intake, and that even among hypertensive individuals, many are not sodium-sensitive.

Both the DOCA and Dahl rat models of hypertension have demonstrated that sodium loading will increase blood pressure. The relevance of these observations to the human experience, though, is unclear. In part, this is due to the requirement for exogenous mineralocorticoid administration in the DOCA model, the excessive quantities of sodium (up to 20 times the normal amount), and renal dysfunction that typically develops in this model. Furthermore, these experiments have not controlled for the concurrent effects of sodium loading on magnesium, calcium, and phosphorus balance. Potassium balance has been maintained in most recent protocols.

A protective effect of potassium was first demonstrated by Meneely et al. A similar conclusion has been suggested by studies in humans. Population surveys have suggested that lower blood pressures exist in societies where dietary potassium intake is relatively high.

Calcium, as a nutritional factor in blood pressure regulation, was first suggested by the observations that water hardness in a region was inversely correlated with cardiovascular mortality and blood pressure. Recent reports of diet surveys have indicated that untreated hypertensives ingest significantly less calcium.
than do normal subjects. These findings contrast sharply with those of dietary sodium and potassium, which have never been shown to differ between hypertensive and normal individuals within a population. Reports from several laboratories have noted either an adverse effect on blood pressure of restricting dietary calcium intake or a protective one of calcium supplementation in both normotensive and hypertensive rats. 

Human data on dietary magnesium intake and blood pressure are virtually nonexistent. As with calcium, a possible link between increased magnesium exposure and lower blood pressure is suggested by the studies of water hardness and cardiovascular mortality. Animal studies have indicated that magnesium-deficient states are associated with an increase in blood pressure and enhanced vascular sensitivity to vasopressors. The dietary exposure to phosphorus has received substantial attention in the past decade, but these reports have failed to note any effect on blood pressure.

Vitamins and trace elements have not been thoroughly assessed in blood pressure investigations. Cadmium and lead toxicity will induce hypertension in experimental animals. Vanadium administration to dogs and rats has been associated with an increase in blood pressure that may be mediated, in part, by neural mechanisms. Copper is essential to the normal integrity of cardiovascular tissue in animals; its deficiency will accelerate vascular disease.

As a final note, a comment should be made about an important, but unessential, nutrient in the diet of many humans — alcohol. Recent reports have suggested that excessive alcohol consumption may contribute to the development of hypertension, while modest alcohol ingestion may be protective. The mechanisms underlying these relationships remain speculative. Future studies in humans must control for this potentially important confounding variable.

Nutrient Interactions and Cardiovascular Research

Nutritional studies related to hypertension must consider not only the fundamentals of cardiovascular regulation, but also basic principles of human nutrition that may be applicable. First, studies should not be limited to evaluation of the diet contents. The source and selection of the diet, its preparation, ingestion, absorption, metabolism, and elimination, and nutrient interactions must all be considered. Second, most nutrients are essential for life as the body is either unable to produce them, or, under certain circumstances, to synthesize them in sufficient quantity. Third, interconversion or substitution among some nutrients can occur, thereby providing partial protection in deficiency states. Fourth, recommended nutrient intake levels may be inadequate under certain conditions of high demand or pathologic processes in which increased or decreased amounts may be required to maintain balance. Fifth, a change in one nutrient should not be viewed in isolation, as it typically dictates that both the intake and bioavailability of other nutrients will also be modified.

The material that follows is intended as a theoretical framework within which the nutrient interactions in the diet and in the body can be assessed. The tables provide both hypothetical and real examples of these interrelationships in terms of diet composition, nutrient absorption, their bioavailability, and ultimate elimination. Preparation of the tables relied on standard textbooks in nutrition and physiology.

Table 1 depicts the theoretical interactions of macronutrients in terms of diet composition. Each of the cells predicts the secondary change in response to a single, primary change in the nutrient at the top of the column. For example, if an individual chose to increase only the carbohydrate content of the diet, calories, and potassium would also increase. However, if the fat content were increased, then there would be an anticipated increase in all the other macronutrients except carbohydrates and potassium.

As a means of demonstrating actual nutrient interactions that occur with diet selection, we analyzed 24-hour dietary recall data collected from 86 subjects at the Oregon Health Sciences University. Each subject provided a single recall. The data were computer analyzed with each nutrient divided into approximately 10 equal groups with logical breaks in the levels, e.g., 0-99, 100-199, etc, and the median observation in the middle group. After each nutrient was distributed into levels, a mean value for all the other nutrients was provided a single recall. The data were computer analyzed with each nutrient divided into approximately 10 equal groups with logical breaks in the levels, e.g., 0-99, 100-199, etc, and the median observation in the middle group. After each nutrient was distributed into levels, a mean value for all the other nutrients was provided a single recall.
2) existing only at the extremes of the reported intake of the primary nutrient (e.g., when protein was very low, calcium intake was decreased; and when protein was very high, calcium was increased); 3) existing only at the upper extreme of the reported intake of the primary nutrient (e.g., when Kcal was reported as very high, protein intake was also increased).

The results of the trend analysis of the diet recall are portrayed in table 2. The resulting dietary trends should be compared to the predicted ones in table 1. Of the 49 predicted effects, 37 (55%) appear in the recall data. Of the 22 unpredicted trends, eight were evident only at the upper extreme of the primary nutrient intake. Therefore, in table 1, 35/49 (71%) of the trends in nutrient interactions that occurred agreed with the theoretical interactions. Three of the predicted trends that appeared included associations between increasing Kcal and increased intake of all other nutrients, between calcium and phosphorous intake, and between fat and sodium consumption. Of the unpredicted trends, several are also noteworthy. Since 65% to 75% of dietary calcium is derived from dairy products, one would predict that an increase in dietary calcium would also increase fat in the diet; that relationship did not emerge. Even though dairy products are high in both sodium and calcium content, no relationship between these two nutrients was evident. Finally, changing the protein intake was not predicted to affect dietary sodium. However, at the upper and lower levels of reported dietary protein consumption, sodium intake paralleled the protein intake. The macronutrients in the diet do follow trends that are relatively predictable based upon our understanding of the Western diet. However, such trends are not absolute ones because when the diet is weighted at the upper or lower extreme for one nutrient, unpredicted changes may occur in one or more of the other macronutrients.

The Kempner diet is an excellent historical example of this effect. As noted in table 3, the Kempner diet was not just a low sodium diet. It was also low in protein, fat, calcium, and phosphorus, as well as high in potassium, magnesium, and carbohydrate. The contributions of any one or all of the other diet changes to the antihypertensive action of this diet may have been as important as that of reducing the sodium content.

Table 2. Observed Interactions of Macronutrients: Association between Changes in the Primary Nutrient and the Secondary Effect

<table>
<thead>
<tr>
<th>Secondary Nutrient Change</th>
<th>Kcal</th>
<th>CHO</th>
<th>Pro</th>
<th>Fat</th>
<th>Ca</th>
<th>P</th>
<th>Na</th>
<th>K</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased: Kcal CHO Pro Fat Ca P Na K</td>
<td>↑↑</td>
<td>↑↑</td>
<td>↑↑</td>
<td>↑↑</td>
<td>↑↑</td>
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</tr>
</tbody>
</table>

Shaded areas represent disagreements between theoretical and observed nutrient intake. Darker shading on a cell represents unpredicted trends occurring only at the upper extreme of the primary nutrient intake. Single arrows show moderate associations, particularly at extremes of intake. Double arrows indicate strong associations between changes in the primary nutrient and the secondary effect. Arrows followed by "ue" indicate associations only at the upper extreme of reported intake of the primary nutrient; and 0 indicates no association.

Table 3. Nutrient Composition of the Kempner Rice-Fruit Diet

<table>
<thead>
<tr>
<th>Composition</th>
<th>Amount</th>
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</thead>
<tbody>
<tr>
<td>Calories</td>
<td>2,000 Kcal</td>
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<tr>
<td>Carbohydrate</td>
<td>465 g</td>
</tr>
<tr>
<td>Protein</td>
<td>30 g</td>
</tr>
<tr>
<td>Fat</td>
<td>4 g</td>
</tr>
<tr>
<td>Calcium</td>
<td>230 mg</td>
</tr>
<tr>
<td>Phosphorus</td>
<td>600 mg</td>
</tr>
<tr>
<td>Potassium</td>
<td>2,200 mg</td>
</tr>
<tr>
<td>Magnesium</td>
<td>300 mg</td>
</tr>
<tr>
<td>Iron</td>
<td>11 mg</td>
</tr>
<tr>
<td>Vitamin A</td>
<td>5,000 IU</td>
</tr>
<tr>
<td>Vitamin D</td>
<td>1,000 IU</td>
</tr>
<tr>
<td>Thiamine</td>
<td>5 mg</td>
</tr>
<tr>
<td>Riboflavin</td>
<td>5 mg</td>
</tr>
<tr>
<td>Nicotinamide</td>
<td>25 mg</td>
</tr>
<tr>
<td>Calcium pantothenate</td>
<td>2 mg</td>
</tr>
</tbody>
</table>

*Calculated from original diet prescribed of 300 g rice (½ brown, ½ white), about 500 Kcal fruit (about seven servings including: apple juice, grapefruit juice, orange, banana, strawberries, apple, nectarine, cantaloupe), 100 g white sugar. (See ref 1.)
TABLE 4. Observed Interactions of Macronutrients: Bioavailability Interrelationships

<table>
<thead>
<tr>
<th>Primary Nutrient Changes</th>
<th>Increased:</th>
<th>Simple Phyto</th>
<th>Pro</th>
<th>Fat</th>
<th>Ca</th>
<th>P</th>
<th>Mg</th>
<th>Na</th>
<th>K</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHO</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
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<tr>
<td>Pro</td>
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<td>Fat</td>
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<td>Ca**</td>
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<td>↑</td>
<td>↑</td>
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<td>P</td>
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<td>Mg**</td>
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<tr>
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<td>↑</td>
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<td>↑</td>
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<tr>
<td>K*</td>
<td>↑↑</td>
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</tbody>
</table>

Upward arrow indicates increased primary nutrient resulting in secondary increases; downward arrow indicates increased primary nutrient resulting in secondary decreases; and 0 indicates no effect.

TABLE 5. Observed Interactions of Macronutrients: Renal Reabsorption Interrelationships

<table>
<thead>
<tr>
<th>Primary Nutrient Changes</th>
<th>Increased:</th>
<th>CHO</th>
<th>Pro</th>
<th>Fat</th>
<th>Ca**</th>
<th>P04</th>
<th>Mg**</th>
<th>Na*</th>
<th>K*</th>
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<tbody>
<tr>
<td>CHO</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
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<td>o</td>
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<td>Pro</td>
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<td>Fat</td>
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<td>o</td>
<td>o</td>
<td>o</td>
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<td>Ca**</td>
<td>↓↓</td>
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<td>↓</td>
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<td>P04</td>
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<td>Mg**</td>
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</tbody>
</table>

Upward arrow indicates increased primary nutrient resulting in secondary increases; downward arrow indicates increased primary nutrient resulting in secondary decreases; and 0 indicates no effect.

TABLE 6. Observed Interactions of Macronutrients: Vascular Smooth Muscle Effects

<table>
<thead>
<tr>
<th>Primary Nutrient Changes</th>
<th>Increased:</th>
<th>CHO</th>
<th>Pro</th>
<th>Fat</th>
<th>Ca**</th>
<th>P04</th>
<th>Mg**</th>
<th>Na*</th>
<th>K*</th>
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<tbody>
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</table>

Upward arrow indicates increased primary nutrient resulting in secondary increases; downward arrow indicates increased primary nutrient resulting in secondary decreases; and 0 indicates no effect.

Observed Interactions of Macronutrients: Bioavailability Interrelationships

- Upward arrow indicates increased primary nutrient resulting in secondary increases; downward arrow indicates increased primary nutrient resulting in secondary decreases; and 0 indicates no effect.

Observed Interactions of Macronutrients: Renal Reabsorption Interrelationships

- Upward arrow indicates increased primary nutrient resulting in secondary increases; downward arrow indicates increased primary nutrient resulting in secondary decreases; and 0 indicates no effect.

Observed Interactions of Macronutrients: Vascular Smooth Muscle Effects

- Upward arrow indicates increased primary nutrient resulting in secondary increases; downward arrow indicates increased primary nutrient resulting in secondary decreases; and 0 indicates no effect.

Associated Factors Contributing to Human Nutrition and Cardiovascular Physiology

Investigations involving nutrition and cardiovascular physiology must also consider a variety of non-nutritional and non-physiological factors. Representative possibilities applicable to human studies are listed below:

1. Cultural Factors
   - Food
     - Collection
     - Preservation
     - Preparation
     - Variety
   - Commercial products
   - Taboos
   - Industrialization
   - Lifestyles
   - Environment
   - Availability of medical services
   - Secular trends
     - Dietary habits
     - Social habits
   - Racial distribution

2. Medical Conditions
   - Endemic diseases
     - Parasites
     - Infectious diseases
     - Genetic disorders
     - Malnutrition
   - Physical conditioning
     - Exercise
     - Weight
   - Diet-related diseases
     - Obesity
     - Diabetes
     - Cardiovascular disease

The net effect of some of the predicted interactions remain speculative, as the net effect of some of the macronutrients on renal physiology is uncertain. Ultimately, interactions of the macronutrients modify the tissue composition. We have projected some of these net changes for vascular smooth muscle cells (table 6). In making these extrapolations, the effect on diet composition, intestinal absorption, renal excretion, and the vascular tissue's transport systems and metabolic responses were all considered. While many of these interactions are speculative, the fundamental point is evident: if both vascular resistance and cardiac output are dependent upon vascular tone, then mean arterial pressure may be altered by changes in any of the macronutrients.
### 3. Geographical Considerations
- Size of the region
- Degree of isolation
- Topography — altitude

### 4. Environmental
- Climate
  - Ambient temperature
  - Rainfall
  - Sun exposure
- Water source
  - Mineral content
  - Treatment additives
- Soil content
  - Minerals
  - Moisture
- Toxin
  - Airborne
  - Waterborne
  - Soilborne

For any given population, the relative importance of these factors will vary. Preparation of the diet can either add nutrients (grinding grain with limestone instruments) or remove them (boiling food). The industrialization of a society will change the diet (fig. 2). Secular and/or religious food taboos may modify the diet. Racial composition of a population may be critical (vitamin D conversion by sunlight is reduced in dark-skinned individuals). Common medical conditions may influence bioavailability (parasitic infections will lower intestinal absorption of many macronutrients). The existence of infant malnutrition may influence future maturation. The level of routine physical exercise will both modify the diet requirements and alter the metabolism of the macronutrients. The prevalence of obesity must be defined for any population study.

Geographical and environmental factors have been the ones most often overlooked in the past. The size of the region will influence the homogeneity of the population. Climate and elevations may be important considerations, since fluid and electrolyte as well as other metabolic requirements will vary accordingly. Increased sunlight exposure will increase vitamin D conversion. The water source may provide as much as 50% of the magnesium and 30% of the calcium in the diet as well as vital trace elements. Alternatively, water treatment in hard water areas may contribute as much as 10% of the sodium in an individual’s diet. The soil’s mineral content will, in part, determine the minerals in the diet. Environmental toxins may influence the bioavailability of the macronutrients, or directly modify cardiovascular physiology itself.

To control for, or even assess, all these factors in population studies may be impossible. Where feasible, though, these associated factors should be defined or, at minimum, considered when data from surveys or intervention studies are analyzed, in order to permit proper comparisons and interpretations. Many of these considerations apply not only to human studies but to animal research as well.

### Study Design of Nutrition and Blood Pressure Research

The need for a more comprehensive assessment of the role of nutrition in the pathogenesis of high blood pressure is apparent. Examples of the specific areas requiring investigation are evident from the papers that follow. In designing those investigations, some limitations or requirements must be acknowledged. Human surveys of nutrition patterns and prevalence of hypertension are single observations in time. Comparisons of surveys require that differences in the populations be clearly defined and that the focus include more than one nutrient. The limitation of sampling populations at single time points is exemplified by the report of Harris et al. They examined child-adolescent blood pressures in Seventh Day Adventist and non-Seventh Day Adventist school-aged youngsters. Blood pressures did not differ between these two groups of youngsters, even though cardiovascular death rates related to hypertension and the diet patterns for the two groups were significantly different. Rather than correlating blood pressure with individual nutrient intake, surveys should seek to identify differences in the diet composition of blood pressure subgroups.

The accurate assessment of all the nutrients in the diet is a vital component in the methodology of future studies. Table 7 lists the techniques for assessing dietary intake of the macronutrients. We have judged the techniques based both on their accuracy and feasibility. For elements such as sodium and potassium, a timed urine collection is ideal. However, such a test
TABLE 7. Assessment of Nutrient Ingestion

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>Carbohydrates</th>
<th>Protein</th>
<th>Fat</th>
<th>PO4</th>
<th>Ca++</th>
<th>Mg++</th>
<th>Na+</th>
<th>K+</th>
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<td>Urine collection</td>
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<td>2</td>
<td>3</td>
<td>2</td>
<td>3</td>
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<td>Diet recall</td>
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<td>3</td>
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<tr>
<td>Diet analysis</td>
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</tbody>
</table>

1 = optimal; 2 = effective; 3 = limited utility; 4 = no utility.

has limited application for other ions such as calcium and phosphorus, and no utility for measuring protein, lipid, and carbohydrate intake. The complete profiling of the nutrient exposure in any population will likely require multiple techniques. The combination of diet analysis and balance studies would assure accurate delineation of nutrient bioavailability. Such a requirement, though, would be prohibitive for most investigations. The observations of Hallenbach et al. provide an example of the value of accurately assessing the intake of a nutrient. These authors measured blood pressures in adolescents living in two neighboring communities that differed in the sodium content of the drinking water (405 mg/liter vs 3 mg/liter). One might have inaccurately concluded that differences in blood pressures found in these two populations were attributable to projected differences in dietary sodium based upon the cation's concentration in the drinking water. However, timed urine collections in the two populations demonstrated that the youngsters living in the town with "high sodium" water content actually excreted less sodium than those subjects residing in the "low sodium" water area. Therefore, the high sodium content of the water had not necessarily resulted in an overall increase in dietary sodium intake.

A more compelling demonstration of the necessity of properly assessing nutrient exposure in human blood pressure studies may be derived from figure 1. As outlined above, this graph included only populations in which blood pressures and dietary sodium estimates were provided. However, in only eight of the 30 populations was sodium intake assessed by urine collections in more than 20% of the study population (Appendix A4, A6, A26, A27, A30). The correlation between sodium intake and blood pressure suggested by figure 1 is no longer evident when only these eight surveys are included in the graphic analysis (fig. 3).

Many of these same design principles apply to animal studies as well. Animal investigations in the proper models can provide the type of control data that may never be attainable in humans. Longitudinal investigations, particularly ones that are initiated in young ani-
mals, may be most valuable. Even investigations without obvious nutritional implications may require careful characterization of the animal’s diet beginning in infancy. The papers of Douglas et al. (pp III-79–84), Kuchel et al. (pp III-93–98), and Moreland et al. (pp III-99–107) in these Proceedings, as well as the recent report of Keller et al., 23 attest to the importance of this consideration.

Finally, animal studies that purport to address the role of various nutrients in the pathogenesis of hypertension should endeavor to modify the diet exposure within a range that approaches the accepted upper or lower limits of the nutrients in the diet. The early work of Dahl and others in sodium chloride-related hypertension, as well as most subsequent investigations in this model, have utilized a sodium chloride content of the diet that is approximately 20 times the standard. 18, 69 Studies of that dosage represent toxicology investigations and not nutrition-related experiments. In addition, the necessity to interpose either end-organ changes (e.g., reduction in renal mass) or hormone administration limits the application to the human situation of results employing such maneuvers. While the utilization of animal models with gross perturbations of diet and/or regulatory mechanisms amplifies our understanding of the components of cardiovascular physiology, the results should not necessarily be extrapolated to the human disorder, essential hypertension.

Summary

Cardiovascular research into the pathogenesis and therapy of hypertension has made tremendous advances over the past four decades. We are now in a position, with this past experience and our present technologies, to continue the unraveling of the relationship between nutrition and hypertension. The complexities of both human nutrition and cardiovascular physiology, however, make it imperative that we interpret with great caution the results of many earlier investigations and plan carefully in our future experiments. Only the complete integration of the principles of both nutrition and cardiovascular physiology (fig. 4) will ultimately permit us to understand better the role of dietary factors in both the pathogenesis and therapy of human hypertension.

References

Appendix

Bibliography on Nutrition and Blood Pressure Regulation


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