WORLD REVIEW OF NUTRITION and DIETETICS

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Preface

In common with many other scientific subjects, that of nutrition becomes more and more difficult to envisage as a whole because of the avalanche of published papers which envelops every worker in this field. Even in specialized aspects of nutrition it is often difficult to keep pace with the course of events and the spate of publications. The role of the review journal becomes thus ever more important in the comprehension of nutritional progress. There are already in existence a number of review journals in America, the United Kingdom, and Europe which fulfil a valuable role in interpreting the nutritional field, but I feel, together with the Advisory Editors, that there is more than ample scope for this new World Review. We hope to provide a forum for more lengthy and discursive reviews than are published in conventional journals, and we hope that these reviews will not be a catalogue of the papers published in the last few years. Each one will be written by an expert in the particular field which is to be covered and should provide a critical evaluation of the field. We hope it will bear the imprint of the author himself, that is to say his interpretation, his views and his theorizing will be welcomed as an integral part of his article.

It is aimed to produce this review annually and to make it truly International. In the present volume the following nationalities are represented: United Kingdom, United States, France, Japan and Guatemala.

These then are the aims and objects of the new review and it is to be hoped that our readers will find that the volumes will live up to them.

It has been a great pleasure and an honour to have as authors in this first volume Prof. E. V. McCollum and Prof. C. G. King, who have carved for themselves a permanent place in the history of nutrition, and the editor and publishers are greatly indebted to them for adding lustre to the new series. We also owe a great debt of gratitude to our other very distinguished contributors for their confidence in us and in the new *World Review* by lending their abilities and their pens to Volume I.

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12th January, 1959.

PUBLISHER'S NOTE

It is regretted that this volume has been seriously delayed by circumstances over which we had no control. We wish to apologize for this delay, and to seek the reader's indulgence if he is surprised at the omission, in certain articles, of references to important recent publications.

Advisory Editors

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The History of Nutrition

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Contents

I. INTRODUCTION

The *World Review of Nutrition and Dietetics*, in its successive volumes, will be written by people with special and expert knowledge of nutrition problems. The objective is to describe the nutritional status of peoples under different geographic, climatic and economic conditions, and to examine all available knowledge in order to find solutions wherever nutrition problems exist. The Editor invited me to introduce this new series of nutritional reviews by writing this chapter on the history of nutrition. I shall endeavour to do this by giving an account of the more important events in thought and experiment by which the science of nutrition developed. In the space available the story of progress in this field must of necessity be considerably abbreviated. Elsewhere (McCollum 1957*a*)[1] I have given a detailed account of experimenters who contributed some hundreds of observations of importance, mostly chemical, which stimulated reflective minds and invited further inquiry, and brought to light important new facts.

The early writers on materia medica, in describing medicinal plants, employed such terms as farinaceous, mucilaginous, saccharine, acidulous, oily, caseous, gelatinous, albuminous and fibrinous principles. Early chemists recognized only these properties in vegetable substances. The pioneer physiologists wondered that foods so unlike each other and unlike any body tissues could be so metamorphosed in digestion as to form the various body structures in growth repair of injuries, and for conversion into wool, eggs, milk, etc. Chemists had no explanation to offer. The problem of what was important in foods and what unimportant was so perplexing that few were motivated to do more than speculate. Nobody knew how to conduct experiments which offered any prospect of important discoveries.

II. PRIMITIVE MAN'S IDEAS ABOUT FOODS

Primitive peoples held very definite ideas about quality in foods. Frazer (1931)[2] in his vast studies of ancient cults and folklore describes many food taboos. Most of these had to do with beliefs that certain foods had magical powers. Perhaps the most common idea was that the eater acquired the qualities of the animal whose flesh he ate, either strength or weakness depending on the strength and courage or the timidity of the creature. Modern experience in general has not confirmed these old beliefs.

Primitive beliefs in the medicinal value of many plant substances contain the germ of the idea that they were composed of different principles, each one effective in curing a different disease. Such ideas were based either on observations or on authority of powerful persons. It was not possible to verify or refute such claims until the advent of the science of chemistry. It is worth our attention to consider what the most outstanding early philosophers thought about the nature of the physical world and especially of the origin of the organic matter of plants and animals.

Thales of Miletus (650–580 B.C.) believed that water was the substance from which, through condensation, a primordial mud was formed and from this plants and animals were derived. More than two thousand years later van Helmont believed that he had proved experimentally that in the growth of a willow tree 164 lb of wood had been formed from water. Even in 1791 Dr. George Fordyce[3], a prominent physician of London, believed that experiments which he entrusted to an assistant proved conclusively that small minnows grew to much larger fish with only water and air available to them. He did not suspect that his assistant secretly fed the fish.

Fordyce was the first man to conduct a nutrition experiment using controls for comparison. He noted that his canary hens looked poorly nourished as the egg-laying season progressed. He reasoned that the hens might need more "calcareous substance" for making egg shells than the ordinary diet of canary seeds provided. He put the question to test. He divided his canary hens into two "parties," to one of which he gave a piece of old mortar. The birds ate it freely. The results showed that the hens which ate of the mortar remained in good condition through the laying season, whereas those which ate seeds only were malnourished and some died.

In 1799 Vauquelin[4], one of the most eminent chemists of his time, believed that he had demonstrated by experiment with a farmyard hen that transmutation of inorganic elements occurred in the metabolic processes. The question whether in the process of vegetation plants generated or transmuted inorganic substances was unsettled until in 1842 Wiegmann and Pollstorff[5] proved conclusively that all mineral substances in plants were derived from the soil.

III. EARLIEST CONCEPTIONS ABOUT FOODS

Reasoning about why herbs possessed medicinal properties was impossible so long as philosophers believed that water, air, fire and earth were the primordial materials from which all things, even the human body (Empedocles), were formed by uniting them in different proportions and that health and sickness depended on the harmony or disharmony of the four humours, blood, phlegm, black bile and yellow bile (Hippocrates).

Paracelsus (1493–1541) introduced the concept of the body as a chemical system. He accepted the idea of the four elements, but assumed the presence in the body of a mysterious force, which he called *archaeus*, and which he conceived to be endowed with the power of dominating the life processes. Health and disease depended upon the mood of the *archaeus*. Van Helmont (1577–1644), the discoverer of carbonic acid gas, accepted the views of Paracelsus.

The actual founder of iatrochemistry (medical chemistry) was F. de le Boe Sylvius (1614–1672)[6], who assumed that processes of physiology and pathology resulted from what he called "fermentation." He attributed *metamorphosis* of food to the action of saliva and a ferment secreted by the pancreas, and believed that peculiar virtues of the blood derived from ferments contributed to it by the bile and the lymph glands. If ferments were in right proportions and amounts the body was in a state of health. Disease was caused by an "acrimony," a superabundance of acid or alkaline substances, generally or locally.

The philosophy of Sylvius, like that of Paracelsus, was inadequate to a comprehension of the properties of foods and of the processes of nutrition. But the view that many plants were endowed with medicinal properties suggested the idea that in the disordered states which their administration corrected, something that was missing in the body was supplied by the remedy. The hundreds of remedies described in early pharmaceutical writings suggested complexity of body chemistry but could not illuminate the relations between food and nutrition.

1. Hilaire M. Rouelle's Design of a System of Chemical Analysis

H. M. Rouelle (1718–1778)[7], an apothecary in Paris, about the middle of the eighteenth century suggested that the best way to "dissect" plant materials was to apply to them successively a series of organic solvents, the poorest one to be applied first, the next poorest second, and so on. By this technique specific substances or simple mixtures having distinctive solubilities were separated and much new information was gained about the kinds of chemical substances contained in plants. His system was modified by later chemists, and by the year 1800 Thomas Thomson, Regius Professor of Chemistry at Glasgow, was able to list twenty-one organic substances which had been derived from various plants and from animal tissues. From Rouelle's time to the present, chemists have followed his principle in seeking to discover unknown constituents of the materials in organic nature. It was the beginning of food analysis.

2. Papin's Pressure-Pot and its Influence on Chemical Thought

In 1679 Denis Papin[8] invented a pot with a close-fitting lid securely fastened and equipped with a safety valve. Its original purpose was the preparation of gelatin from bones. Hitherto no one had heated organic substances with superheated steam. The instrument was of great interest to chemists, and soon various kinds of animal tissues—bone, muscle, nerve, cartilage, ligament, horn, etc.—were separately heated with superheated steam. When the brown liquor formed by this process was evaporated it appeared to the uncritical eyes of chemists of that period that every animal tissue yielded gelatin. The idea was accepted that animal tissues of different appearance and properties were derived from gelatin combined with different proportions of water. Albrecht von Haller, the great Swiss physiologist (1707–1777), expressed his belief that about half the human body was gelatin. Upon the evidence presented this conclusion seemed warranted.

3. Beccari's Observations on Wheat Gluten

In 1742 Beccari[9] prepared wheat gluten by washing the starch out of dough. Since it easily putrefied like flesh he concluded that it was "animalized" matter, and drew the further deduction from the evidence that man, with the exception of the spiritual part of his being, was made from the "animalized" matter of his principal food, wheat. Sixty-four years later Vauquelin and Fourcroy, leaders in chemical thought and experiment, after discovering that beans were rich in "animal matter," attributed to this vegetable product high nutritive value because of its high content of *aliment*, from which blood could be formed, and which could therefore nourish other tissues. Their criteria for identifying "animal matter" were the odour on burning, precipitation by nut-galls and certain heavy metals, and susceptibility to putrefaction.

Common observations of animals losing their accumulation of fat when underfed or starved, and its restoration when good feed was supplied, early suggested that an animal could prolong life by expending its fat. Lavoisier established by experiment that respiration involves oxidation. Starch had been known since Pliny's time (A.D. 23–79). It had been washed out of cereal grains for use as an adhesive. Oils were pressed out of various seeds from early times. The fact that ordinary foods contained starch and fat as well as "animal matter" was known to Lavoisier.

In 1811 Gay-Lussac and Thenard devised the first method for quantitatively determining the percentages of carbon, hydrogen and nitrogen in organic compounds. The method was not accurate but was improved by several chemists during the next thirty years. A new era was thus opened and increasing numbers of organic substances occurring in foods were subjected to chemical analysis for their content of these elements. Especially important was the observation of the high nitrogen content of animal tissues with the exception of fat. In 1841 Liebig[10], the most influential chemist of his generation, suggested that the nutritive values of foods could be estimated on the basis of their nitrogen content. The "albuminous" or flesh-forming food he called "plastic" food. In his view the essentials of an adequate diet were sufficient *plastic* (protein) and fuel foods (carbohydrates and fats), the former to build muscle and other body tissues and to furnish energy for muscular work; the latter, through respiration (combustion), to keep the body temperature normal under conditions of cooling. About the year 1840 Mulder[11] interpreted his experimental observations to signify that there was but one *protein* in nature, and that such contrasting "albuminous" substances as casein of milk, fibrin of blood and egg albumen, differed from one another because in them protein was combined with different amounts of phosphorus or sulphur or both to form "protein compounds." Liebig accepted this view. It was also accepted by the earliest and later agricultural chemists who studied animal nutrition, and was abandoned by notable investigators only toward the end of the nineteenth century.

IV. THE CHEMICAL ANALYSIS OF FOODS

In 1860 Henneberg and Stohmann (1885)[12], director and chemist, respectively, of the first agricultural experiment station to be supported at public expense (Weende, near Göttingen), adopted the most important ideas which earlier chemists had applied to the analysis of plant substances. They devised a system of food analysis which became standard practice throughout the world for half a century. By this method a sample was dried to determine its moisture content. Another sample was extracted with ether to remove what was called "crude fat." Another was used to determine its nitrogen content. and another was burned to estimate its ash. The nitrogen found was multiplied by a factor 6·25 and the result was called protein. A sample was digested successively with dilute acid and dilute alkali, and the part which was not dissolved was called "crude fibre." This consisted principally of cellulose and lignin, which were supposed to be unchanged in the digestive tracts of animals. The sum of the protein, fat, ash and crude fibre was subtracted from 100 to obtain a fraction called "nitrogen-free extract," which was thought to represent utilizable carbohydrates. For half a century chemists and physiologists assumed that this analysis represented like nutritive worth in foods regardless of their source, *e.g.* seeds, roots, tuber or leaf of different kinds of plants, and that protein and fat from milk, egg and meat had the same nutritive values as those from vegetable substances. Tens of thousands of analyses were made of foods and feeds grown on different soils in different geographical areas. The data were believed to be important for planning rations for farm animals and for assessing the values of human dietaries.

Meanwhile agronomists were occupied through five decades with studying the cost of producing protein and energy in different farm crops. The hope was entertained that when sufficient data were available farmers could use tables of food composition for calculating animal rations so as to secure the nutrients at the lowest cost and so realize the greatest profit in animal production. The results gained from this system of judging food values were disappointing, and by 1890 the chemical analysis had fallen into disrepute. However, not even the most experienced chemists and physiologists ventured suggestions for remedying the difficulty.

At the end of the nineteenth century protein and energy requirements of human subjects for various kinds of work, and of domestic animals for growth and for milk, egg and wool production, dominated the discussion of nutrition in agricultural bulletins and in books on diet in relation to health. For another decade a vigorous controversy was carried on over the allowance of protein which best promoted health (McCollum 1957*b*)[13]. Voit, Atwater, Benedict and Sir James Crichton-Browne believed in the merits of high protein consumption in the interest of physiological well-being, while Chittenden, Irving Fisher and J. H. Kellogg in America, and Hindhede in Denmark, urged abstemiousness in protein-eating. The views of the former group received strong support from a study by McKay, *The Protein Element in Nutrition* (1912). He assessed a number of racial group dietaries of people in India on the basis of their protein content only and attributed the high standards of physical vigour of some groups to high protein consumption, and the poor physical status of other groups to deficiency of this element in their diets.

Throughout the nineteenth century little attention was given to the physiological importance of the inorganic moiety of dietaries. A few experimental tests were made by animal husbandmen to find to what extent the bones of domestic animals could be increased in size and breaking strength by the use of supplements of bone meal, calcium carbonate or wood ashes. Bone size and strength were improved by this means. Acid-base balance was considered by von Bunge to be important in nutrition. Still earlier the need of animals for sodium chloride had been discussed, for opinions differed on the subject. That an ash-free diet could not support life of animals was first proved by Forster in 1873. In 1889, in his famous text-book of physiological chemistry, G. von Bunge discussed potassium only in relation to the need for sodium chloride by grazing animals, whose intake of potassium was high because of their ingestion of potassium-rich plants. Sodium salt, he believed, was essential for assisting herbivores to excrete the excessive intake of potassium. Plant physiologists in the nineteenth century were far in advance of animal physiologists in seeking to determine inorganic requirements. It was not until after 1920 that it emerged that this was a field of great importance.

V. THE DISCOVERY OF VITAMINS

The first man to suggest that a diet which supplied only protein, carbohydrate and fat was inadequate for the support of life was J. B. A. Dumas[14], the famous French chemist. In 1871 he described in the siege of Paris the accompanying shortage of food, especially for infants and young children. The high mortality among these was attributed to the shortage of milk and eggs. Efforts were made to construct artificial milk by making an emulsion of fat in a solution of albuminous substance and sugar. When given this milk substitute infants soon died. No one knew why. Dumas declared that no chemist could justly claim to be able to make a food equivalent to milk by such means. He clearly expressed his belief that there were in milk chemical substances still unknown and of nutritional significance. He did not follow up this observation by experimental inquiry into the nature of these hypothetical constituents which were so important to life.

First to restrict animals (mice) to a diet consisting of purified protein (casein), milk sugar and milk fat, together with what were believed to be the essential inorganic elements, was N. Lunin (1885)[15]. At the suggestion of his famous teacher, von Bunge, he tried feeding this simplified diet of purified food substances to determine whether the animals would die of acid intoxication from sulphuric acid and phosphoric acid formed from oxidation of the phosphorus and sulphur in the casein, when alkali bases were not present in sufficient amounts to neutralize them. On this diet the mice soon sickened and died, whereas when he gave other mice only milk as food they remained in apparently normal condition for sixty days. Lunin stated that milk must contain essential nutrients other than the principal constituents, casein, lactose, and milk fat, and that they were in the whey constituents. Everything that Lunin observed and concluded from his results can be deduced from the observations of Dumas on the fate of infants fed "synthetic milk."

Space does not permit giving an account of twelve experimental inquiries, published between 1881 and 1906, on simplified diets, the chemical constituents of which were known. The author has given a description of these elsewhere (McCollum 1957*a*)[1]. Each investigator met with failure to nourish mice or chickens on such diets. In 1844 Gobley discovered lecithin in egg yolk and found that it contained both nitrogen and phosphorus. In 1881 Miescher isolated nucleoprotein from the heads of salmon sperm. Hoppe-Seyler had prepared a similar substance from pus from an abscess, and in 1874 Picard observed that the purines guanine and xanthine were liberated on hydrolysis of nucleoproteins. A few men who were curious about the cause of failure of mice on diets made of purified food substances naturally wondered what was missing, and so efforts were made to supplement such mixtures with lecithin or with nucleic acids. These additions did not improve the status of experimental animals.

The step taken by Pekelharing in 1905[16] to demonstrate the extreme importance of small amounts of unidentified nutrients was the most meaningful to that date. He observed that while mice could not surive many days on a diet of purified food substances they were greatly improved in health by a small allowance of whey. This contained so little of anything which was recognized as a food principle that Pekelharing concluded that unidentified nutrients existed in the whey. He did not influence the thought of any investigators of his generation.

After Pekelharing the most important experiments with foods were carried out by Röhmann and reported in 1908[17]. He proved that young animals failing in health on a diet of protein, carbohydrate, fat and salts, were greatly benefited by small supplements of several kinds of natural foodstuffs. This clearly pointed to the existence in natural foods of unidentified nutrients, but his results had no immediate influence on the course of nutrition studies. He did not attempt to inquire into the nature of these substances.

In 1907 McCollum[18] undertook to test the possibility of turning failure into success by making diets of purified food substances more palatable. Failure again resulted. However, by good fortune he prepared an experimental diet the milk sugar of which contained unrecognized impurities derived from whey. His experimental rats also had access to their faeces, which they ate in considerable amount and from which they derived unidentified substances. On this basal diet young rats soon sickened and died when the fat supplied was lard or olive oil, but were able to grow for a time when butter fat or egg yolk fat was used as a supplement. This was the earliest conclusive proof that certain fats contain an essential nutrient which is absent in others. They were able to transfer this new something from butter fat to olive oil by making soap from butter oil and shaking olive oil with this soap solution to form a fine emulsion. The emulsion was broken with ether and the olive oil recovered in this solvent. Feeding tests showed that it had acquired the nutrient property of the butter fat. This factor was called vitamin A.

Mention of the great discovery of Eijkman and Grijns[19] in 1896–1901 is made at this point because although in the perspective of history it was epoch-making, it did not influence thought by nutrition investigators until a decade later. Eijkman observed that chickens fed solely on polished rice developed multiple neuritis, with head retraction and paralysis, and that when given unhusked rice they quickly recovered. Water or alcohol extracts of rice polishings when administered to helpless birds cured them dramatically. He noted the similarity of symptoms of birds with the rice sickness to those of human subjects with beriberi, then a disease causing high incidence of disability and mortality among peoples whose staple article of diet was polished rice. As the explanation for the aetiology of the disease he postulated the existence in the endosperm of rice kernels of a nerve poison for which there was a pharmacological antidote in the outer layers of the grain. Vordermann[20] eradicated beriberi from prisons and asylums, where it was very common, by changing the diet of the inmates from polished to unpolished rice. Grijns (1901)[19] correctly interpreted the phenomena as due to a deficiency of some essential nutrient. There were, however, a number of dissenting opinions concerning the cause of beriberi and it was not until the publication in 1910 of the studies of Fraser and Stanton[21] that all were forced to accept the deficiency hypothesis.

These studies were all published in journals devoted to hygiene or medicine, not usually read by chemists. The present writer was unaware of them until the appearance of E. B. Vedder's Cartwright Prize Essay, *Beriberi* in 1913[22], and Funk's volume *Die Vitamine*[23] in 1914. The latter received wide publicity because in it Funk proposed his vitamin hypothesis. This postulated the existence of a number of unidentified nutrients, a deficiency of one causing beriberi, another rickets, another scurvy, another pellagra, etc.

In the first decade after 1900 text-books by Lusk and Sherman, and bulletins on foods and nutrition published by the U.S. Department of Agriculture in which Atwater was the leading authority, still taught that protein, carbohydrate and fat were the only nutrients which need be emphasized in assessment of quality in diets. The view taken of mineral elements in nutrition was that any mixed diet which provided sufficient of the organic dietary essentials would doubtless contain enough inorganic substances.

VI. NEW VIEWPOINTS ON PROTEIN NUTRITION AFTER 1900

About the year 1900 the protein element in nutrition assumed new aspects. Had someone written a good history of the progress of thought and experiment in animal nutrition and the chemistry of foods, progress would have been advanced by more than a decade. It has been mentioned that Mulder, Liebig, Voit, Henneberg and their followers assumed that protein from every source had the same nutritive value. That this could not be true had been shown in 1818 by Braconnot[24], who reported that one kind of amino acid, glycine, was crystallizable from the mixture formed by hydrolysis of gelatin and another kind, leucine, crystallized from the mixture derived from hydrolysis of muscle or wool with sulphuric acid. Further evidence that proteins differed in composition was reported in 1872 by O. Nasse[25], who hydrolysed with sulphuric acid several kinds of proteins from plant and animal sources, then made the solution alkaline and distilled and measured the ammonia which came over. The amounts of ammonia yielded by his samples differed so much that there could be no doubt that proteins manifested strongly contrasting chemical composition. This being the case, reflection should have convinced investigators that they had different nutritional values. These facts were completely ignored for many years.

In 1886 Schulze and Steiger[26] first used phosphotungstic acid to precipitate an amino acid from an aqueous extract of germinating seeds. From the precipitate they isolated arginine. Drechsel, Kossel and

Hedin later employed this reagent for precipitating basic amino acids and discovered lysine and histidine. Hausmann (1900)[27] applied the method of Nasse, and of Schulze and Steiger to measure the amounts of ammonia and of basic amino acids in several protein hydrolysates. The results were so contrasting with respect to both these types of nitrogenous substances that it convinced biochemists that proteins must have different nutritive values since certain of them were so differently constituted.

Willcock and Hopkins[28] in 1906 demonstrated by experiments with mice the importance of the amino acid tryptophan in nutrition. Hopkins and Cole had recently discovered it and had found that it gave a certain colour reaction with a reagent which had long been employed as a test for protein. Zein, the principal protein of maize, did not give this colour test, which indicated that it did not yield tryptophan on digestion. They employed a "synthetic" diet in which the sole protein was zein. Mice were able to survive on an average only fourteen days on the basal diet, but with a supplement of tryptophan they survived twenty-eight days.

About 1902 E. Fischer devised a method for fractionally distilling the ethyl esters of various amino acids contained in protein hydrolysates. Partial separation of amino acids was effected by this means. Although it was far from giving quantitative results, this method of analysis clearly showed that different proteins yielded strongly contrasting amounts of various amino acids. This confirmed the conclusions of others mentioned above. In the light of the new observations it became evident that the nutritive values of proteins depended on their yield of amino acids in terms of the nutritive needs of the body for each. Evidently nitrogen multiplied by a factor did not represent the same nutritional values in proteins from different sources.

In 1909 Osborne and Mendel[29] began their experiments on Osborne's collection of purified proteins. Using rats as their subjects and growth and reproduction as criteria, they sought to determine the relative values of a wide variety of proteins. They first attempted to use a diet of purified food substances. Having failed in this they next used a diet containing 28·3 per cent of whey solids prepared by heating acidified whey to coagulate lactalbumen, filtering and evaporating the filtrate to dryness. This adjuvant provided all water-soluble vitamins and a favourable mixture of inorganic compounds together with some vitamin A. By feeding young rats this basal diet to which different purified proteins were added, they dramatized the fact that proteins were, indeed, as different in biological values as the chemical analyses had suggested they should be. The studies of Hopkins and of Osborne and Mendel formed one of the monuments on the path of nutrition investigations.

1. The "Biological Analysis" of Cereals

In farm practice in America pigs were often fed exclusively on corn (maize), on which they did not make satisfactory gains. In 1912 McCollum (1957*d*)[30] undertook to determine whether it was possible to identify the nature of the shortcomings of this cereal when it served as the sole food for rats. Amino acid requirements and different composition of proteins were then much discussed. The discovery of the fat-soluble vitamin A afforded another factor the distribution of which it was desirable to study. McCollum had noted that the ashes of all cereals were very low in calcium, and might not be adequate for growing pigs. Animal husbandry studies had shown that bone size could be improved by supplements of calcium compounds.

On the basis of these ideas, McCollum compared the effects on young rats of feeding (1) corn alone, (2) corn plus a calcium salt, (3) corn plus a protein (casein) to provide additional amino acids, (4) corn plus butter fat to provide the new fat-soluble nutrient. Rats given rations (2), (3) and (4) were distinctly better nourished than on ration (1). When they were given corn plus both calcium and protein, or calcium and butter fat, or protein and butter fat, they were in decidedly better condition than when given only one supplement, but they still did not grow at the maximum rate nor present the healthy appearance which they presented when given all three supplements. These results showed that several dietary factors in corn were present at far below optimum levels. Comparable experiments with wheat and rolled oats demonstrated that the three cereals were similar in their dietary properties. They were all improved by the same supplements.

The response of young rats to rolled oats plus the three supplements was less satisfactory than with wheat and corn. The cause of this remained unexplained for some years. It was eventually shown to be due to the riboflavin deficiency of the oat kernel.

VII. SUPPLEMENTARY RELATIONS AMONG COMMON FOODSTUFFS

McCollum and his co-workers investigated the effectiveness of various combinations of natural foods. They observed that combinations of two or more cereal grains when fed to young rats were not superior to the grains fed singly. This was easily explained on the basis of their having like deficiencies. But the combination of a cereal grain with the leaf of a plant (alfalfa leaf flour) yielded a mixture of nutrients which nourished young rats far better than did any combination of seeds. It became clear that the leaf of a plant is very differently constituted as a source of dietary essentials from any seed and that it serves as an excellent supplement to the latter. This discovery afforded an explanation of the soundness of the practice of some farmers of feeding growing pigs corn or other cereal while allowing them daily access to green forage plants as pasture. The experiments with rats demonstrated no new fact, but afforded an understanding of the basis of a sound agricultural system of swine production already believed in by some intelligent farmers. These new viewpoints McCollum presented in a lecture before the Harvey Society (New York) in 1917[31].

1. Dietary Deficiencies of Polished and of Whole Rice

In 1915 McCollum and Davis[32] reported the results of supplementing polished rice with the same additions that improved whole rice and other cereals as food for the growing rat. They found that these supplements were insufficient for polished rice. In addition a water extract of some natural food was necessary to support well-being in the animals. Since they had become acquainted in 1913 with the studies of Eijkman, Grijns *et al.* through the publication of E. B. Vedder's Cartwright Prize Essay, *Beriberi*[22], and Funk's *Die Vitamine*[23], they assumed that the water-soluble substance required by rats fed polished rice supplemented with chemically characterized nutrients was identical with the anti-beriberi factor of the Dutch investigators. After further experimenting McCollum and Kennedy (1917) asserted their belief that only two unidentified food factors existed, viz., the fat-soluble factor, vitamin A, and the factor preventive of beriberi.

The two-vitamin hypothesis was widely accepted for a few years. However, H. H. Mitchell, A. G. Hogan, and A. D. Emmett, working independently, produced convincing evidence that at least two unidentified dietary factors were contained in the water extracts of natural foods. The time had arrived when interest in nutrition studies was to increase greatly and at a rapid rate, and the new viewpoints were voiced by several men who, collectively, broadened the outlook in this field. These will be briefly mentioned.

2. A. F. Hess's Contribution to Knowledge of Infantile Scurvy

From the observations of Lind (1753) it had been known that scurvy in man could be prevented or cured by fresh fruits or vegetables, and Holst and Froelich had produced experimental scurvy in guinea pigs in 1907, by dry or cooked diets, but the medical profession, even as late as 1915, was not in general taking measures to prevent scurvy in infants since it had but recently appeared. After about 1890 ordinances requiring pasteurization of milk sold in cities became common, and bottle-fed babies often developed the disease. About 1914 A. F. Hess[32], paediatrician to a foundling home, saw many cases of scurvy among his patients who were fed pasteurized or boiled milk and barley-water. Influenced by the work of Holst and Froelich, he rediscovered the fact that heated foods for infants must be supplemented with fresh fruit or vegetable juices in order to safeguard the health of the blood-vessels. Having convinced himself of the widespread error in the feeding of bottle babies and young children, then common, he devoted himself to making known his system for safeguarding infants against scurvy. The fact that rats, swine and other animals generally employed for experiments with foods at that period remained in health on dried foods confused most investigators of nutrition.

3. Pellagra Proved to be a State of Malnutrition

Although pellagra had been long known it did not constitute a great human scourge in the United States until after 1900. Opinions among medical men differed widely as to its cause. The theories that it was caused by eating mouldy maize, that it was an infection, and that it was a manifestation of sensitization to sunlight were the principal ones discussed.

First to describe the cure of pellagrins by dietetic treatment was Voegtlin (1914)[33]. But the conclusion of the Thompson–McFadden Commission, after several years of epidemiological study, that the disease was caused by the bite of the stable fly, prevented Voegtlin from making much impression on medical opinion. Joseph Goldberger was the outstanding investigator who supplied incontrovertible evidence that the disease was caused by some deficiency in the diet (1915*a*, *b*, 1916, 1925, 1928*a*, *b*)[34]. The experimental study of pellagra in man was complicated by the frequent occurrence of riboflavin deficiency among sufferers from the disease, and also by the development of bronzing of the skin only when it was exposed to sunlight. Hence symptoms of pellagra were not uniform and accordingly clinicians were confused in their diagnoses.

As in the case of other deficiency diseases later to come to light, the solution of the pellagra problem was achieved through the experimental production of the disease in an animal followed by systematic study of the factors involved in its aetiology. First to discover in dogs what he believed to be the analogue of pellagra in man, was T. N. Spencer, a veterinarian in North Carolina. In 1916[35] he reported his conclusions concerning the cause and nature of "blacktongue" in dogs, and described the cure of the