NUTRITION:
THE CHEMISTRY OF LIFE

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NUTRITION:

The Chemistry of Life.

BY

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TO

A. F. M.

PREFACE

THE Charles M. Hitchcock Endowment Fund was established by the late Mr. Hitchcock as an endowment for "a professorship in the University of California for free lectures upon scientific and practical subjects but not for the advantage of any religious sect nor upon political subjects." The present volume constitutes the thirteenth course of lectures on this foundation. They were announced under the title of "Viewpoints in the Study of Nutrition." The author has not attempted to present an elaborate summary of the current knowledge of the subject. The lectures represent merely an effort to indicate some of the more recent contributions to the science of nutrition and also some problems which await further study.

The writer acknowledges with appreciation the generous support of the Carnegie Institution of Washington, D. C., which has made possible some of the studies referred to in these lectures.

L. B. M.

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I.

THE SCIENCE OF NUTRITION: A RETROSPECT

IN an essay on physiology and national needs Professor F. G. Hopkins[1] wrote:

In many departments of human knowledge the teaching and guidance of science are accepted as final, because in these departments the knowledge arose in the first instance from scientific studies and from these alone. Progress in such categories depends entirely upon controlled and recorded observation or upon experiment, and these are the methods of science.

It is otherwise, one might be tempted to say, in regions where mankind can claim abundant and accumulated empirical experience. In connexion with his own nutrition Man's experience has been—needless to say—coterminous with his whole existence. Science may explain that experience, but is unlikely, it might seem, to improve upon experience as a guide. It may supply theory, but where experience has been so great and so continuous it seems unlikely that it could do much to guide practice. This consideration, consciously or subconsciously, accounts, I think, for a widespread feeling that the teachings of science about our food supply are of academic interest only. (P. 27.)

Human welfare is closely bound up with the provision of food, shelter and clothing; and in the orderly conduct of our daily life the nutrition as well as the various forms

[1] Hopkins, F. G.: *Physiology and National Needs,* edited by W. D. Halliburton, Constable and Company, London, 1919.

of activity of the body play an important part. The problems of nutrition therefore quite properly constitute a subject of pertinent interest and inquiry which has engaged the attention of man from early times. He is not always content with the mere knowledge of facts—with the simple observation of phenomena; the thinking person soon seeks to ascertain not only *what* happens but also *why* it occurs. The ever recurring question of what the fundamental character of our nutrients is and why certain substances are nutritious has given rise to varied answers. These are reflected in the history of the science of nutrition.

What, then, constitutes a food? As early as the time of Hippocrates (460-370 B.C.) there existed a belief in the occurrence of some specific universal nutrient substance present in the various products that enter into the dietary and abstracted therefrom through the alimentary functions. The idea persisted in many quarters until the early part of the last century. How it was formulated in a popular textbook as late as 1813 is indicated by the following quotation from the American edition of Richerand's *Elements of Physiology:*[2]

> By aliment is meant whatever substance affords nutrition, or whatever is capable of being acted upon by the organs of digestion. Substances which resist the digestive action, those which the gastric juice cannot sheathe, whose asperities it cannot soften down, whose nature it cannot change, possess, to a certain degree, the power of disturbing the action of the digestive tube, which revolts from whatever it cannot overcome. . . . However various our aliments may be, the action

[2] Richerand, A.: *Elements of Physiology,* translated from the French by De Lys, G. J. M., Thomas Dobson, Philadelphia, 1813.

of our organs always separates from them the same nutritious principles; in fact, whether we live exclusively on animal or vegetable substances, the internal composition of our organs does not alter; an evident proof, that the substance which we obtain from aliments, to incorporate with our own, is always the same, and this affords an explanation of a saying of the father of physic. "There is but one food, but there exist several forms of food." (P. 87.)

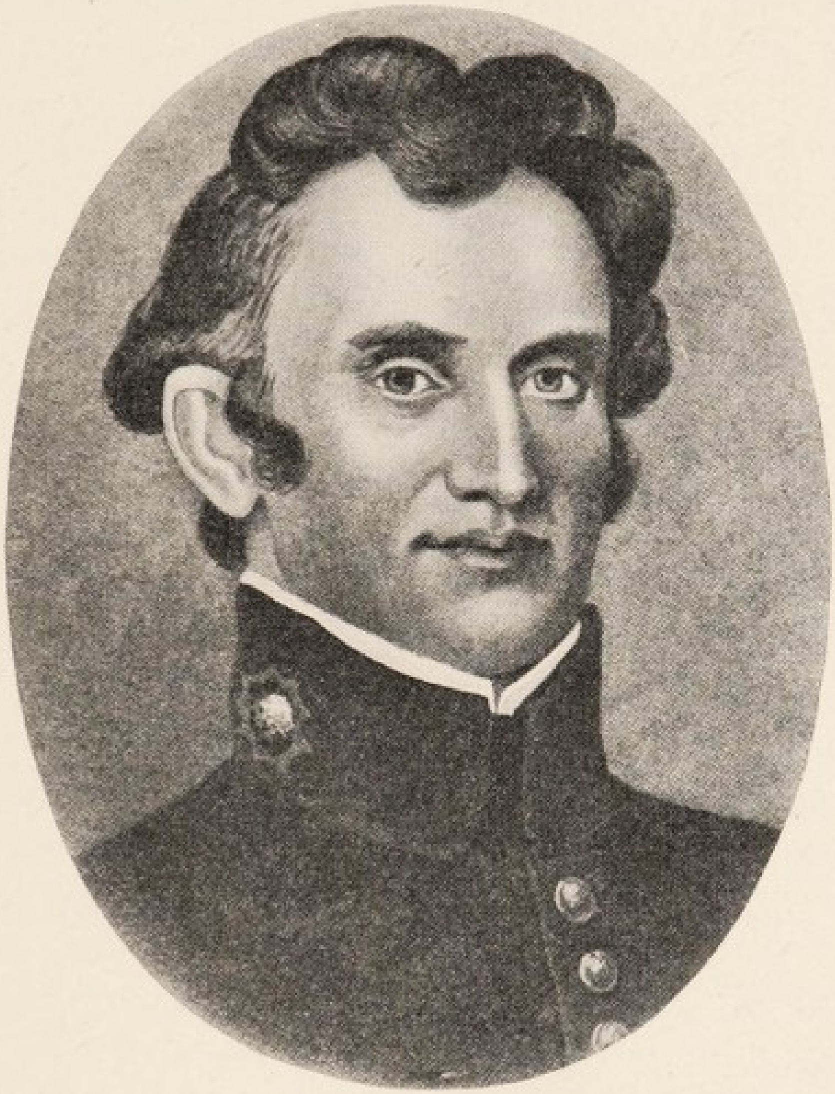
How far away from the subsequent conceptions of nutritive values such writers on nutrition were is indicated by the following further quotation from Richerand:

Attempts have been made to ascertain the nature of this alimentary principle, common to all nutritive substances, and it is conjectured, with some probability, that it must be analogous to gummy, mucilaginous, or saccharine substances; they are all formed from hydrogen and carbon, are well known to differ chemically, only in the different proportions of oxygen which they contain. Thus, sugar is a kind of gum, containing a considerable quantity of oxygen; and which is reduced, in a certain degree, to the state of starch, when brought to a very fine powder by means of a rasp, for, the friction disengaging a portion of its oxygen, deprives it in part of its flavour, and leaves it an insipid taste, similar to that of farinaceous substances. Nothing, in fact, nourishes better, more quickly, and from a smaller bulk, than substances of this kind. The Arab crosses the vast plains of the desert, and supports himself by swallowing a small quantity of gum arabic. The nourishing quality of animal and vegetable jellies is well known; saccharine substances soon cloy the appetite of those who are fondest of them. In decrepid old age, some persons live exclusively on sugar; I know several in that condition, who spend the day in chewing this substance, which is a laborious employment for their feeble and toothless jaws. Lastly, milk, the sole nourishment of the early periods of life, contains a great proportion of gelatinous and saccharine matter. (P. 88.)

The same fundamental viewpoint is expressed by Dr. William Beaumont in his classic studies of Alexis St. Martin, published in this country in 1833.[3] Although there were intimations in the publications of Haller before the end of the eighteenth century that the different substances in foods have unlike nutritive significance Beaumont had evidently not become converted from the Hippocratean doctrine. Thus he wrote:

The ultimate principles of nutriment are probably always the same, whether obtained from animal or vegetable diet. It was said by Hippocrates, that "there are many kinds of aliments, but that there is at the same time but one aliment." This opinion has been contested by most modern physiologists; but I see no reason for scepticism on this subject. Some imperfect experiments which I instituted on the operations of the hepatic and pancreatic juices, and which will be found in a subsequent part of this volume, tend to throw some light on the subject. Chyme was submitted to the action of these fluids, and they invariably produced similar effects. A fluid was separated, varying slightly in colour, but of the same apparent consistence and identity; and was increased or lessened in proportion to the quality of the food of which the chyme was formed. Whether this fluid was or was not imperfectly formed chyle, is a matter of opinion only. The circulating fluids of the system are always nearly the same, in health, and that which goes to supply and replenish them, should consequently possess the same invariable properties. Chyle, after its separation in

[3] Beaumont, William: *Experiments and Observations on the Gastric Juice, and The Physiology of Digestion,* F. P. Allen, Plattsburgh, 1833.



WILLIAM BEAUMONT

(Reproduced from Myer's *Life and Letters of Dr. William Beaumont.*)

the intestines, is probably further changed and perfected by the action of the lacteal absorbents and sanguiferous vessels, before it is completely assimilated. Chyme, from which this nutrient principle is obtained, is a compound of gastric juice and aliment. It may be regarded as a *gastrite* of whatever it is combined with, varied according to the kind of aliment used. The perfect chyle, or assimilated nutriment, probably contains the elements of all the secretions of the system; such as bone, muscle, mucus, saliva, gastric juice, etc., etc., which are separated by the action of the glands, the sanguiferous and other vessels of the system. (P. 36.)

"Assimilation" has been one of numerous vague expressions with which the science of nutrition has conjured since before the days of Galen (131-201 A.D.). In the earlier period it referred to a process whereby the varied constituents of the organism were supposed to arise from the single universal aliment already referred to. The word "assimilate" itself implies transformation into a product resembling something else—in this case, the tissue components. How the "ultimate principles of nutriment" were supposed to be "assimilated" to form the "perfect chyle" through digestive and other agencies has already been indicated in the quotation from Beaumont's monograph.

It remained for the rapid development of chemistry—the beginning of biochemistry in its present significance—finally to dispel this belief in a single, universal food principle. The change came a century ago with the better realization of the existence of unlike types of substances in the products termed foods. Thus William Prout (1785-1850) considered that all organized bodies are constituted of three great staminal principles—saccharina, oleosa, albuminosa—all found in milk, the prototype of a perfect food.

One may recognize here the earlier development of the classification of foodstuffs in vogue today. In his Bridgewater Treatise on *Chemistry, Meteorology, and The Function of Digestion*, printed at Philadelphia in 1834, Prout stated:

Organized matters, however apparently dissimilar, yet, chemically speaking, are often nearly related. Of this relation we gave as an example, the composition of the extensive class of substances, denominated the *saccharine group;* all of which, notwithstanding the endless diversity of their appearance, we showed to be essentially alike in their composition, and to consist of carbon associated with water. Saccharine substances are chiefly found in the vegetable kingdom, of which they form the characteristic staminal principle.

Another well known class of bodies, existing both in vegetables and in animals, are those whose character is *oily*. Oleaginous bodies occur in an infinite variety of forms, some being solid, others fluid; yet, in every instance, their peculiar properties are so strongly marked, that we seldom hesitate about their nature. In this distinctness of outward appearance, oily bodies are strongly contrasted with the saccharine group before mentioned; many of which have few *apparent* and sensible properties in common. The composition of all the bodies of this oleaginous group, which we have hitherto had an opportunity of examining in a satisfactory manner, we have found to be essentially the same: they are either composed of olefiant gas and water, or have a reference to that composition. Such is also the composition of the well known proximate principle termed *spirit of wine,* or *alcohol;* into which, most substances belonging to the saccharine group, under favourable circumstances, are readily convertible by the process termed fermentation.

When almost any part of an animal body (with the exception perhaps of those matters of a purely oleaginous character) is boiled in water, it is separated into two portions,—one soluble in water, and forming with the water a tremulous jelly, or *gelatine*—the other remaining insoluble, indeed becoming harder, the longer it is boiled; and which, from the identity of its properties to those of the white of an egg, is denominated *albumen*. These animal principles exist in very different proportions in the different textures; some of these textures, as the skin, being convertible almost entirely into gelatine; while others yield comparatively little gelatine, and consist principally of albumen. In no animal compound does gelatine exist as a fluid; hence, it has been supposed to be produced by boiling; but the supposition does not appear to be well founded. One of the most remarkable properties of gelatine is its ready convertibility into a sort of sugar, by a process similar to that by which starch may be so converted. Gelatine may be considered as the least perfect kind of albuminous matter existing in animal bodies; intermediate, as it were, between the saccharine principle of plants, and thoroughly developed albumen: indeed, gelatine in animals, may be said to be the counterpart of the saccharine principle in vegetables. Albumen exists in the fluid state as a component of the blood: small quantities of fluid albumen are also contained in certain animal secretions: but there is much more of the principle in a solid state; forming what is termed coagulated albumen. The blood likewise contains *fibrin,* another modification of the albuminous principle, in a fluid, or at least in a suspended state: though the most frequent condition of fibrin, is that of a tough fibrous mass, in which condition, together with albumen, it forms the basis of the muscular or fleshy parts of animals. The *curd* of milk is also a modification of the albuminous principle. Another modification of the same principle is the substance called *gluten;* this substance though most abundant in vegetables, so far resembles the fleshy parts of animals, as to be, in like manner, capable of separation into two portions, analogous to gelatine and albumen. Neither of these modifications of albumen exhibits the quality possessed by gelatine, of being artificially convertible into saccharine matter; at least by any known process; but all of them, including gelatine, differ from the oleaginous and the saccharine principles, in this respect; that they contain a fourth elementary principle, namely, azote. The exact composition of the albuminous group cannot at present be stated. (P. 257.)

To Prout it seemed logical to assume that inasmuch "as all the more perfect organized beings feed upon other organized beings their food must necessarily consist of one or more of the above three staminal principles." Thus it appeared that the proximate principles apparently identical in the various structures serving as food become transferred as such into the organism which consumes them; in other words, the body is constructed directly of the foodstuffs ingested. The doctrine of a single specific aliment thus gave way to the view that there are several nutrient principles. It is interesting to read Prout's interpretation of the "wisdom" of this order of nature. He writes:

It may be considered as a general rule, that organized beings adopt, as aliments, substances lower than themselves in the scale of organization. . . . Thus plants, and perhaps the very lowest kinds of animals, have the power of assimilating carbonic acid gas: the powers of assimilation of plants, and of such animals, may also extend to other inorganic compounds of carbon—indeed they seem to derive their chief nourishment from matters of that nature. Higher in the zoological scale, we find that animals almost invariably prey on those that are inferior to themselves, either in magnitude, in organization, or in intelligence; till we arrive at man himself. He, as his necessities, or as his fancies may dictate, appropriates every nourishing substance, even carbonic acid gas; which his stomach, perhaps in common with that of all animals, seems to have the power of assimilating. Of course a lion, or even a crab, can feed on the body of a man, as well as on that of an ox or of an insect. But no one, we presume, will assert, that man is the natural prey or food of these animals; and that alone is the degree of immunity, for which we here contend: for in all the operations of nature, we must try to discover and bear in mind, not the exception, but the rule; otherwise we shall be constantly liable to error.

By this beautiful arrangement in the mode of their nutrition, the more perfect animals are exonerated from the toil of the initial assimilation of the materials composing their frame; as in their food, the elements are already in the order which is adapted for their purpose. . . .

Another great purpose is effected by this arrangement without which, organization, at least as at present constituted, could hardly exist. If organized beings did not prey on each other, their remains would, in time, accumulate in such quantity as to be nearly incompatible with life; certainly with animal life in its most perfect condition, as it is at present known to us. But by the arrangement that animals are food to each other, not only is an opportunity afforded for the existence of a greater number of animals, and of a greater variety among them; but the obtrusion of the bodies of animals, in whom life has become extinct, is entirely prevented: nor is the removal of the dead animal matter the only good accomplished, but many other important results are obtained. To enter upon the consideration of these, would be foreign to our present object:

there is, however, one consequence of this system of universal voracity, which more immediately concerns us, since it is of a nature so comprehensive, as to suggest a natural classification of alimentary substances; we allude to the similarity of composition among the staminal principles which constitute the fabric of organized beings. (P. 256.)

There is no intimation, in Prout's theory of nutrition, of any special difference in the nutritive functions of the "staminal principles" to which he refers. "A diet to be complete," he remarks, "must contain more or less of all the three staminal principles." And he adds:

The composition of the substances, by which animals are usually nourished, favours the mixture of the primary staminal alimentary principles; since most of these substances are compounds, of at least two, of the staminal principles. Thus, most of the gramineous and herbaceous matters contain the saccharine and the glutinous principles; while every part of an animal contains at least albumen and oil. Perhaps, therefore, it is impossible to name a substance constituting the food of the more perfect animals, which is not essentially a natural compound of at least two, if not of all the three great principles of aliment. But it is in the artificial food of man that we see this great principle of mixture most strongly exemplified. He, dissatisfied with the spontaneous productions of nature, culls from every source; and by the force of his reason, or rather of his instinct, forms in every possible manner, and under every disguise, the same great alimentary compound. This after all his cooking and his art, how much soever he may be disinclined to believe it, is the sole object of his labour; and the more nearly his results approach to this object, the more nearly do they approach perfection. Even in the utmost refinements of his luxury, and in his choicest delicacies, the same great principle is attended to; and his sugar and flour, his eggs and butter, in all their various forms and combinations, are nothing more or less, than disguised imitations of the great alimentary prototype MILK, as furnished to him by nature. (P. 260.)

It was the great desert of Magendie (1783-1855) to have demonstrated the unlike nutritive values of the three foremost groups of foodstuffs still accepted today. I sometimes feel that too little recognition is being accorded nowadays to the pioneer efforts of this French physiologist who has been designated as the founder of modern experimental investigation in the science of nutrition. His work, carried out between the period of Lavoisier's epoch-making discoveries in chemistry and that of Liebig's widely heralded contributions to physiology, has been largely overshadowed. Magendie was among the first to differentiate between various kinds of foods. To him is due the clear distinction between the nitrogenous and non-nitrogenous groups. He conducted experiments in which animals were fed on diets consisting essentially of non-nitrogenous food materials—sugar, gum, olive oil, butter, etc.,—and observed failure of nutrition in every case. The untoward outcome was not due to the lack of formation of "chyle"—the supposed symbol of "assimilated nutriment" in the writings of earlier physiologists. From his researches he concluded that the nitrogen of the tissues is derived from food nitrogen and that non-nitrogenous foods are not converted into nitrogenous components in the organism.

Magendie also stressed the presence of nitrogenous substances in many of the food products of vegetable origin. This emphasis upon the possible physiological significance of the nitrogenous foods served to supplement the entirely different work of Lavoisier, Dulong, Des-

FRANÇOIS MAGENDIE

(Reproduced from *Some Apostles of Physiology* by William Stirling.)

pretz and others which laid the foundations for the modern theory of metabolism. It is easy to understand, in the light of present-day knowledge, wherein many of the experiments of Magendie and his contemporaries were incorrectly planned and why they were bound to give inconclusive or even fallacious answers. Their labors preceded the firm establishment of the doctrine of the Conservation of Energy; they overlooked the importance of other food factors which are appreciated today. But after all, the method of Magendie is essentially that pursued at present whenever it is desired to depart from statistical inquiry and subject a theory to the direct test of experiment.

The recognition of the relative importance of the nitrogenous foods for nutrition ushered in a new era of progress; indeed, before long it brought about, as we shall learn, a glorification of the albuminous substances—an apotheosis which has persisted in its extreme form almost until the present time. The Dutch physiological chemist, G. J. Mulder (1802-1880), who coined the name "protein" in 1839,[4] early recognized the resemblance between the albuminous substances that can be extracted from animal and plant tissues respectively. In *The Chemistry of Animal and Vegetable Physiology* he wrote:

In both plants and animals a substance is contained, which is produced within the former, and is imparted through their food to the latter. To both, its uses are numberless. It is one of the most complicated substances, is very changeable in com-

[4] Mulder, G. J.: *Jour. f. prak. Chem.*, 1839, xvi, 129. Students of nutrition may be interested to read the paragraph containing the original suggestion of this word, which is reproduced in facsimile on page 16.

G. J. MULDER

(Reproduced from a photograph in the possession of the author.)

position under various circumstances, and hence is a source of chemical transformations, especially within the animal body, which cannot even be imagined without it. It is unquestionably the most important of all known substances in the organic kingdom. Without it no life appears possible on our planet.

XXXV.

Ueber die Zusammensetzung einiger thierischen Substanzen.

Von

G. J. MULDER.

(Bullet. de Néerlande p. 104.)

Ich habe mich seit einiger Zeit mit der Untersuchung der wesentlichsten Substanzen des Thierreiches, des Faserstoffes, des Eiweissstoffes und der Gallerte beschäftigt. Seit der Bekanntmachung dieser Arbeit fuhr ich fort, diese Körper zu untersuchen. Berzelius theilte mir über die veröffentlichten Resultate einige Bemerkungen mit und ertheilte mir gute Rathschläge, für welche ich ihm meinen aufrichtigen Dank sage.

- -

Das Atomgewicht der Substanz ist nach I. 57971, nach II. 55458, nach III. 53622.

Es ist also kein Zweifel mehr, dass das Atomgewicht gehörig bestimmt ist. Die organische Substanz, welche in allen Bestandtheilen des thierischen Körpers, so wie auch, wie wir bald sehen werden, im Pflanzenreiche vorkommt, könnte *Proteïn* von *πρωτεῖος*, *primarius*, genannt werden. Der Faserstoff und Eiweissstoff der Eier haben also die Formel $\bar{P}r + SP$, der Eiweissstoff der Serums $\bar{P}r + SP$.

(From *Journal für praktische Chemie*, 1839, Vol. 16, pp. 129 and 138.)

Through its means the chief phenomena of life are produced.

It is present in all parts of plants, in roots, stems, leaves, fruits, and in their several saps. It is contained in very unlike parts of the animal body. In plants it assumes three different forms, in which it is either soluble in water, or insoluble in water, or soluble in alcohol. In animals it also exists in various forms, being either soluble or insoluble in water. In the insoluble form its structure is variable. It forms different compounds with sulphur, with phosphorus, or with both,—and hence the differences it presents in appearance and physical properties. This substance has received the name of *protein,* because it is the origin of so many dissimilar bodies, and is itself therefore a primary substance. (P. 291.)

More than half a century later the belief that the nitrogenous factor plays the preeminent rôle in nutrition was still voiced in the statement that "the life-processes consist in the metabolism of the proteins."[5]

The earliest attempts to formulate direct comparisons of feeding stuffs for use in animal nutrition were the summaries of so-called hay values published by Thaer in Germany in 1809. Inasmuch as good meadow hay was universally regarded as a complete feed suitable for most feeding purposes in agricultural practice, efforts were made to establish from the results of experience and experiment what amounts of different feedstuffs would replace a unit weight of hay. The sum of the ingredients extractable with water, alcohol, dilute acids and dilute alkalies was taken, without distinction as to kind, to represent the nutritive value, and the hay values were computed in proportion to them.[6] Boussingault (1802-1887), who published his *Économie Rurale* in 1844, was so highly impressed by the importance of the nitrogenous constituents of the rations of the domestic animals that he rated feeds largely in accordance with their content

[5] Verworn, M.: *General Physiology,* 1899.

[6] For a discussion of the subject see Armsby, H. P.: *The Nutrition of Farm Animals,* New York, 1917, p. 591.

of nitrogen, although he realized that the non-nitrogenous constituents are not without value. He wrote:

> The alimentary virtues of plants reside above all in the nitrogenous substances, and consequently their nutritive potency is proportional to the quantity of nitrogen entering into their composition. . . . I am far from believing that nitrogenous substances alone are sufficient for nutrition; but it is a fact that a highly nitrogenous vegetable food is usually accompanied by other organic and inorganic constituents, useful or indispensable to nutrition. (*Économie Rurale,* ii, 263, Paris, 1851.)

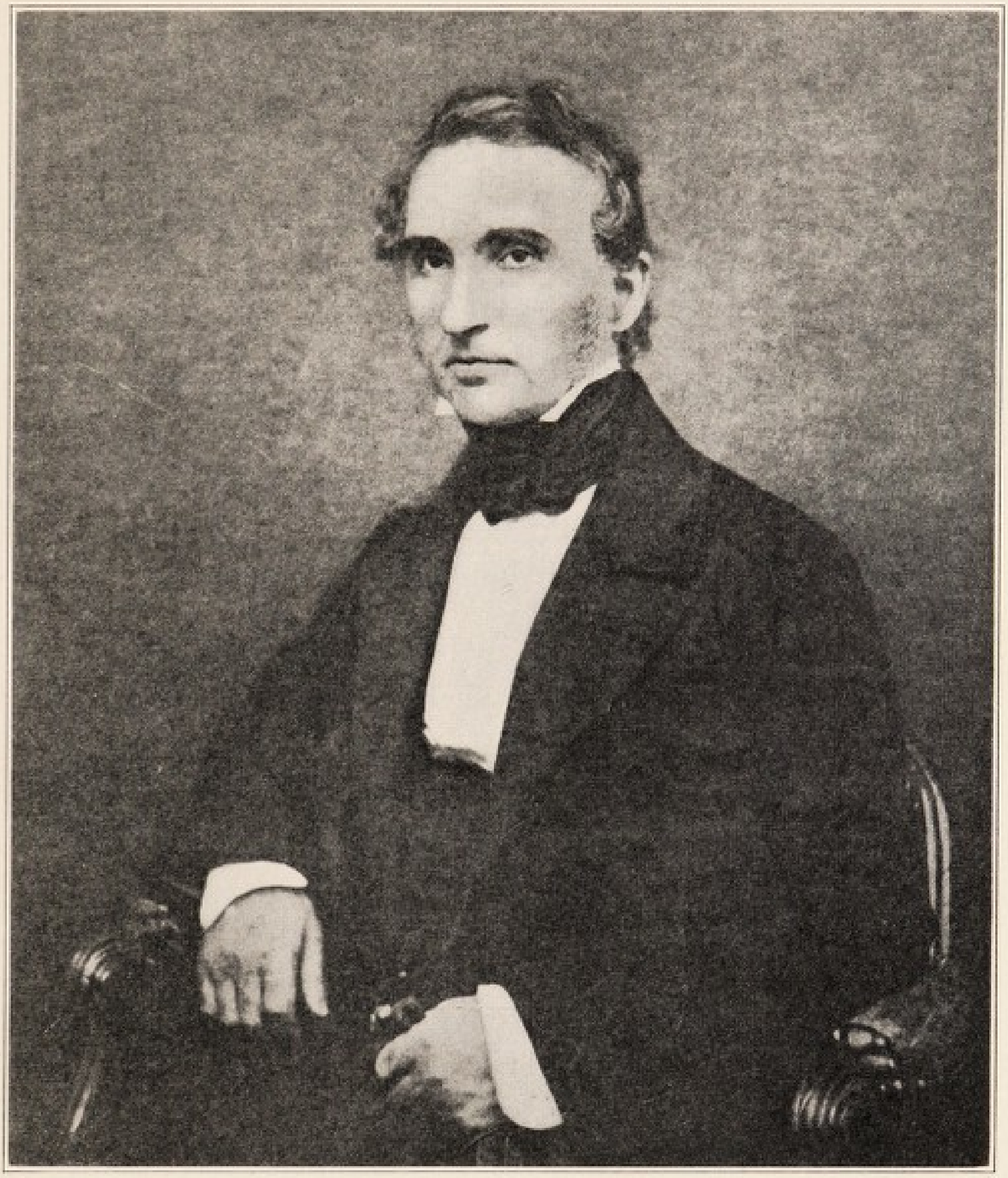
A specimen portion of one of Boussingault's charts showing the comparisons of agricultural foods in terms of equivalents based on the nitrogen content is reproduced here.

TABLEAU

DE LA CONSTITUTION DES SUBSTANCES VÉGÉTALES ALIMENTAIRES.

DÉSIGNATION.	EAU.	PHOSPHATES et autres sels.	LIGNEUX et cellulose.	MATIÈRES GRASSES.	AMIDON, SUCRE ou analogues.	ALBUMINE, legumine, caseine.	AZOTE.	EQUIVALENTS nutritifs déduits de l'azote.	MATIÈRES NUTRITIVES NON AZOTÉES en excès dans l'équival.	manquant dans l'équival.	Paille à ajouter pour compléter l'équivalent.
Foin de prairie.	13,0	7,6	24,4	3,80	44,4	7,2	1,15	100	»	»	»
Regain de foin.	14,1	8,0	21,5	3,50	40,5	12,4	1,98	58	»	25	51
Trèfle rouge en fleurs, fané. . . .	20,0	5,0	22,0	3,20	39,2	10,6	1,70	67	»	20	44
Trèfle rouge en fleurs, vert.	77,0	1,4	6,5	0,90	11,5	3,1	0,50	230	»	20	44
Trèfle rouge avant la fleur, fané.	12,2	8,1	21,1	4,00	41,5	13,5	2,13	54	»	24	53
Id. en vert.	82,4	1,6	4,2	0,80	8,3	2,7	0,43	267	»	24	53
Luzerne en fleurs, fanée.	15,0	5,7	22,0	3,50	41,8	12,0	1,92	60	»	21	47
Id. en vert.	80,4	1,3	5,1	0,80	9,6	2,8	0,45	256	»	21	47
Paille de froment (Alsace).	26,0	5,1	28,9	2,20	35,9	1,9	0,30	383	98	»	»

Specimen portion of one of Boussingault's charts.



JUSTUS VON LIEBIG

(From an autographed photograph in the possession of the author.)

To the teachings of Liebig (1803-1873) above all others, however, is due the prominence which began to be attached before the middle of the last century to the nutritive rôle of proteins. He regarded the blood—the immediate source of the organic products which are involved in the transformation of matter and energy in the organism—as the prototype of a real food. Thus Liebig wrote in his classic *Thier-Chemie:*[7]

> If it is borne in mind that the growth or increase of mass in the animal body, the development of its organs and their reproduction, proceed from the blood, that is, the constituent parts of the blood, only those substances can be designated foods which are capable of being converted into blood. The investigation of substances adapted to this purpose is accordingly restricted to the determination of the composition of foods and a comparison thereof with the make-up of blood. (P. 45.)

In the *Familiar Letters on Chemistry*[8] the dominant importance of protein is expressed as follows:

> Everywhere throughout organised nature, where animal life is developed, we find the phenomena of life depending on the presence of albumen. The continuance of life is indissolubly connected with its presence in the blood, that is, in the nutrient fluid.
>
> In so far as the notions of formation, nutrition, or the nutritive property are inseparable from that of a substance, whose properties and composition are collected in the word albumen; only those substances are in a strict sense, nutritious articles of

[7] Liebig, J.: *Die Thier-Chemie oder die organische Chemie in ihrer Anwendung auf Physiologie und Pathologie,* Braunschweig, 1846. (Dritte Auflage.)

[8] Liebig, J.: *Familiar Letters on Chemistry,* third edition, London, 1851.

food, which contain either albumen, or a substance capable of being converted into albumen.

If we look at alimentary substances from this point of view, we obtain a knowledge of a natural law of the most admirable simplicity. (P. 346.)

Again, in pointing out that vegetable as well as animal products contain more or less identical protein substances Liebig wrote:

How admirably simple, after we have acquired a knowledge of this relation between plants and animals, appears to us the process of formation of the animal body, the origin of its blood and of its organs! The vegetable substances, which serve for the production of blood, contain already the chief constituent of blood, ready formed, with all its elements. The nutritive power of vegetable food is directly proportional to the amount of these sanguigenous compounds in it; and in consuming such food, the herbivorous animal receives the very same substances which, in flesh, support the life of the carnivora. (P. 350.)

As Voit has pointed out, Liebig's exposition helped to make clear why hay in the diet of the herbivora can perform the same service as meat consumed by the carnivora: both foods contain albuminous substances which can replace proteins that may be destroyed in the body. For an adequate understanding of Liebig's conception of food values it is necessary, however, to refer to his theory of metabolism. To him the various physiological functions such as muscular contraction and glandular activity appeared to proceed at the expense of the albuminous tissue structures. Thus the source of the energy liberated when work is performed was referred by Liebig to the muscle protein. The function of nutrition from his standpoint, therefore, was to replace the destroyed tissue protein. How simple it seemed! And on the basis of such views Liebig early enunciated his formerly well-known classification of the foodstuffs into the nitrogenous and the non-nitrogenous groups. The former can be converted into blood; the latter lack this property. In his own words (*Thier-Chemie,* p. 120):

Out of the foods adapted to the formation of blood the constituents of the organs are built; the other foods serve under normal conditions of health to maintain the respiratory processes. The nitrogenous group are designated as *plastic* foods; the non-nitrogenous as *respiratory* foods. They are as follows:

Plastic Foods	*Respiratory Foods*
Plant fibrin	Fat
Vegetable albumin	Starch
Vegetable casein	Gum
Meat and blood of animals	Sugars
	Pectin
	Bassorin
	Beer
	Wine
	Brandy

Liebig himself has furnished this résumé of his conceptions:

If the albumen of the blood, which is derived from the plastic portion of the food, possessed in a higher degree the power of supporting respiration, it would be utterly unfit for the process of nutrition. Were albumen as such, destructible or liable to be altered, in the circulation, by the inhaled oxygen, the relatively small quantity of it, daily supplied to the blood by the digestive organs, would quickly disappear; and the slightest disturbance of the digestive function would of necessity put an end to life.

As long as the blood contains, besides albumen, other substances, which surpass it in attraction for oxygen, so long will the oxygen be unable to exert a destructive action on this, the chief constituent of the blood; and the significance of the non-nitrogenous part of the food is thus made clear.

Starch, sugar, and fat, serve to protect the organised tissues, and, in consequence of the combination of their elements with oxygen, to keep up the temperature of the body.

The sulphurised and nitrogenous constituents of food determine the continuance of the manifestations of force; the non-nitrogenous serve to produce heat. The former are the builders of organs and organised structures, and the producers of force; the latter support the respiratory process; they are *materials for respiration.*

The necessity for the simultaneous presence of both, of the plastic and respiratory materials, and for their due admixture, is now obvious. The sum of both, daily required by the body, depends on the amount of oxygen taken up; their relative proportion depends on the causes of loss of heat and expenditure of force. (*Familiar Letters,* p. 373.)

It may interest those concerned with the development of the home economics movement to know that Liebig early paid his tribute to the culinary art, not forgetting even in this instance, however, to refer to the blood-producing efficacy of a properly prepared meal. In his *Familiar Letters* he wrote:

Among all the arts known to man, there is none which enjoys a juster appreciation, and the products of which are more universally admired, than that which is concerned in the preparation of our food. Led by an instinct, which has almost reached the dignity of conscious knowledge, as the unerring guide, and by the sense of taste, which protects the health, the experienced cook, with respect to the choice, the admixture, and the preparation of food, has made acquisitions surpassing all that chemical and physiological science have done in regard to the doctrine or theory of nutrition. In soup and meat sauces, he imitates the gastric juice; and by the cheese which closes the banquet, he assists the action of the dissolved epithelium of the stomach. The table, supplied with dishes, appears to the observer like a machine, the parts of which are harmoniously fitted together, and so arranged, that, when brought into action, a maximum of effect may be obtained by means of them. The able culinary artist accompanies the sanguigenous matter with those which promote the process of solution and sanguification, in due proportion; he avoids all kinds of unnecessary stimuli, such as do not act in restoring the equilibrium; and he provides the due nourishment for the child as well as the old man, as well as for both sexes. (P. 449.)

Even today the belief is still widespread that the production of "flesh and blood" requires a liberal consumption of protein, which in turn is commonly interpreted to mean meat. Liebig's teachings abound in much that has spelled progress in scientific knowledge; but owing to the force of his great reputation many demonstrably wrong conceptions formulated by him were fostered unduly long. The doctrine that protein—and particularly the muscle protein itself—is the only source of the energy liberated in work has long been disproved. The artificial distinction between nitrogenous and non-nitrogenous foods as sources of energy is untenable. It was fallacious to teach that starch or fat do not serve nutrition, but merely facilitate the respiratory processes. In this con-

CARL VOIT

(Reproduced from an autographed photograph in the possession of the author.)

nection it may not be amiss to quote the clear-cut comment of Voit in his classic monograph on nutrition:[9]

The momentous consequence of this false conception was that at the time of its formulation and long thereafter attention was centered on protein, which was regarded as the chief and foremost foodstuff—indeed, as the sole one inasmuch as it alone was supposed to replace the losses entailed in the metabolism; and nutrition was regarded as identical with the reconstruction of tissue destroyed by work. (P. 339.)

And then Voit adds significantly in criticism of Liebig's views:

Thus the *one* universal and unchangeable aliment, preexisting in the food, as postulated by Hippocrates and the iatrochemist was replaced by protein which became endowed with exclusive nutritive powers and into which every nutritious substance had to be converted. (P. 339.)

Meanwhile much experimental progress was being made in the last third of the nineteenth century, notably by the Munich School of physiologists under the leadership of Carl Voit (1831-1908). It would take us too far afield to review their contributions in detail. The energy aspects of nutrition were becoming recognized and the "flexibility" of an adequate regimen, *i.e.*, the interchangeability of the organic foodstuffs to a certain extent, was demonstrated. In many respects Voit's definition, expressed in 1881, remains unchallenged today. He wrote:

The foodstuffs are those substances which bring about the deposition of a substance essential to the composition of the body, or diminish and avert the loss thereof. (*Die Ernährung*, p. 330.)

[9] Voit, C.: *Die Ernährung*. Hermann's *Handbuch der Physiologie*, vi, Part 1, Leipzig, 1881.

In explanation of this dual function of food in replacing losses or preventing them Voit referred to the older view that the sole use of the food components is to restore what has been destroyed within the organism. This, he says, is true when protein and fat are replaced after starvation; but the ingestion of food serves primarily, he adds, to avert loss because by being themselves consumed the constituents of the diet for the most part avert the necessity for the destruction of body tissues and thus protect the latter from disintegration. It matters not whether muscular activity or some other transformation of energy results; the question as to what forces are set into play by the transformations is not concerned in the definition of a food.

When Atwater, a pupil of Voit, compiled his widely circulated bulletin on *Methods and Results of Investigations on the Chemistry and Economy of Food*[10] in 1895 the energy-yielding functions were somewhat more directly emphasized as follows:

> Food may be defined as material which, when taken into the body, serves to either form tissue or yield energy, or both. This definition includes all the ordinary food materials, since they both build tissue and yield energy. It includes sugar and starch, because they yield energy and form fatty tissue. It includes alcohol, because the latter is burned to yield energy, though it does not build tissue. It excludes creatin, creatinin, and other so-called nitrogenous extractives of meat, and likewise thein or caffein of tea and coffee, because they neither build tissue nor yield energy, although they may, at times, be useful aids to nutrition. (P. 16.)

[10] U. S. Department of Agriculture, Office of Experiment Stations, *Bulletin 21*, Washington, 1895.

And one of the newer textbooks of nutrition states:

A foodstuff is a material capable of being added to the body's substance, or one which when absorbed into the blood-stream will prevent or reduce the wasting of a necessary constituent of the organism.

The foodstuffs are:

Proteins (including albuminoids).
Carbohydrates.
Fats.
Salts.
Water.

A food is a palatable mixture of foodstuffs which is capable of maintaining the body in an equilibrium of substance, or capable of bringing it to a desired condition of substance. The ideal food is a palatable mixture of foodstuffs arranged together in such proportion as to burden the organism with a minimum of labor. These definitions are Voit's. (Lusk, G.: *Science of Nutrition,* Philadelphia, 1917, p. 152.)

II.

THE IMPORTANCE OF "LITTLE THINGS" IN NUTRITION

VOIT pointed out what few before him seem to have recognized adequately, namely, that the chemical analysis of a substance does not necessarily afford any true index of its possible food value. The chemist, as such, can indicate the probabilities of nutritive worth suggested by his analyses; but they must nevertheless be tested by the expedient of physiological experimentation on man or animals. The foundations of the current theories of nutrition have been laid in actual feeding trials. The idea of a "balanced" ration which began to gain popularity a quarter of a century ago was based upon fragments of experimental evidence which showed: on the one hand the indispensability of protein and on the other the limitations to the necessity for large amounts thereof; the function of the mineral nutrients; the apparent isodynamic replacement of foods; and the actual energy needs under a great variety of circumstances. Theoretically it seemed easily possible therefore to construct a balanced ration largely on the basis of analytical data expressed in grams of digestible proteins, fats, carbohydrates and inorganic salts, and in total calories of metabolizable foodstuffs.

An elaborate investigation begun about fifteen years ago at the Wisconsin Agricultural Experiment Station[1]

[1] Hart, E. B., McCollum, E. V., Steenbock, H., and Humphrey,

presently showed in a most striking way that there are physiological values to a ration not measurable by the current chemical methods or dependent upon mere supply of available energy. The theory of the "balanced" ration which assumed, with a mathematical precision expressed in formulas, that a proper supply of carbohydrate, fats, and proteins with an adequate total energy intake will subserve an animal's requirements was put to a direct test. Comparisons were made of the effect of rations balanced from the corn, oat, and wheat plants respectively upon growth and reproduction in cattle. Rations restricted to the corn plant were highly successful for both growth and reproduction, while rations restricted to the wheat plant were disastrous to successful growth and reproduction. The tests with a ration made from the oat plant indicated at that time (1911) that it was not possible to make a highly successful ration from rolled oats and oat straw. McCollum, who participated in some of these feeding tests, has summarized the outcome as follows:[2]

The object was to determine whether rations for cattle so made up as to be alike insofar as could be determined by chemical analysis, but derived each from a single plant, would

G. C.: "Physiological Effect on Growth and Reproduction of Rations Balanced from Restricted Sources," *Res. Bull. 17*, Wis. Agr. Exp. Sta., 1911; Hart, E. B., McCollum, E. V., Steenbock, H., and Humphrey, G. C.: "Physiological Effect on Growth and Reproduction of Rations Balanced from Restricted Sources," *Jour. Agr. Res.*, 1917, x, 4, 175; Hart, E. B., Steenbock, H., and Humphrey, G. C.: "Influence of Rations Restricted to the Oat Plant on Reproduction in Cattle," *Res. Bull. 49*, Wis. Agr. Exp. Sta., 1920.

[2] McCollum, E. V.: *The Newer Knowledge of Nutrition*, Mac-

Bulletin 21, Washington, 1895.

prove to be of equal nutritive value for growth and the maintenance of vigor.

The ration employed for one group of animals was derived solely from the wheat plant, and consisted of wheat straw, wheat gluten and the entire wheat grain. The ration of a second group consisted of the entire corn plant, which included the kernel, stalk, and the leaf, together with a portion of corn gluten, a by-product of the cornstarch industry. The third group obtained their ration solely from the oat plant, being fed entirely on rolled oats and oat straw and leaf. There was a fourth group, which it was supposed would serve as controls, that was fed a ration having the same chemical composition, but derived from about equal portions of wheat, corn and oat products.

The animals employed were young heifer calves weighing about 350 pounds, and were as nearly comparable in size and vigor as could be secured. They were restricted absolutely to the experimental ration. They were given all the salt ($NaCl$) they cared to eat, were well cared for, and were allowed to exercise in an open lot free from vegetation. Their behavior during growth and during the performance of the functions of reproduction was extremely interesting. All groups ate practically the same amounts of feed and digestion tests showed that there were no differences in the digestibility of the three rations.

It was not until the animals had been confined to the experimental rations for a year or more that differentiation in their appearance was easily observable. The corn-fed group was sleek and fine, and evidently in an excellent state of nutrition. In marked contrast stood the wheat-fed group. These animals were rough coated and gaunt in appearance, and small of girth as compared with those fed the corn-plant ration. The weights of the two groups did not differ in a significant degree. The groups fed the oat-plant ration and the mixture of the three plants, leaf and seed, stood intermediate between the lots just described. The assumption that the animals receiving the mixture of products would fare better than the others, and thus serve as the standard group for controls, did not prove correct. The corn-fed animals were at all times in a better state of nutrition than were those receiving the greater variety of food materials.

The reproduction records of these animals are of special interest. The corn-fed heifers invariably carried their young to full term. The young showed remarkable vigor, and were normal in size and able to stand and suck within an hour after birth, as is the rule with vigorous calves. All lived and developed in a normal manner. The young of the wheat-fed mothers were the reverse in all respects. They were born three to four weeks too soon, and were small, weighing on an average 46 pounds, whereas the young of the corn-fed animals weighed 73 to 75 pounds each. The latter weight is normal for newborn calves. The young of the wheat-fed mothers were either dead when born or died within a few hours. The young of the mothers which had grown up on the oat-plant ration were almost as large as those from the corn-fed mothers, the average weight being 71 pounds. All of the cows in this group produced their young about two weeks too soon. One of the four was born dead, two were very weak and died within a day or two after birth. The fourth was weak but with care it was kept alive. The young of the cows which were fed the mixture of the three-plant products were weak in most cases. One was born dead and one lived but six days. The mothers were continued on the experimental rations and the following year they repeated in all essential details the reproduction records observed in the first gestation periods.

Records were kept of the milk production during the first thirty days of the first lactation period. The average production per day per each individual of the corn-fed lot was 24.03

pounds; for the wheat-fed animals 8.04, and for the oat-fed animals 19.38 pounds. Those fed the mixture of the three plants produced an average of 19.82 pounds of milk per cow per day during the first thirty days. In the second lactation period the average figures for milk production were 28.0, 16.1, 30.1, and 21.3 pounds, respectively, per day during the first thirty days.

Through autopsy and analysis of the tissues of the young, and analysis of the feeds and excreta of the animals of the several groups, an elaborate attempt was made to solve the problem of the cause of the marked differentiation of the animals fed these restricted diets. Interesting data were secured which showed marked differences in the character of the fat in the milk of the cows of the different lots. The observation was made that the urine of the wheat-fed animals was invariably distinctly acid in reaction, whereas that of the other lots was alkaline or neutral. It was not possible by any means known to biological chemistry to work out a reason as to the cause of the pronounced differences in the physiological well-being of the different lots of cows. (P. 6.)

Some impression of the untoward effects is afforded by the pictures of animals (with their offspring) maintained on some of these rations.

Following the experience gained in the continued study of the subject, later investigations, in which additions were made to the oat-plant rations found to be inadequate for efficient nutrition of breeding cows, showed somewhat better results. The improvement due to suitable mineral supplements containing calcium was noteworthy, even though the outcome was not ideal from a nutritive standpoint.

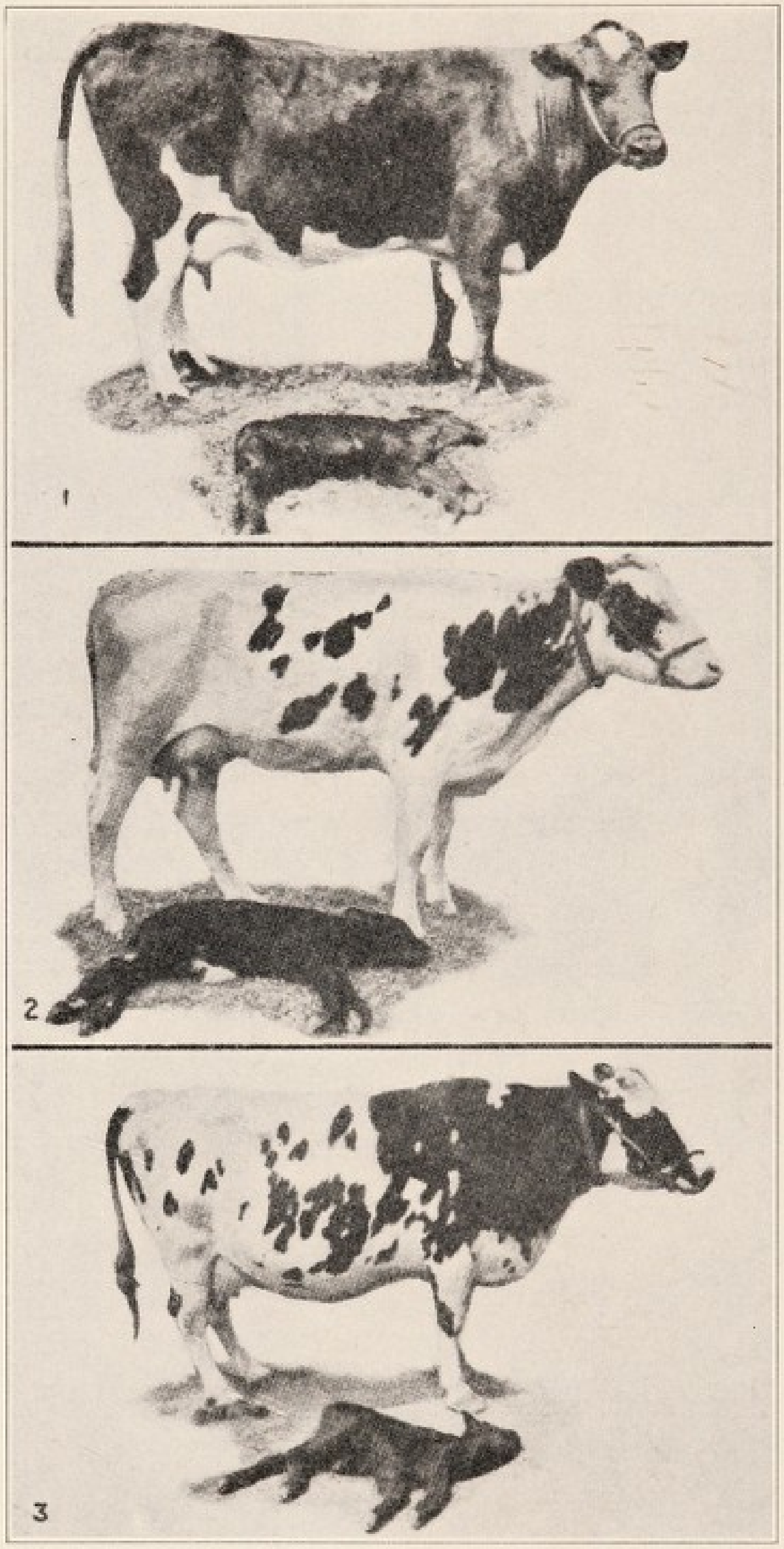
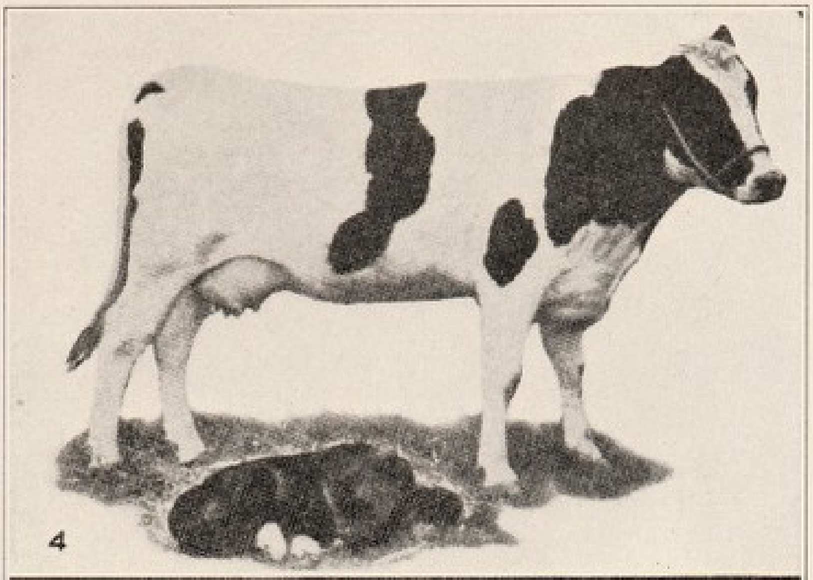


Fig. 1. Cow No. 648 and her calf. Illustrates how disaster in reproduction will follow the continuous use of a ration of ground oats and oat straw in the proportion of 1 : 1. Too poor mineral content of the straw was the primary cause of this result.

Fig. 2. Cow No. 661 and her calf. Fed the same ration as 1 with a similar result.

Fig. 3. Cow No. 653 and her calf. Fed a ration of ground oats and oat straw + 2 pounds of butter fat per 100 pounds of grain. Dead or weak calves were produced. The addition of more fat soluble vitamine did not, as a single addition, improve this ration for reproduction.

(From *Research Bulletin 49*, University of Wisconsin Agr. Exp. Sta., November, 1920.)



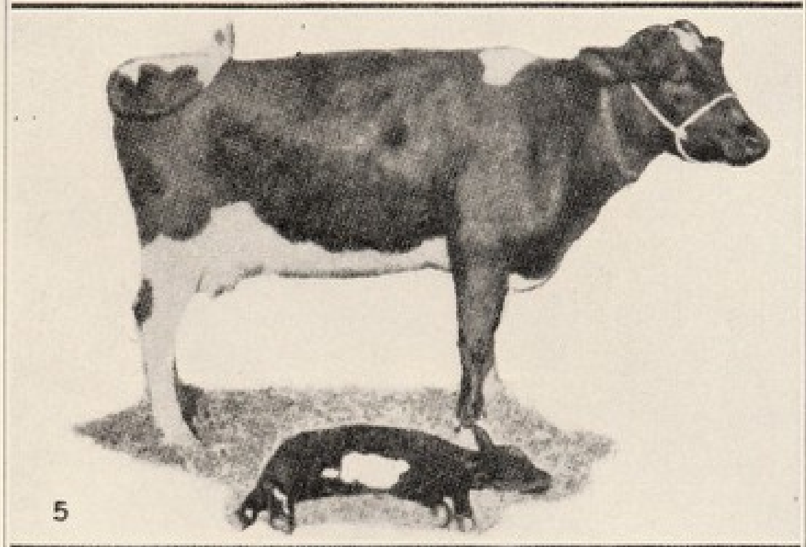


Fig. 4. Cow No. 656 and her calf. Fed the same ration as 1 with results of a similar character. Note deflection of the head and neck in both these cases.

Fig. 5. Cow No. 660 and her calf. Improving the oat plant ration with casein addition did not prevent disaster in reproduction. The ration fed consisted of 6.7 parts of ground oats, 0.3 parts of casein and 7 parts of oat straw.

Fig. 6. Cow No. 670 and her calf. The ration fed was a duplicate of that used for No. 660 and the results were of the same order. Weak, premature calves were born in both cases.

(From *Research Bulletin 49*, University of Wisconsin Agr. Exp. Sta., November, 1920.)

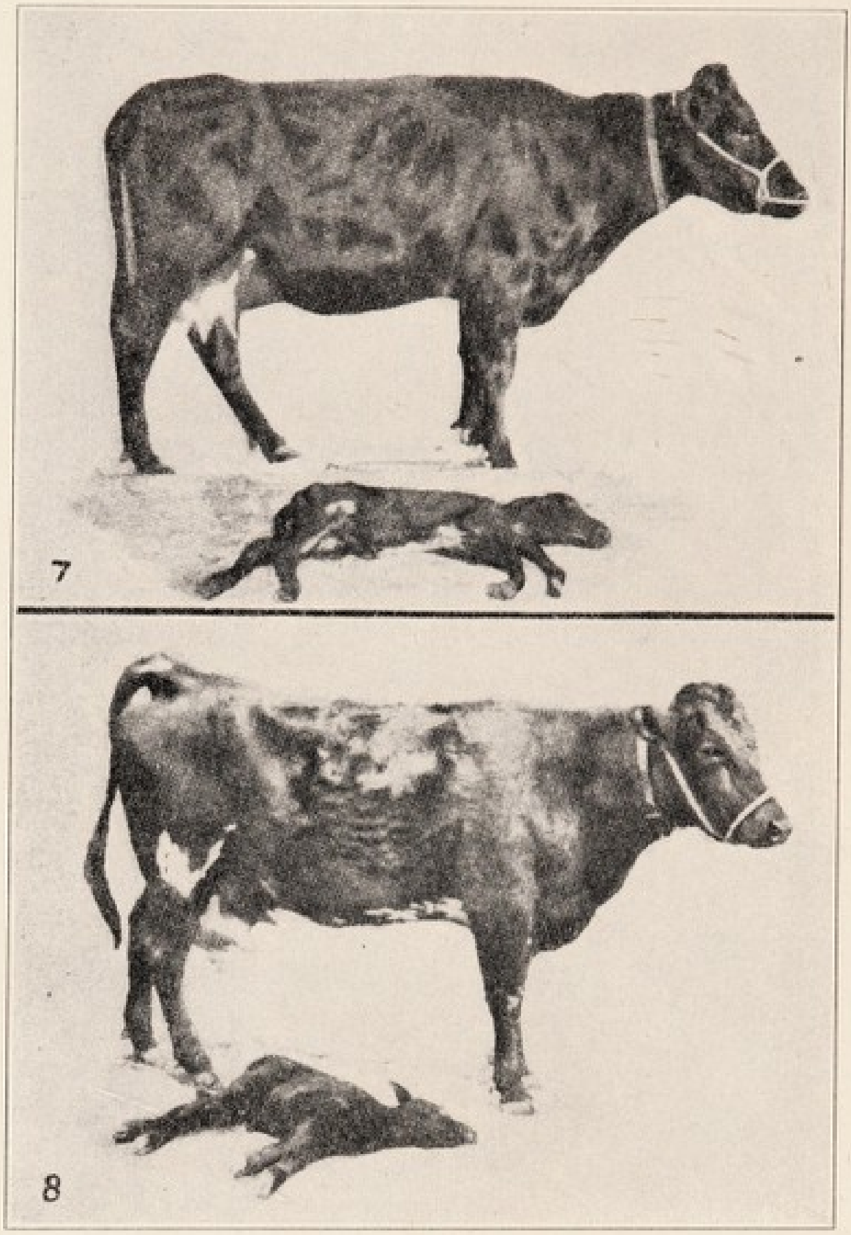
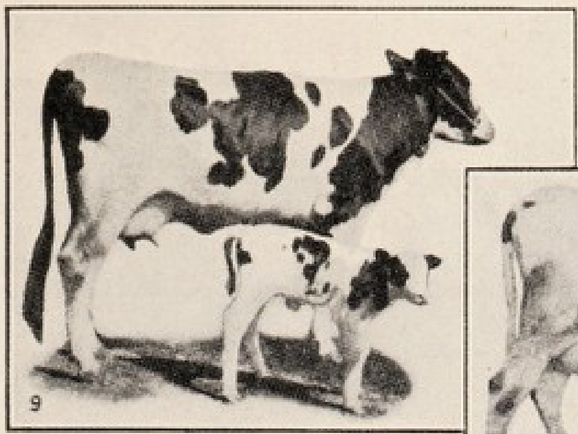
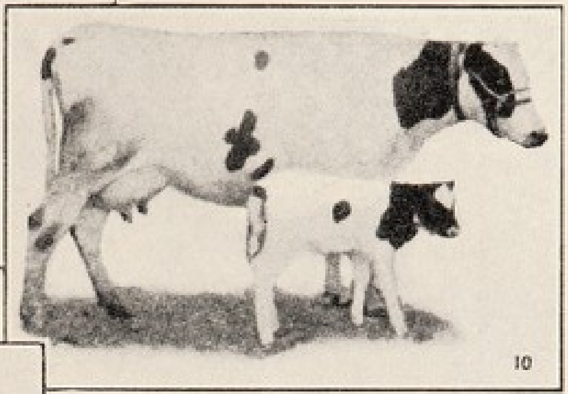


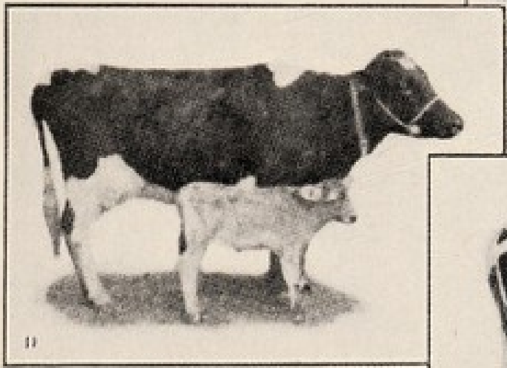
Fig. 7. Showing the effect of the addition of both casein and butter fat to a ration made from the oat plant. The two improvements were ineffective in making the ration a suitable one for reproduction. Cow No. 670 received 6.7 parts of ground oats, 0.3 parts of casein, 7 parts of oat straw and 2 pounds of butter fat to 100 pounds of grain. The calf was born dead.

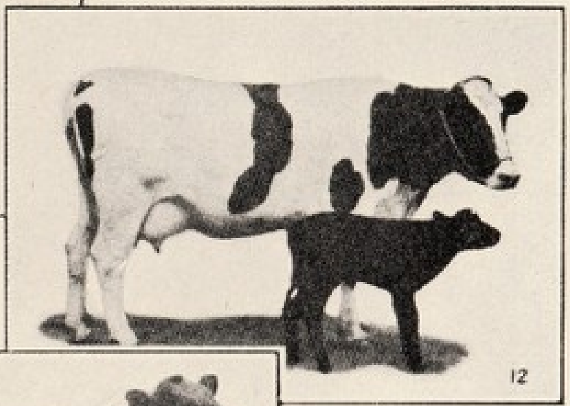
Fig. 8. A duplicate of preceding both in ration and results. Cow No. 671. The calf was extremely weak.

(From *Research Bulletin 49*, University of Wisconsin Agr. Exp. Sta., November, 1920.)









The effect of calcium additions to the oat-plant ration.

Fig. 9. Cow No. 676 and her calf. She received a ration of 7 parts of ground oats, 7 parts of oat straw and 2 pounds of wood ashes per 100 pounds of grain. A successful reproduction resulted.

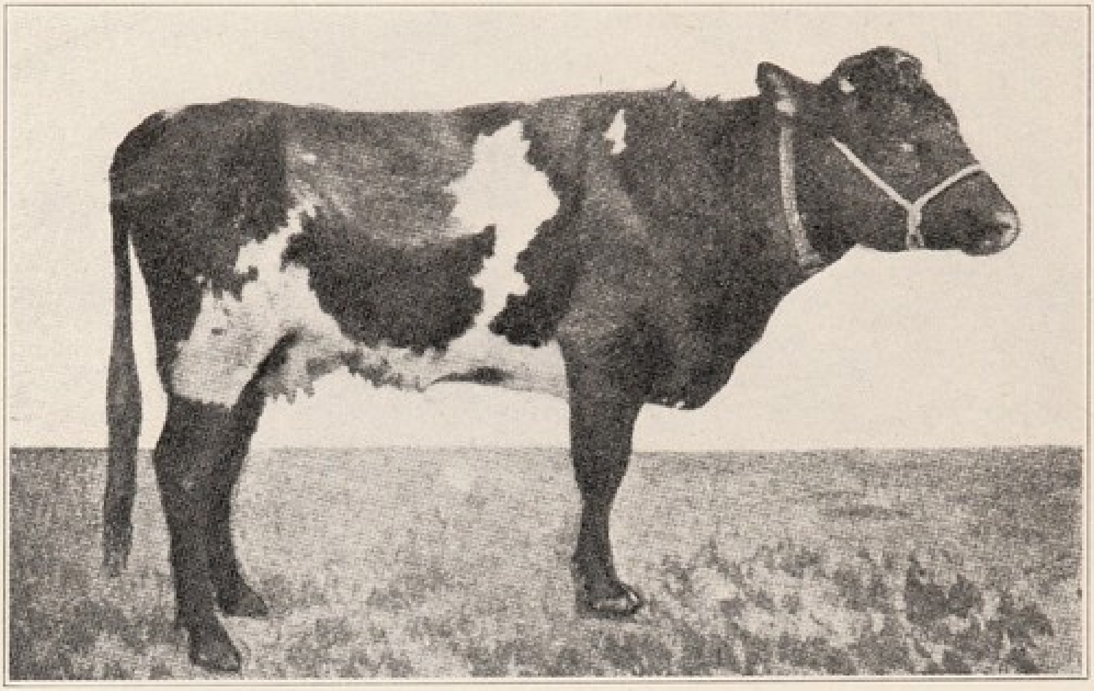
Fig. 10. Cow No. 668 and her calf. She received a ration of 7 parts of ground oats, 7 parts of oat straw + 2 pounds of calcium acetate to 100 pounds of grain. Another successful reproduction.

Fig. 11. Cow No. 660 and her calf. This animal received a ration of 6.7 parts of whole oats, 0.3 parts of casein, 7 parts of oat straw and 2 pounds of ground rock phosphate to 100 pounds of grain. A fairly successful reproduction. Note the record of this same cow in 5.

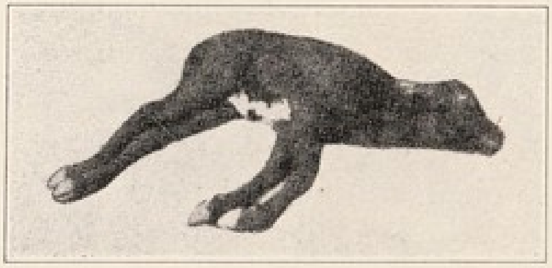
Fig. 12. Cow No. 656 and her calf. She received 7 parts of whole oats, 7 parts of oat straw, 2 pounds of butter fat and 2 pounds of calcium acetate to 100 pounds of grain. A fair success in reproduction resulted. Note the record of this cow in 4.

Fig. 13. Cow No. 671 and her calf. She received a ration of 6.7 parts whole oats, 0.3 parts of casein, 7 parts of oat straw, 2 pounds of butter fat and 2 pounds of wood ashes to 100 pounds of grain. A fairly strong calf was produced. Contrast this record with the record of this cow in 8.

(From *Research Bulletin 49*, University of Wisconsin Agr. Exp. Sta., November, 1920.)

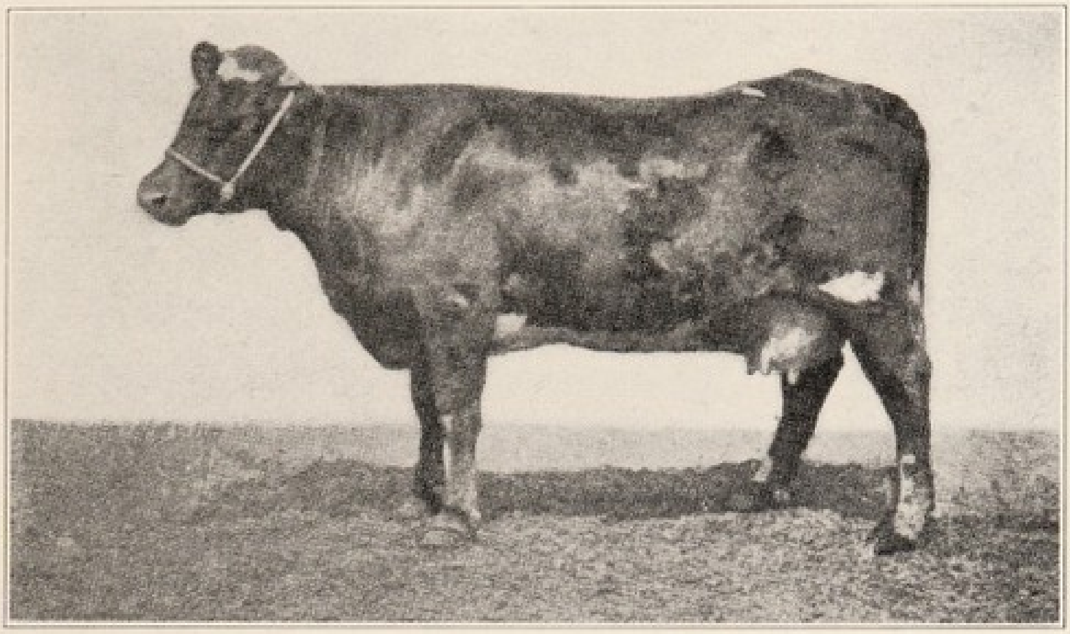


Wheat cow 570. 1910.

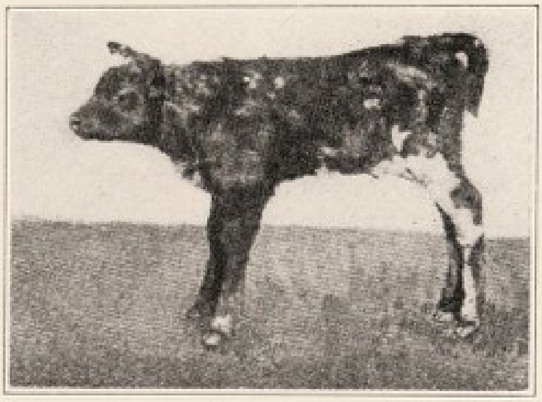


Wheat calf 1910. Mother 570.

(From *Research Bulletin 17,* University of Wisconsin Agr. Exp. Sta., June, 1911.)



Corn cow 566. 1910.



Corn calf 1910. Mother 566.

(From *Research Bulletin 17*, University of Wisconsin Agr. Exp. Sta., June, 1911.)

TABLE X. YIELD AND COMPOSITION OF MILK FOR THIRTY DAYS AFTER THE CESSATION OF PRODUCTION OF COLOSTRUM MILK

1909

Lot.	*Number of animals.*	*Total yield per lot, lbs.*	*Average individual daily yield, lbs.*	*Per cent solids.*	*Per cent total proteins.*	*Per cent casein.*	*Per cent fat.*	*Per cent ash.*	*cc. N/10 alkali required for 25 cc. milk.*
Corn	4	2884.9	24.03	12.43	3.19	2.50	3.45	.66	5.6
Wheat	4	965.8	8.04	12.30	3.08	2.50	3.55	.72	6.6
Oat	4	2326.8	19.38	13.03	3.09	2.55	4.25	.67	5.9
Mixture	3	1784.	19.82	14.10	3.10	2.50	5.65	.69	5.7

(From *Research Bulletin 17*, University of Wisconsin Agr. Exp. Sta., June, 1911.)

TABLE XI. YIELD AND COMPOSITION OF MILK FOR 1910

Lot.	*Number of animals.*	*Total yield per lot, lbs.*	*Average individual daily yield, lbs.*	*Per cent solids.*	*Per cent total proteins.*	*Per cent casein.*	*Per cent fat.*	*Per cent ash.*	*cc. N/10 alkali required for 25 cc. milk.*
Corn	4	3375.1	28.0	12.40	2.87	2.40	3.80	.74	6.1
Wheat	2	975.5	16.1	12.80	3.12	2.70	4.10	.76	7.6
Oat	2	1810.8	30.1	12.52	2.75	2.30	3.90	.74	6.7
Mixture	2	1281.2	21.3	13.81	2.90	2.30	4.40	.73	6.5

(From *Research Bulletin 17*, University of Wisconsin Agr. Exp. Sta., June, 1911.)

The Wisconsin series of experiments have emphasized in a very striking way the importance of "little things" in nutrition. They have shown the limitations of the conventional answers given only a few years ago to the question: "What constitutes a food?" Some of these will be discussed further in the pages following.

Besides the so-called proximate principles or organic foodstuffs other factors have been stressed from time to time as desirable if not actually indispensable components of a satisfactory diet. The importance of suitable inorganic ingredients has perhaps received far more theoretical than practical consideration. The value of common salt (sodium chloride) has been regarded foremost in this respect. The need of calcium has until recently been treated for the most part in an academic way except by workers in animal husbandry. Sherman[3] has collected the records of about 100 cases each of reasonably comparable experiments designed to measure the maintenance requirements for protein, phosphorus, and calcium respectively, in normal adult human nutrition.

> 109 experiments upon protein requirement show a mean of 44.4 gm., a standard deviation of 9.07 gm., a coefficient of variation of 21, and a probable error of the mean of ±0.58 gm.
>
> In 95 experiments upon phosphorus requirement the mean with its probable error is 0.88 ±0.01 gm., the standard deviation is 0.15 gm., and the coefficient of variation is 17.
>
> 97 experiments upon calcium requirement . . . give a mean result of 0.45 gm. with a probable error of ±0.008 gm. and show a standard deviation of 0.12 gm. and a coefficient of variation of 27. (P. 25.)

[3] Sherman, H. C.: "Calcium Requirement of Maintenance in Man," *Jour. Biol. Chem.*, 1920, xliv, 21.

These are the most dependable data now available for adult man. Bearing in mind that the figures presumably represent an approximation to the minimum requirements, and that the needs of calcium and phosphorus are probably modified by other factors in the diet which may alter the comparative retention of the elements in question, it is safe in planning a dietary to advise a liberal excess of each of them above the figures just cited. The possibility that the vitamine content of the diet may effect either an improved absorption or a decreased elimination, and consequently a better retention of calcium, magnesium, and phosphorus has been suggested by experiments of Bogert and Trail[4] on women. The effects of increased intake of magnesium on the excretion of calcium and vice versa, which Benedict and I[5] pointed out several years ago in experiment on animals may also apply to the human subject according to the observations of Bogert and McKittrick.[6]

Basing his opinion on the careful study of a large number of records Sherman[7] apprehends no danger that a freely chosen American dietary will be deficient in phos-

[4] Bogert, L. J., and Trail, R. K.: "Studies in Inorganic Metabolism. III. The Influence of Yeast and Butter Fat upon Calcium Assimilation," *Jour. Biol. Chem.*, 1922, liv, 387; "Studies in Inorganic Metabolism. IV. The Influence of Yeast and Butter Fat upon Magnesium and Phosphorus Assimilation," *ibid.*, 1922, liv, 753.

[5] Mendel, L. B., and Benedict, S. R.: "The Paths of Excretion for Inorganic Compounds. V. The Excretion of Calcium," *Amer. Jour. Physiol.*, 1909-10, xxv, 1; 23.

[6] Bogert, L. J., and McKittrick, E. J.: "Studies in Inorganic Metabolism. I. Interrelations between Calcium and Magnesium Metabolism," *Jour. Biol. Chem.*, 1922, liv, 363.

[7] Sherman, H. C.: "Phosphorus Requirement of Maintenance in Man," *Jour. Biol. Chem.*, 1920, xli, 173.

phorus in so far as the requirements of maintenance are concerned. This statement does not necessarily apply to the requirements of growth, pregnancy, and lactation, which remain to be more accurately determined. With respect to calcium Sherman estimates that the food supply should contain at least 1.0 gram of calcium for every 100 grams of protein. He states that, in the large majority of American food supplies of families and larger groups, as indicated by dietary studies made before the war by the United States Department of Agriculture and the New York Association for Improving the Condition of the Poor, this has not been the case. According to Sherman it does not follow that the calcium content was necessarily too low in the majority of dietaries, but rather that the food supply furnished a more liberal surplus of protein than of calcium.

With reference to the period of growth complete balance experiments of the intake and output of calcium (and in most cases also of phosphorus) are now available for a considerable number of children between the ages of 3 and 14 years, as the result of the studies of Sherman and Hawley.[8] The findings indicate that such children require an intake of a gram of calcium per day to induce optimal storage of the element. Calculated on the basis of size the results show fair uniformity on such an intake and indicate an average daily storage of 0.01 gm. of calcium and 0.008 gm. of phosphorus per kilo of body weight in growing children of 3 to 13 years of age. Milk serves as the foremost source of calcium. Children do not seem to utilize the calcium of vegetables as efficiently as they

[8] Sherman, H. C., and Hawley, E.: "Calcium and Phosphorus Metabolism in Childhood," *Jour. Biol. Chem.*, 1922, liii, 375.

do that of milk. In the experiments of Sherman and Hawley the calcium balances were more variable and always less favorable when vegetables replaced about half of the milk as a source of calcium. Although entertaining no doubt as to the desirability of a liberal use of vegetables in the feeding of children, these investigators contend that the vegetables should be used in addition to a liberal allowance of milk and should not be allowed to reduce the amount of milk consumed. It is desirable, they state, to emphasize the importance of a quart of milk per day for every child, and they regard it best to maintain this level of milk intake up to at least the age of 12 to 14 years.

How a pronounced deficiency of some of the inorganic elements in an otherwise adequate ration can affect the growth of animals is shown in the charts in which the results are indicated graphically with respect to the influence on the rate of growth of young rats. The failure to make suitable gains on foods poor in calcium or phosphorus was to be expected inasmuch as such indispensable constituents of bones and other tissues cannot arise *de novo* in the organism. The less serious effect of withdrawing some other elements of which traces inevitably were present in the food mixture, indicates a lesser need thereof, or a better conservation of the small quantities available.[9]

[9] Certain aspects of the effects of diets low in potassium have recently been reviewed by Miller, H. G.: "Potassium in Animal Nutrition. I. Influence of Potassium on Urinary Sodium and Chlorine Excretion," *Jour. Biol. Chem.*, 1923, lv, 45; "Potassium in Animal Nutrition. II. Potassium in Its Relation to the Growth of Young Rats," *ibid.*, 1923, lv, 61.

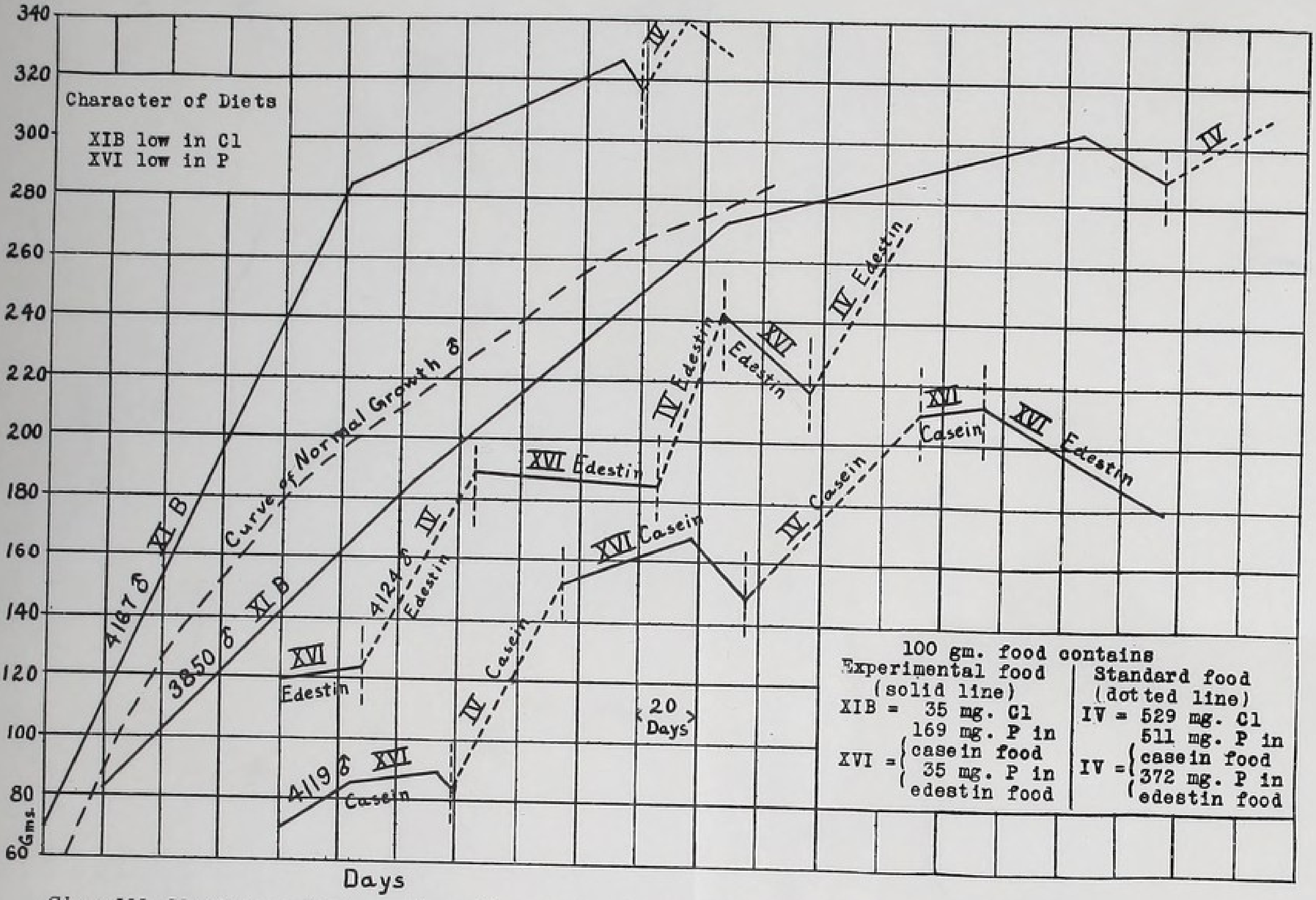


Chart III. Showing excellent growth on diets low in chlorine (Rats 4167 and 3850, Period XIB) and the failure to grow on diets poor in phosphorus (Rats 4124, 4119, Period XVI). It will be noted in the latter cases that the nutritive failure was far more rapid when the phosphorus-free protein edestin was fed than when the phospho-protein casein entered into the diet. In the Period IV, edestin, Rat 4124, practically all of the phosphorus was supplied in inorganic form. Period IV at the end of the feeding trials marks the return to the "standard food."

(From Osborne and Mendel: *Jour. Biol. Chem.*, 1918, xxxiv, 131.)

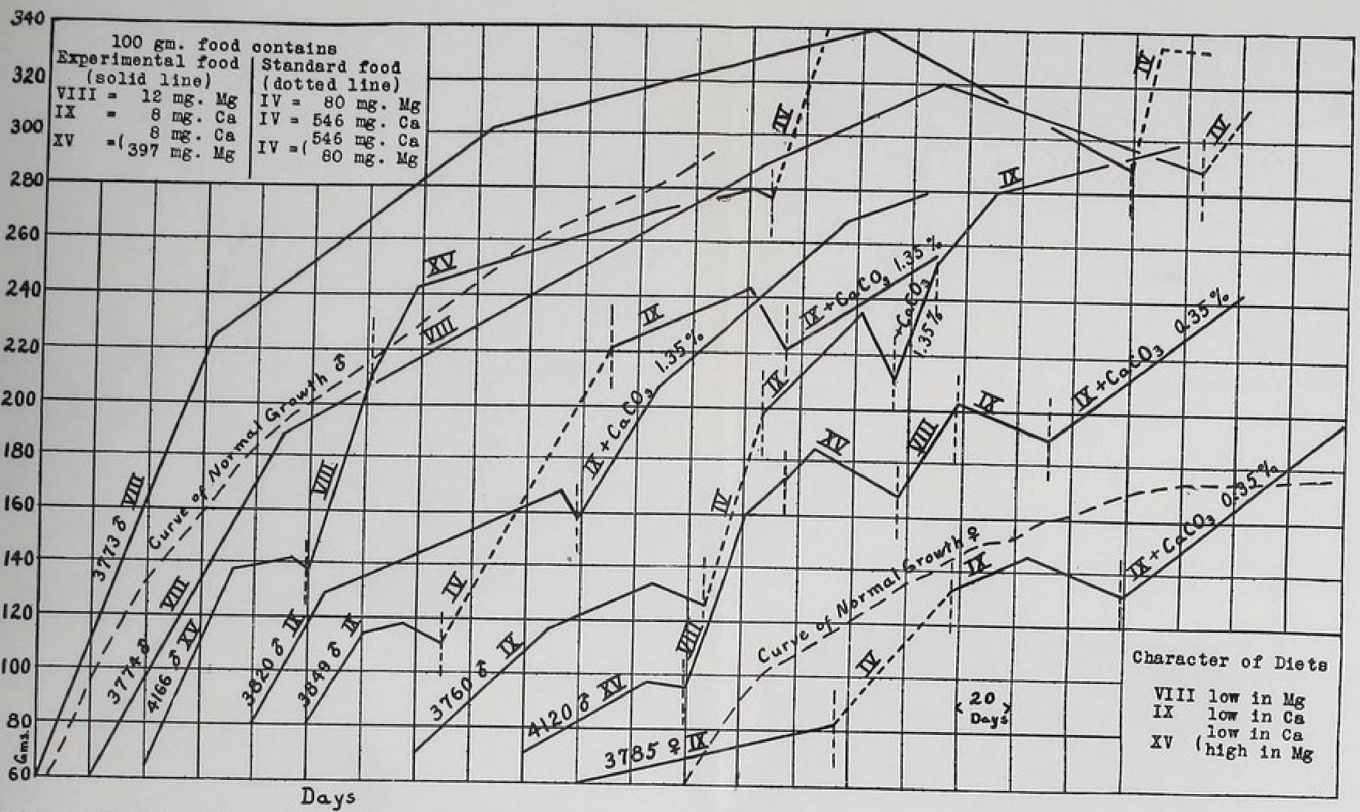


Chart II. Showing good growth on diets comparatively low in magnesium (Rats 3773 and 3774). When the diet was low in calcium (Period IX, Rats 3820, 3849, 3760, 3785) growth invariably stopped sooner or later and usually decline ensued until calcium was reintroduced into the diet in some form. Where the "standard food" was employed the recovery was prompt and rapid (Period IV, Rats 3849, 3760, 3785). It will be noted that when restoration was brought about by addition of calcium carbonate in the periods after the decline on diets poor in calcium (Period IX, Rats 3820, 3849, 3760, 4120, 3785) the response was usually more pronounced with a higher content of calcium (1.35 per cent $CaCO_3$) than with the lower supplement (0.35 per cent $CaCO_3$). Rats 4166 and 4120, which received during Period XV a diet poor in calcium failed to thrive despite a largely augmented supply of magnesium. This is only another illustration of the now established fact that magnesium cannot replace calcium in the body. Period IV at the end of the feeding trials marks the return to the "standard food."

(From Osborne and Mendel: *Jour. Biol. Chem.*, 1918, xxxiv, 131.)

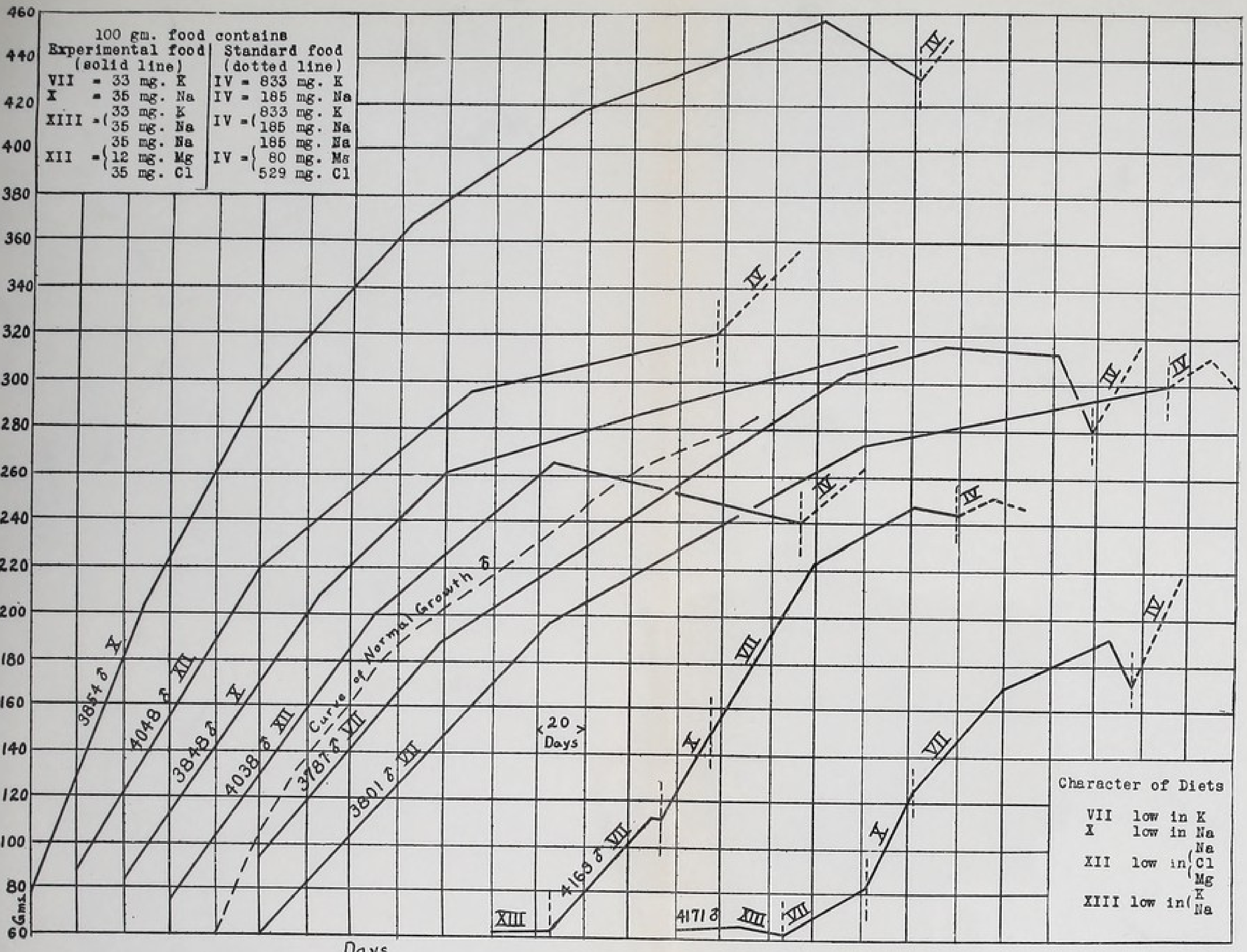
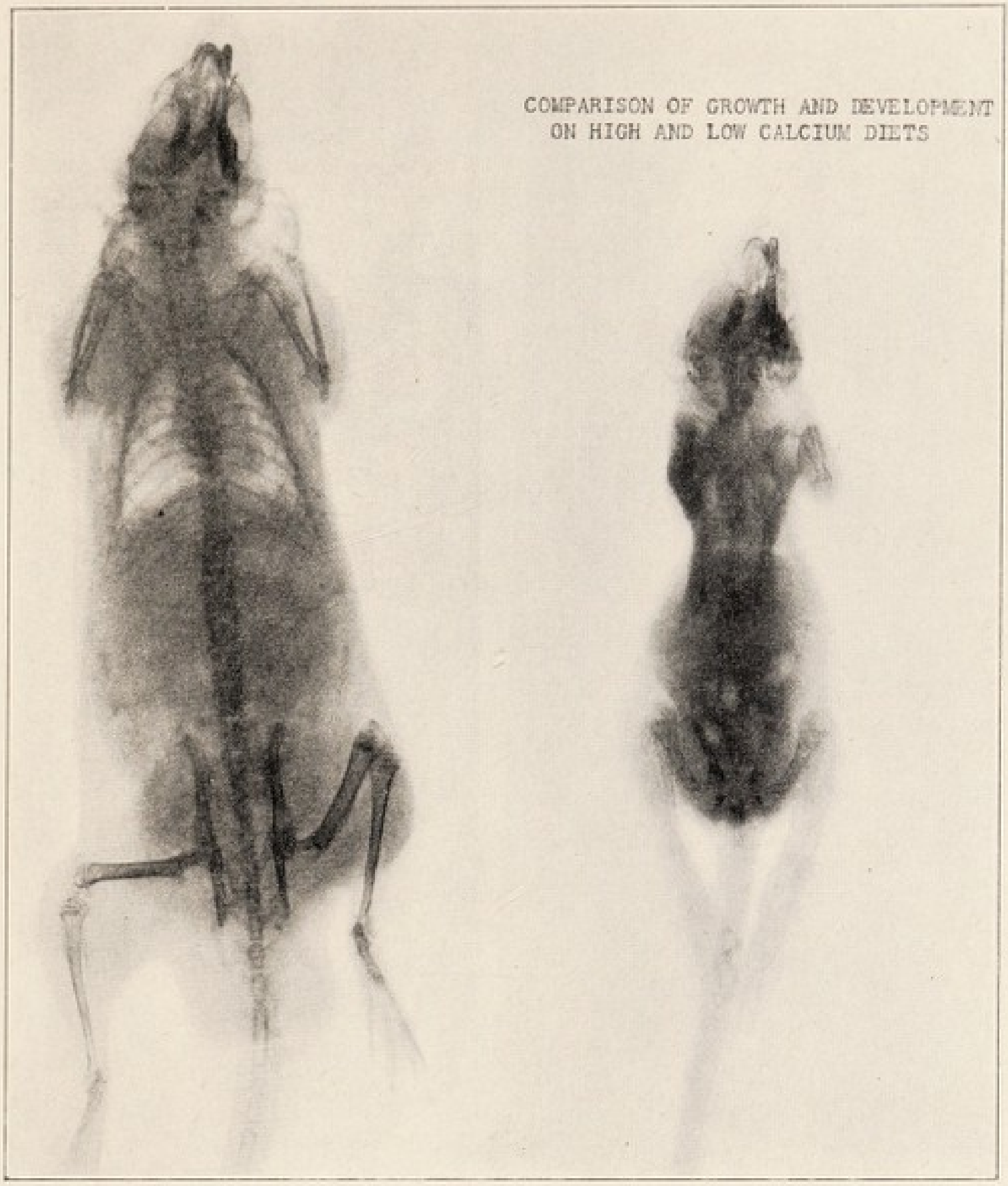


Chart I. Showing excellent growth of albino rats on diets low in sodium (Rats 3854 and 3848), and on diets low in sodium, chlorine, and magnesium (Rats 4048 and 4038). Very considerable growth was also obtained on diets decidedly low in potassium (Rats 3787 and 3801). In the case of Rats 4163 and 4171 no growth was obtained during the first period (XIII) in which the diet was low in both sodium and potassium. Growth was not satisfactory in these animals until potassium had been introduced for a time (Period X) into the diet. Period IV at the end of the feeding trials marks the return to the "standard food."

(From Osborne and Mendel: *Jour. Biol. Chem.*, 1918, xxxiv, 131.)



Diet High in Calcium. Diet Low in Calcium.

These rats were the same age and had been on the experimental diets less than five weeks when this picture was taken. Note the difference in size, development and chest cavity especially.

(From X-ray photographs taken by Dr. Helen S. Mitchell.)

A comparison of the effects of diets respectively rich and poor in calcium upon the growth and development of rats of the same age is afforded by the X-ray photographs.

In considering the practical aspects of this subject one must bear in mind that some of the commonest of human foods—the milled cereals, meats, fats, sugar, etc.,—which form a large bulk of the intake of many persons are all exceptionally poor in calcium. Where the drains on certain inorganic resources are particularly large, as in pregnancy or in milk production, the balance of calcium may tend to become negative unless adequate dietary provision is made to supply this element. From the standpoint of agricultural practice the situation has been well summarized in a bulletin of the Wisconsin Station:[10]

Grains are deficient in calcium, but rich in phosphorus. Rations wholly made up of grains will supply to the growing animal an amount of calcium dangerously near a critical level of intake.

Swine, growing or breeding, and confined wholly to grain rations should receive an additional supply of calcium either as calcium carbonate, calcium phosphate, or legume hay.

For continued and high milk production, with its extra drain of calcium, the supply may be dangerously low unless legume hays form a part of the ration or calcium is furnished in other forms.

When grains form a liberal part of the ration the supply of phosphorus will be abundant under almost all conditions of animal life. (P. 27.)

[10] Hart, E. B., Steenbock, H., and Fuller, J. G.: "Calcium and Phosphorus Supply of Farm Feeds and Their Relation to the Animal's Requirements," Agricultural Experiment Station of the University of Wisconsin, *Res. Bull. 30,* February, 1914.

How real such a deficiency may be has been demonstrated by a number of recent elaborate investigations on milch cows. Those of Forbes[11] and his collaborators in Ohio indicate that milk production, on winter rations, involves considerable drafts upon the mineral substance of the skeleton. It appears as if during most active lactation the organism of cows, at least, is unable to keep pace with the growing demands for calcium as a component of the milk. This may be true even under seemingly favorable and liberal intakes of calcium in the feeds. The Ohio investigators picture the situation as follows:

> Parturition turns loose a pent-up flood of nutriment which has been stored for the growth of the calf. This outpouring of mineral-rich food proceeds in large measure independently of the food supply; that is, if the food is sufficient to maintain the life of the cow she will produce milk even though this involves extensive drafts upon the tissues of the body.
>
> This impulse to secrete milk has been greatly intensified by selective breeding. We have to do, therefore, not alone with nature's adjustments, but especially with the effects of man's interference with nature by the creation within the cow of an impulse to produce very much more milk than does the cow as nature made her.
>
> Now, in intensifying this tendency, we have developed the power of the cow to draw upon the nutrient stores which compose her own tissues to such an extent that the results are often

[11] Forbes, E. B., Beegle, F. M., Fritz, C. M., Morgan, L. E., and Rhue, S. N., Ohio Agric. Exp. Station, *Bull. 295*, 1916; Forbes, E. B., Beegle, F. M., Fritz, C. M., Morgan, L. E., and Rhue, S. N., Ohio Agric. Exp. Station, *Bull. 308*, 1917; Forbes, E. B., Halverson, J. O., and Morgan, L. E., Ohio Agric. Exp. Station, *Bull. 330*, 1918, 11-118; Forbes, E. B., Schulz, J. A., Hunt, C. H., Winter, A. R., and Remler, R. F., "The Mineral Metabolism of the Milch Cow," *Jour. Biol. Chem.*, 1922, lii, 281.

matters not only of practical importance but also of serious concern.

At some point between the middle and the end of the period of lactation, when the impulse to secrete milk has largely spent itself, the milk production comes to be more definitely related to and dependent upon the feed intake, and falls off in amount to such extent that retention of calcium, the dominant factor of the whole mineral system, comes to prevail.

In the meantime, under conditions of practice, the cow has been bred. The demand of the fetus for mineral substance is slight, in the light of the capacity of the cow to metabolize mineral substance in the elaboration of milk. True, toward the end of the period of gestation the fetus increases greatly its appropriation of mineral substance, but this factor remains a minor one in the mineral metabolism of the cow.

In the unimproved cow lactation ceases when the calf is weaned, long before the end of the next period of gestation, but with many cows of improved breeding the milk production may persist up to the time of parturition, and the history of cattle breeding embraces accounts of cows which have produced milk for several years after birth of a calf.

The most successful breeders have learned, however, that the feeding and management of the highly developed milch cow during the latter part of the period of gestation is a matter of critical importance, and it is in this connection that the results of this experiment are of greatest interest.

Our findings and the most successful practice both indicate that a cow must have a dry, resting period of sufficient length to permit the entire replacement of the preceding mineral overdraft, if the vitality, fecundity, and productiveness of the cow are to remain unimpaired; and to this end it is desirable that the dry cow be fed as liberally as practicable, without undue risk of milk-fever subsequent to the following parturition. (*Jour. Biol. Chem.*, 1922, lii, 305.)

And again they state:

> Two facts with reference to the utilization of calcium by the cow stand out with great prominence, first that the cow's ability to assimilate calcium from winter rations, either with or without the addition of organic or inorganic supplements, is more definitely limited (at least under experimental conditions), than is its ability to assimilate other nutrients; and second, that the freedom with which cows can draw upon the calcium of their own bones, and the extent of this draft in cases in which it is necessary, shows that, at least above a certain amount, the calcium of the skeleton is more readily available than is that of winter rations and calcium supplements fed in the usual way. (P. 309.)

Other investigators,[12] at the University of Wisconsin, have recently pointed out that the character of the rations may determine the degree to which calcium is utilized. Whether and to what extent vitamines come into play here—factors varying with the treatment of certain fodders like alfalfa and timothy by drying and curing, in contrast with the green feeds—remains to be ascertained. If the mere difference between the same feed in its green, fresh state and its harvested form makes the calcium sources in the intake more available, as now seems to be possible in the light of the newer studies, important problems at once arise. Here the contrasts between summer and winter feeding, with fresh pasturage in the one case

[12] Hart, E. B., Steenbock, H., Hoppert, C. A., and Bethke, R. M.: "Dietary Factors Influencing Calcium Assimilation. III. The Comparative Efficiency of Timothy Hay, Alfalfa Hay, and Timothy Hay Plus Calcium Phosphate (Steamed Bone Meal) in Maintaining Calcium and Phosphorus Equilibrium in Milking Cows," *Jour. Biol. Chem.*, 1922, liv, 75.

and dried feeds in the other, are brought out. Hart and his associates have remarked:

> It is very probable that a condition of negative calcium balance in milking cows does widely prevail especially in the winter time and in regions where low calcium-carrying roughages are used—a condition that must have an important bearing on the yield of milk, resistance to disease, and reproduction. (*Jour. Biol. Chem.*, 1922, liii, 21.)

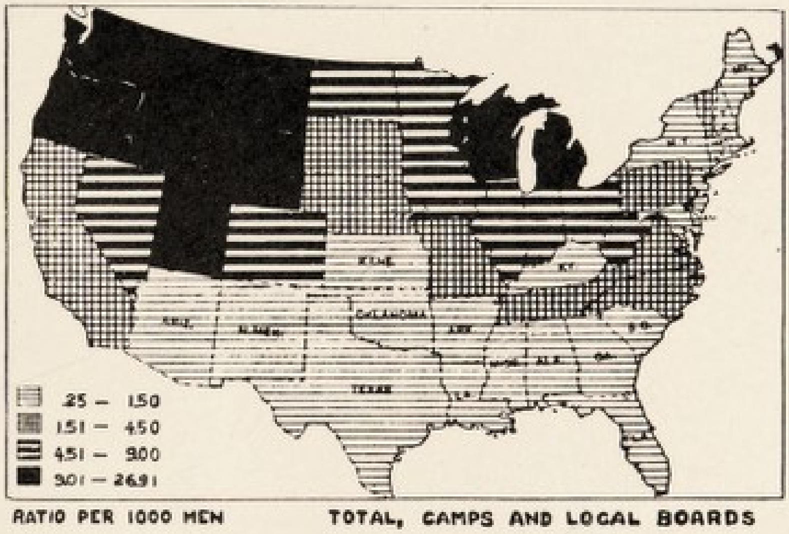
The poverty of certain rations in phosphorus may lead to the remarkable phenomenon of bone eating in cattle, some details of which have been reported by Green[13] from South Africa. Acute osteophagia is displayed by almost all the cattle in particular regions for ten months of the year, only abating while the grass is still very young. The abnormal craving is shown to be due to phosphorus deficiency in soil and vegetation, can be produced experimentally upon phosphorus-low rations, and removed by administration of phosphorus compounds or by phosphatic manuring. In itself osteophagia is relatively harmless and has no independent mortality incidence, although it may affect the growth of young stock and the milk yield of cows. Its great economic importance arises from its position in the etiological chain of lamziekte, a disease attributed to (1) a toxin which poisons the cattle, (2) produced by toxicogenic saprophytic anaerobes, (3) in carcass débris, (4) which is only eaten by cattle suffering from osteophagia, (5) due to phosphorus deficiency in soil and vegetation.

In this connection it may be worth while to recall that

[13] Green, H. H.: "Osteophagia in Cattle," *Jour. Biol. Chem.*, 1921, xlvi, p. xix.

the once debated question of the superiority of calcium, phosphorus and iron when furnished in some "organic" form or combination no longer excites interest, since it has been observed that inorganic sources of these elements can apparently serve the requirements of animals adequately. Furthermore the evidence available points to the probability that these elements are ionized in any event before they enter the blood stream to serve the purposes of nutrition.

Since the discovery by Baumann in 1895 of iodine as an essential constituent of the thyroid gland the serious importance of this element for normal physiological function has gradually been established. That it plays a part in the complex which regulates certain aspects of metabolism seems now to be beyond question. A striking objective illustration of the need of iodine is afforded by the studies on children of school age at Akron, Ohio. This city is within one of the regions of the North Ameri-



Defects Found in Drafted Men. Goiter, Simple.

(Davenport: *Scientific Monthly*, Jan. 1920.)

can continent in which simple goiter is endemic as indicated in the goiter map (p. 51) prepared by the Draft Board at the close of the recent war.

The incidence of simple goiter grows with increasing distance from the sea, so that the region of the Great Lakes is quite goitrous. McClendon[14] has argued that iodine is so rapidly leached out of the soil that the natural supply may depend upon salt spray blown from the sea. Whatever may be the reason for the lack of iodine, if this deficit is the essential cause of goiter, it should be easily overcome by the administration of the element without other changes in physiological routine. Marine and Kimball[15] conducted the now classic demonstration at Akron by comparing the occurrence or progress of goiter in school pupils taking or not taking prophylactic treatment consisting of two grams of sodium iodide given over a period of two weeks and repeated twice yearly. The investigators believe that this dosage has prevented enlargement of the thyroid in more than 99 per cent of children treated in this mildly goitrous region. In the summary of observations on children with whom the

[14] McClendon, J. F.: "Are Iodides Food?" *Science*, April 7, 1922, lv, No. 1423.

[15] Marine, D., and Kimball, O. P.: "The Prevention of Simple Goiter in Man," *Jour. Lab. and Clin. Med.*, 1917, iii, 40 (First Paper); Kimball, O. P., and Marine, D.: "The Prevention of Simple Goiter in Man," *Arch. Int. Med.*, 1918, xxii, 41 (Second Paper); Kimball, O. P., Rogoff, J. M., and Marine, D.: "The Prevention of Simple Goiter in Man," *Jour. Am. Med. Assn.*, 1919, lxxiii, 1873 (Third Paper); Marine, D., and Kimball, O. P.: "Prevention of Simple Goiter in Man," *Arch. Int. Med.*, 1920, xxv, 661 (Fourth Paper). A good review of the subject has been published by Kimball, O. P.: "The Prevention of Simple Goiter in Man," *Am. Jour. Med. Sci.*, 1922, clxiii, 634; also *Am. Jour. Public Health*, February, 1923.

PROFESSOR E. BAUMANN

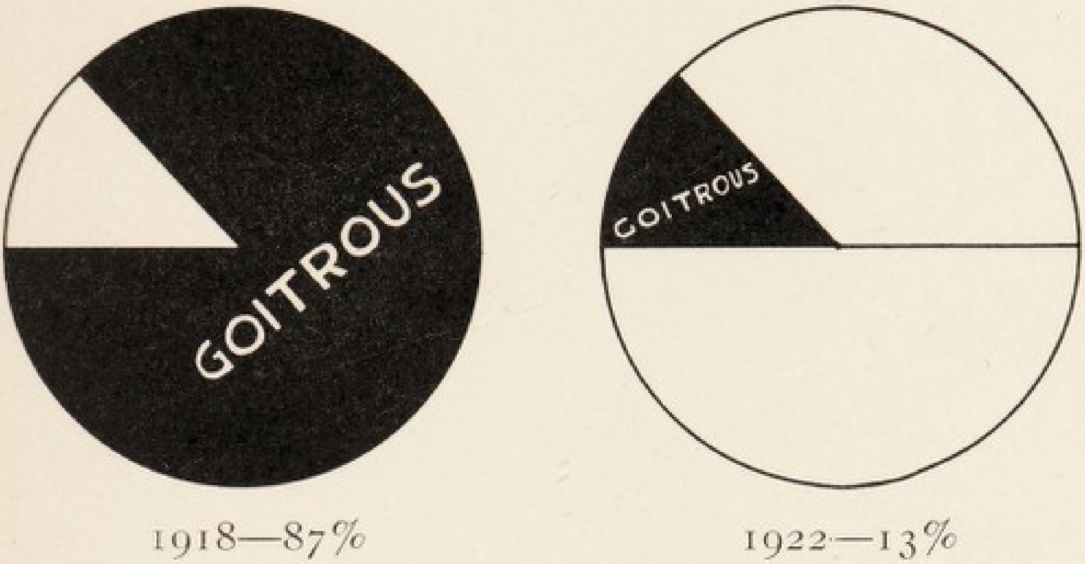
WHO IN 1895 DISCOVERED IODINE IN THE THYROID GLAND treatment has been carried out over two years and who had at least two or more consecutive examinations the

Statistics of the Akron Investigation on Goiter

RECORDS OF PUPILS TAKING AND NOT TAKING PROPHYLACTIC TREATMENT

	Taking		*Not Taking*	
	Totals	Per Cent.	Totals	Per Cent.
Normal:				
Unchanged	906	99.8	910	72.4
Increased	2	0.2	347	27.6
Slightly Enlarged:				
Unchanged	477	41.9	698	72.8
Increased	3	0.3	127	13.3
Decreased	659	57.8	134	13.9
Moderately Enlarged:				
Unchanged	29	20.3	57	64.0
Increased	0	0.0	21	23.6
Decreased	114	79.7	11	12.4
Total	2,190	....	2,305	....

striking differences between those pupils who have taken iodine and those who have not are manifested both in prevention of enlargement and in a decrease in the size of existing enlargements, *i.e.*, in therapeutic effects. This plan of prophylaxis supplying small amounts of the essential iodine where it is not easily secured in natural ways has also been tried on school children with distinct success in goitrous regions elsewhere. Kimball has therefore remarked that the same imagination which developed the practical application of the principle of the prevention of goiter can now see, a few generations hence, the closing of the chapters on endemic goiter and cretinism in every civilized nation in the world.



Effects of iodine prophylaxis for three years, on all the school children in three cantons of Switzerland: St. Gaulin, Berne, and Zurich.

(From O. P. Kimball, 1923.)

Of late various other suggestions have been made for securing the certainty of the inclusion of sufficiently large traces of iodine into the diet to avert deficiency phenomena on the one hand and iodism on the other. Most of the plans center in the use of table salt having some slight admixture of iodide.[16] The benefits are not limited to man. Fetal athyrosis, the "hairless pig malady" of the

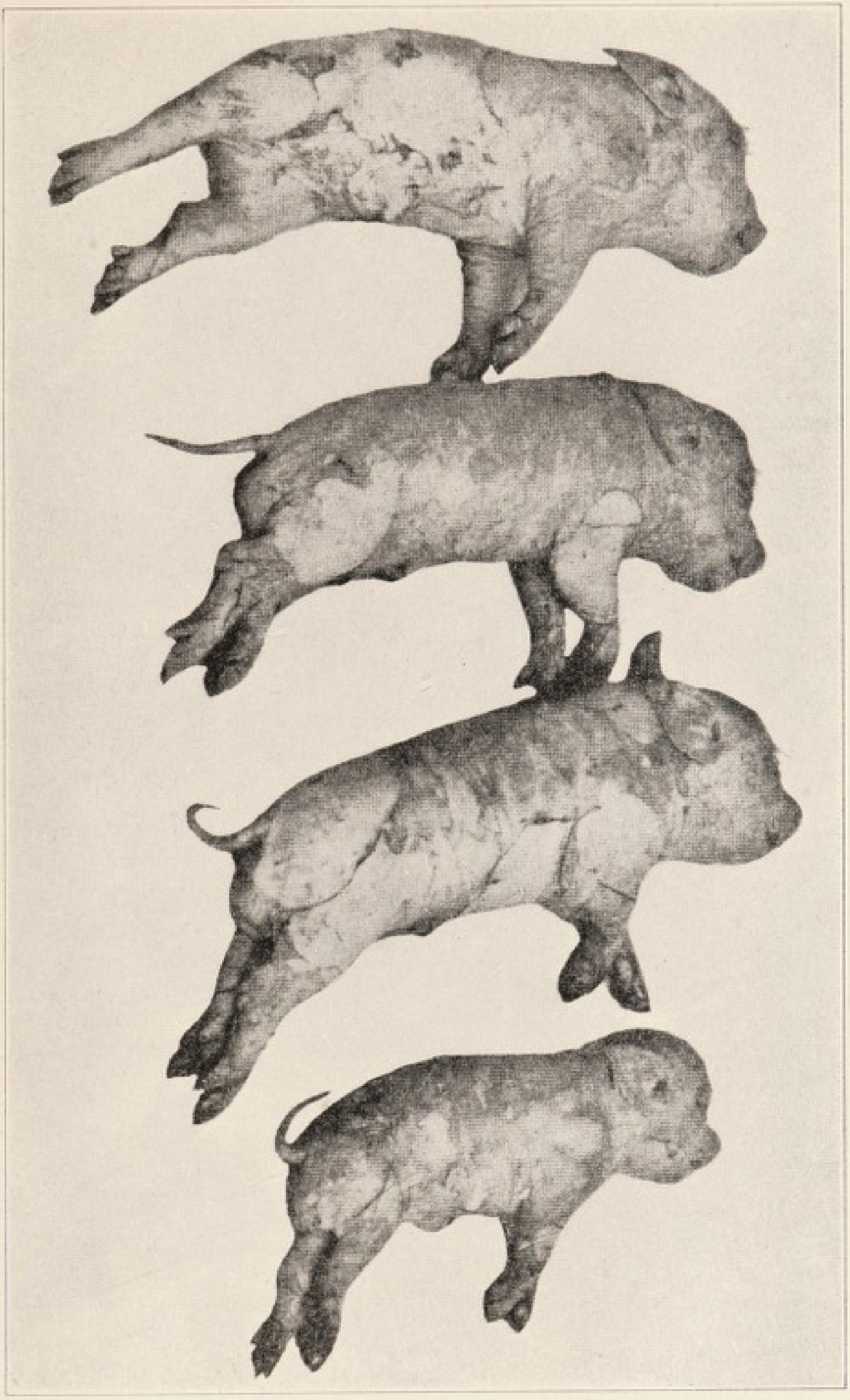
[16] It should perhaps be noted that E. Bircher (*Schweiz. Med. Wochschr.*, 1922, lii, 713) has sounded a warning against making a popular fad of prophylaxis through administration of iodine. He asserts that the indiscriminate use of iodide has already done harm in certain goiter districts by causing undue deposition of the element in the body.

western states, likewise disappears before a prophylaxis which supplies iodine as a part of the intake.

It has been found[17] that a large percentage of the sows in some sections of Montana have given birth to hairless and otherwise defective young. Many of these pigs were born dead; others died in an hour or two and very few lived more than 24 to 36 hours. The resulting loss in Montana amounted to about 1,000,000 young pigs annually. While the loss was heaviest among swine, there were numerous cases among sheep and occasionally among cattle and horses. Losses of the same nature have been reported from other Western states. Hart and Steenbock[18] of Wisconsin also observed that the hairless pig malady is associated with a hyperplasia of the thyroid gland and can be corrected by the use of iodine. They regard the disease to be occasioned through a low iodine assimilation by either intestine or thyroid, resulting in a goitrous condition in both mother and young. This interferes more severely with fetal development than with the normal maintenance of the mother. The feeding of iodide to the brood sows is a prompt remedy.

[17] Smith, G. E.: "Fetal Athyrosis," *Jour. Biol. Chem.*, 1917, xxix, 215.

[18] Hart, E. B., and Steenbock, H.: "Thyroid Hyperplasia and the Relation of Iodine to the Hairless Pig Malady. I," *Jour. Biol. Chem.*, 1918, xxxiii, 313.



(Hart and Steenbock: *Hairless pig malady*. I.)

Fig. 1. Dead and hairless pigs. Note the thick necks, indicating a goitrous condition. The mother of these pigs had been reared on a high protein and low roughage diet, consisting of 15 parts of alfalfa, 25 of corn, 25 of oats, 25 of middlings, and 10 of oil meal, and kept under strict confinement. She had produced two litters of hairless pigs before being changed to a ration of 33 parts of clover, 33 of corn, and 33 of oats, on which the above pigs were produced.

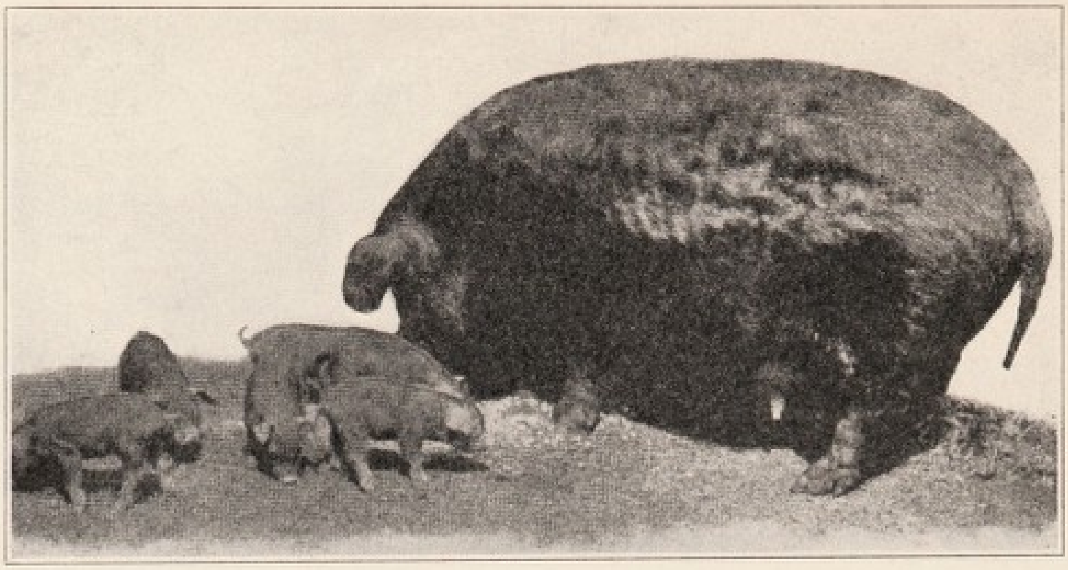


Fig. 2.

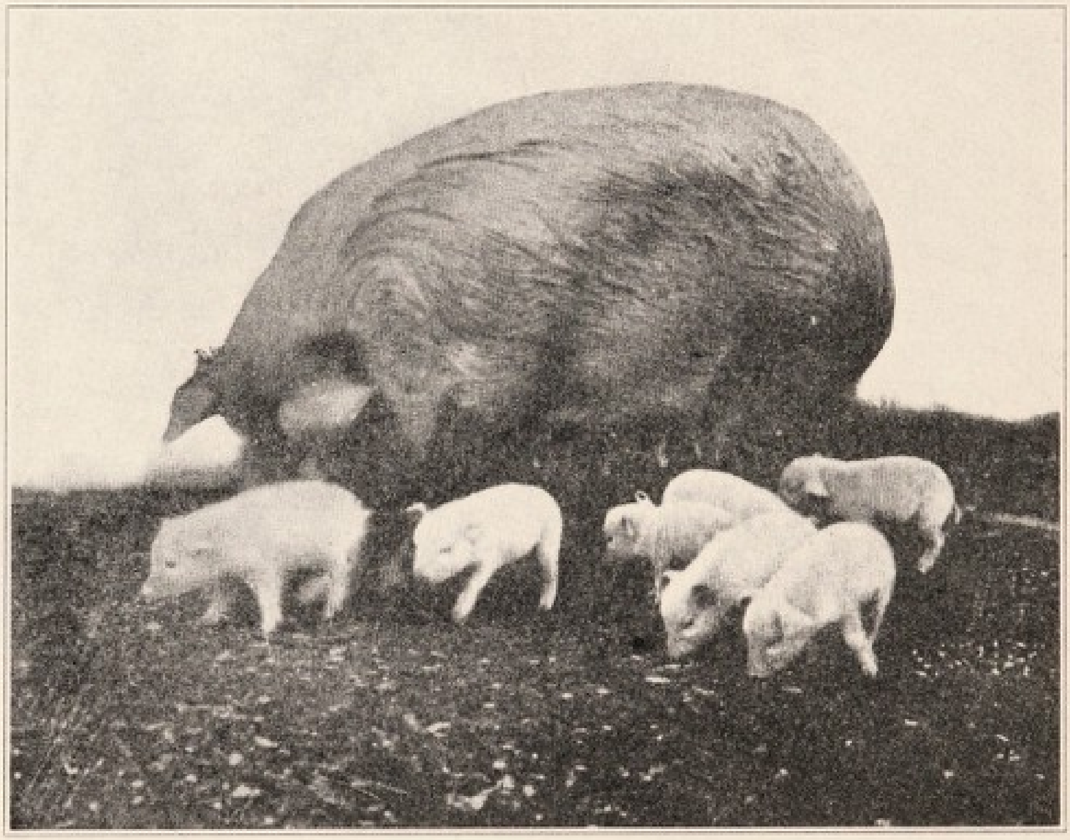


Fig. 3.

Fig. 2. The same sow that produced the pigs shown in Fig. 1. On the same ration,—33 parts of corn, 33 of oats, 33 of clover,—but fortified with 10 gm. of potassium iodide per 100 pounds of feed, a normal litter was produced.
Fig. 3. Reared on a ration of low protein and comparatively high roughage content, 75 parts of corn, 25 of alfalfa. The iodine content of this ration was not unlike that of the ration which produced the results shown in Fig. 1; the two rations, however, differed in their protein and roughage content and in this case the low protein diet was consumed during the life of the animal, including the growing period.

(Hart and Steenbock: *Hairless pig malady.* I.)

III.

THE VITAMINES

THE importance of the "little things" in nutrition is not confined to the illustrations already cited nor is appreciation of the subject entirely new. For example, in the preface of Pereira's *Treatise on Food and Diet,*[1] published in 1843, it is stated:

> The author did not venture, without considerable hesitation and doubt as to its propriety, to deviate from Dr. Prout's beautifully simple and generally admitted classification of alimentary principles, into the *aqueous,* the *saccharine,* the *albuminous,* and the *oleaginous.* After mature consideration, however, he satisfied himself of the impossibility of reducing all nutritive principles to these four heads. Common salt, for example, which a recent writer justly observes, "can by no means be considered only as a luxury, but as a substance as essential to life as nitrogenous or non-nitrogenous food and water," can be referred to no one of these four classes. Moreover, lemon juice, which constitutes one of our most valuable antiscorbutic foods, does not owe its efficiency to water, sugar, albumen, or oil.

It remained to ascertain by actual experiment—by the method initiated by Magendie—whether there was justification for assuming that proteins, fats, carbohydrates, salts and water are all that is necessary for the nutritive requirements of the body. Voit clearly appreciated this when in discussing metabolism he wrote, in 1881:

[1] Pereira, Jonathan: *A Treatise on Food and Diet,* edited by C. A. Lee, J. and H. G. Langley, New York, 1843.

Unquestionably it would be best for the purpose if one could feed only pure chemical compounds (the pure foodstuffs)—for example, pure protein, fat, sugar, starch, ash constituents, or mixtures of the same. However, inasmuch as men and also animals only rarely tolerate continuously such tasteless mixtures, it is necessary in most cases to choose foods as they are provided by nature. Nevertheless, it would probably be possible and very desirable to repeat the tests with the natural food products by using the pure substances, although the results yielded thereby might not be essentially different. (*Die Ernährung,* p. 19.)

There is no intimation, in these words of a master of the science of nutrition, of the probability of an unfavorable outcome of experiments with the purified foodstuffs except in so far as it might be limited by perversion of appetite or anorexia, an unexplained factor often conveniently called upon to excuse experimental failures. Nevertheless attempts to follow Voit's suggestion of feeding supposedly adequate mixtures of purified foodstuffs invariably failed, because such diets were deficient. It is now known that an important part in nutrition is played by substances which are not identical with the long familiar nutrients—the proteins, fats, carbohydrates and inorganic salts—and which, despite the minimal amounts thereof present in the diet, are nevertheless indispensable for growth and the maintenance of life. They have been called "accessory diet factors" or "vitamines."

It would carry us too far here to review the entire history of the circumstances which have led to the general acceptance of the vitamine hypothesis. Indeed, in view of the numerous recent monographs dealing specifically with this topic it would be superfluous to do so.[2] If in this connection attention is more specifically drawn here to some of the results of studies in which I myself have participated and to the personal experience of my coworkers and myself in this field, I am not unmindful or unappreciative of the numerous important splendid researches in many laboratories throughout the world. It is sometimes easier to emphasize the facts gained from personal investigation. It must be counted as a fortunate circumstance that the fundamental observations regarding vitamines have been repeatedly verified by various independent investigators, and that indications for the existence and physiological importance of these dietary essentials have been secured from a diversity of somewhat unrelated experiments.

Those who have reviewed the literature of the past decade on the subject of vitamines and nutrition have sometimes failed to appreciate that the growth of knowledge in this field has been gradual and progressive. Fi-

[2] For example: *National Health Insurance,* Medical Research Committee, *Report on the Present State of Knowledge Concerning Accessory Food Factors* (*Vitamines*), Special Report Series, No. 38, London, 1919; Hess, A. F.: *Scurvy Past and Present,* J. B. Lippincott Co., Philadelphia, 1920; Harrow, B.: *Vitamines,* E. P. Dutton and Co., New York, 1921; Eddy, W. H.: *The Vitamine Manual,* Williams and Wilkins Co., Baltimore, 1921; Funk, C.: *The Vitamines,* Williams and Wilkins Co., Baltimore, 1922; Sherman, H. C., and Smith, S. L.: *The Vitamins,* The Chemical Catalog Company, Inc., New York, 1922; McCollum, E. V.: *The Newer Knowledge of Nutrition,* The Macmillan Co., New York, 1922; Ellis, C., and Macleod, A. L.: *Vital Factors of Foods. Vitamins and Nutrition,* D. Van-Nostrand Co., New York, 1922; Plimmer, V. G., and Plimmer, R. H. A.: *Vitamins and the Choice of Food,* Longmans, Green and Co., London, 1922.

nality is rarely attained in any field of human interest. By the mistakes and misconceptions of the past we are guided into more fruitful paths. Each contribution should therefore be considered in the light of what was known when it was offered. Lord Moulton[3] has remarked that

> the answer that is wrung from Nature by an experiment today holds good for all time. The numberless errors into which scientific men have fallen and into which for a time they may have led the scientific beliefs of their generation are due to their misunderstanding the answer which Nature has given, and these errors are inevitably corrected by others who have put the question more skilfully or have more accurately read the answer. The replies that she gives to our questions are always truthful and will therefore in due time be recognised as consistent.

It was by the method of feeding mixtures of isolated foodstuffs that Osborne and I had planned to approach the problem of what nitrogenous units are essential for nutrition and whether individual proteins from different sources and already known to differ in respect to their chemical make-up vary in their nutritive efficiency. Fifteen years ago there was a growing appreciation that some of the commonest sources of human foods, such as the cereals, contain proteins unquestionably unlike the typical tissue proteins of animals in their structural composition. Obviously the comparisons could not be made satisfactorily by additions to the usual mixed diet which commonly contains a diversity of proteins. Even milk, which is looked on as a comparatively simple food, furnishes at least two proteins—casein and lactalbumin—

[3] *Science and the Nation*, edited by A. C. Seward, Cambridge, 1917, p. xii.

decidedly unlike in structure and amino-acid yield, and present in widely different proportions in the mammary secretion of different species. It was necessary, therefore, to devise a ration in which all of the essential food ingredients except proteins were present in abundance, and to which these nitrogenous food substances can be added one by one and tested separately. In this way the protein factor becomes the sole variable in the diet.

Our own earlier numerous attempts to feed mixtures of more or less purified proteins, fats, carbohydrates and inorganic salts ended, like the trials of other investigators, in failure. Sooner or later the animals refused to eat the food mixtures in sufficient amounts and declined in nutritive condition. They could usually be restored by a supply of "natural" foods.[4] We are emboldened, however, to repeat the attempts again and again, because other animals throve on a food as simple as milk seemingly is.

Accordingly, we determined presently to supply the mineral ingredients of our artificial diets in the form of what we termed "protein-free milk," that is, the dried residue of milk after separation of its fats and proteins. Aside from traces of unremoved albuminous ingredients, it contains the milk sugar and inorganic elements along with small amounts of unidentified components.

The "protein-free milk," which we first prepared in 1911, proved to hold a secret to success in our experimentation. On mixtures of such "protein-free milk," sugar, starch, and purified fats along with selected iso-

[4] Osborne, T. B., and Mendel, L. B.: "Feeding Experiments with Isolated Food-Substances," Carnegie Institution of Washington, 1911, *Publication No. 156*, Part I.

lated proteins, young white rats have grown to maturity and have in turn produced young even in the third generation. Evidently, the "protein-free milk" contained something present in small amounts, not represented by the familiar salts and organic nutrients, yet essential to adequate nutrition.[5] At first we were inclined to ascribe the good results to a more favorable supply of salts in the "protein-free milk" component of the mixture of isolated food substances. Presently, however, we were led in common with other investigators working in different ways to appreciate that we were dealing with unique factors requisite for physiological well-being.

It may be worth while to digress here in order to refer to an animal—the albino rat—which has played so large a part in recent years in investigations of nutrition. This animal resembles the human species in respect to its omnivorous feeding habits, the general character of its alimentary apparatus, and its "curve of growth," the cycle of development to adult form being completed, however, in less than ten months, whereas the attainment of a comparable stage in human growth requires more than twice ten years. Furthermore the small size of the animal, taken in connection with the facts just enumerated, makes it possible to conduct experiments with even relatively expensive food materials. The choice of this animal, which has lately formed the subject of so many elaborate investigations in nutrition, has been abundantly justified; and much of the information secured through experi-

[5] Osborne, T. B., and Mendel, L. B.: "Feeding Experiments with Isolated Food-Substances," Carnegie Institution of Washington, 1911, *Publication No. 156*, Part II.

mentation upon rats has direct application to the problems of human well-being.[6]

The word vitamine, coined by Funk in 1912, has come into vogue to designate the hitherto unrecognized dietary substances that are essential to nutrition. It is interesting to note that as early as 1906 F. G. Hopkins expressed somewhat the same conclusion as that of Voit already quoted. Hopkins stated that

> no animal can live upon a mixture of pure protein, fat, and carbohydrate, and even when the necessary inorganic material is carefully supplied the animal still cannot flourish. The animal body is adjusted to live either upon plant tissues or the tissues of other animals, and these contain countless substances other than the proteins, carbohydrates, and fats.
>
> Physiological evolution, I believe, has made some of these well-nigh as essential as are the basal constituents of diet. . . . The field is almost unexplored; only it is certain that there are many minor factors in all diets of which the body takes account.
>
> In diseases such as rickets, and particularly in scurvy, we have had for long years knowledge of a dietetic factor; but, though we know how to benefit these conditions empirically, the real errors in the diet are to this day quite obscure. They are, however, certainly of the kind which comprises these minimal qualitative factors that I am considering.
>
> Scurvy and rickets are conditions so severe that they force themselves upon our attention; but many other nutritive errors affect the health of individuals to a degree most important to themselves, and some of them depend upon unsuspected dietetic factors.
>
> I can do no more than hint at these matters, but I can assert

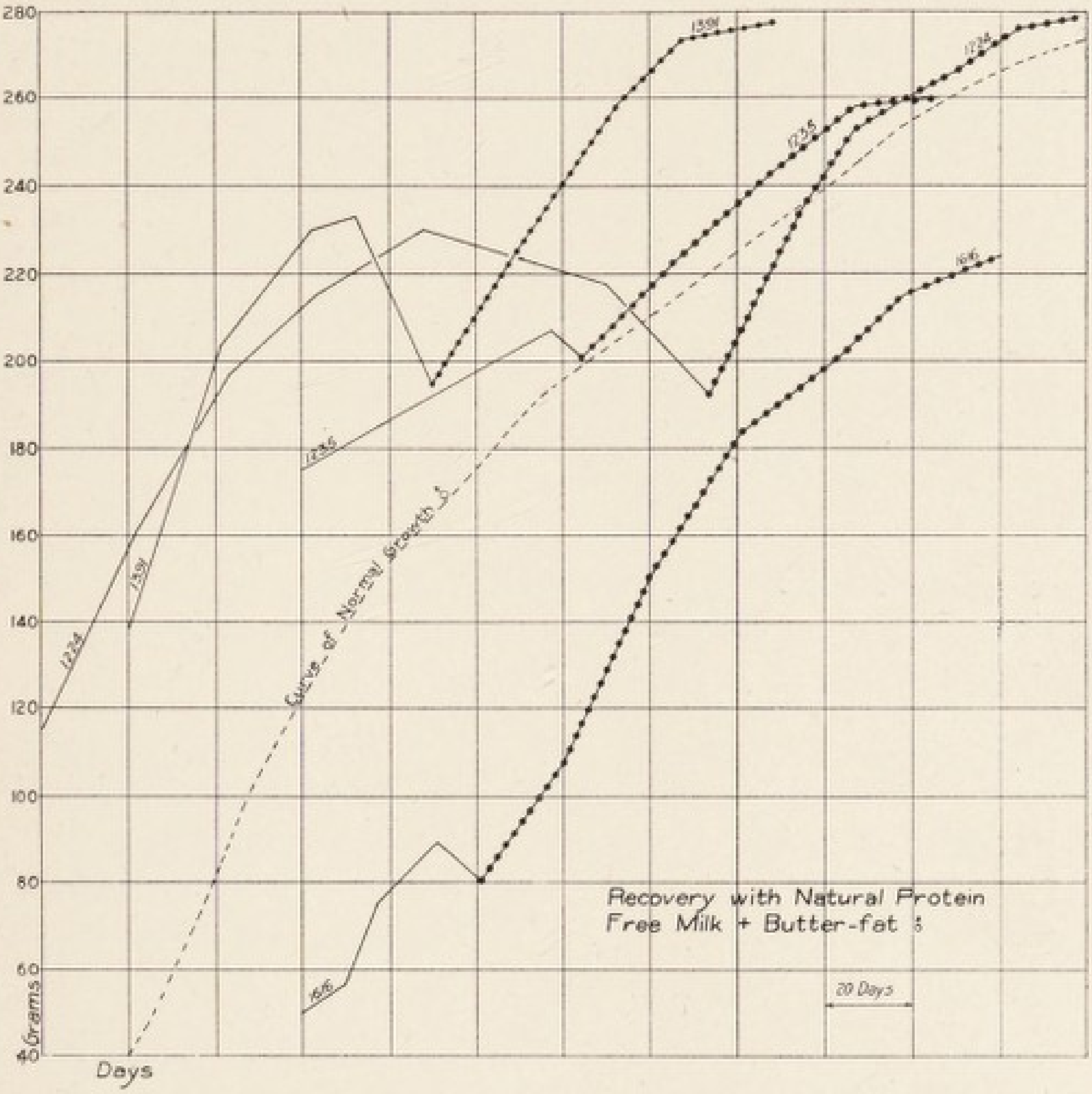
[6] For statistics regarding the rat consult Donaldson, H. H.: *The Rat,* Philadelphia, 1915. (A new edition is in preparation.)

that later developments of the science of dietetics will deal with factors highly complex and at present unknown.

The truth of this prophecy has since been firmly established.

After we had succeeded, about ten years ago, in preparing mixtures of isolated food substances (including protein-free milk with its unrecognized essential factor) so that animals could be nourished with some success, it was observed by us that growth invariably ceased after a time and nutritive disaster ultimately ensued unless certain changes were made in the diet. Osborne and I had kept rats through two generations on a diet consisting of whole-milk-powder, lard and starch. When we attempted to grow young animals on a comparable diet of isolated protein, "protein-free milk," carbohydrate and lard there was a suspension of growth, sometimes quite sudden and usually more gradual, before adult size was reached. The essential difference between the adequate and the inadequate ration just described lies in the absence of the milk fat or cream element of the latter. We found that addition of unsalted butter or of butter fat to the inadequate diets in which lard formed the fat component, prevented the suspension of growth in ungrown rats and promptly restored growth when it had failed. Milk fat—which includes all the milk constituents soluble in the fats proper—therefore contains something essential for the nutrition of growth.

Similar observations of the existence of such an unidentified "essential" had been made by McCollum and his collaborators. Since these experiences, published in 1913, comparable "potencies" have been discovered in a number



Curves of body weight of male rats which have ceased to grow and have declined on foods containing the natural "protein-free milk," and have recovered when 18 per cent of butter fat *replaced the same quantity of lard in the diet, as indicated by the interrupted lines (-o-o-o-o). The proteins furnished in the different experiments were as follows: casein, Rats 1224, 1235; edestin, Rat 1391; zein + casein, Rat 1616.*

The ordinates represent grams of body weight, as indicated. The divisions of the abscissa represent 20-day periods.

(From Osborne and Mendel: *Jour. Biol. Chem.*, xvi, 1913, 423.)

of animal fats, notably the tissue fats, among which liver oils (including cod liver oil, which we first tested) are striking illustrations; whereas they are missing in most other edible fats, particularly those of plant origin.[7] Potency is exhibited, however, by various parts of plants, particularly the green leaves or suitably prepared extracts thereof.

Reference is frequently made in the literature of nutrition to earlier observations of Stepp on the behavior of mice fed upon foods extracted with solvents which remove fats and other substances having similar solubilities. Although he came to the conclusion that certain lipoid substances must be essential to life his experiments are not conclusive in the light of present-day knowledge because several factors may have been concerned in the deficiencies which he produced.

The effects of the lack of the second type of essential food factor—that contained in milk fat—is promptly shown by the retardation of growth and nutritive decline, whereas there is improvement of nutrition when the missing factor is added to the otherwise adequate diet. The then known facts led me to state in a lecture before the Harvey Society of New York in 1914:

> It is not unlikely—to speak conservatively—that there are at least two "determinants" in the nutrition of growth. One of these is furnished in our "protein-free milk" which insures proper maintenance even in the absence of growth. When this was fed we have maintained rats without growth for very long periods. Without this "determinant" (as, for example, in diets

[7] The history of this subject is reviewed in McCollum's *The Newer Knowledge of Nutrition* and in the various recent monographs on vitamines.

Fig. 3. These pigs received a ration in dry lot consisting mainly of white corn, oil meal, oats, tankage and lime salts, adequate except for vitamine A. They weighed only 30 pounds at four months of age.

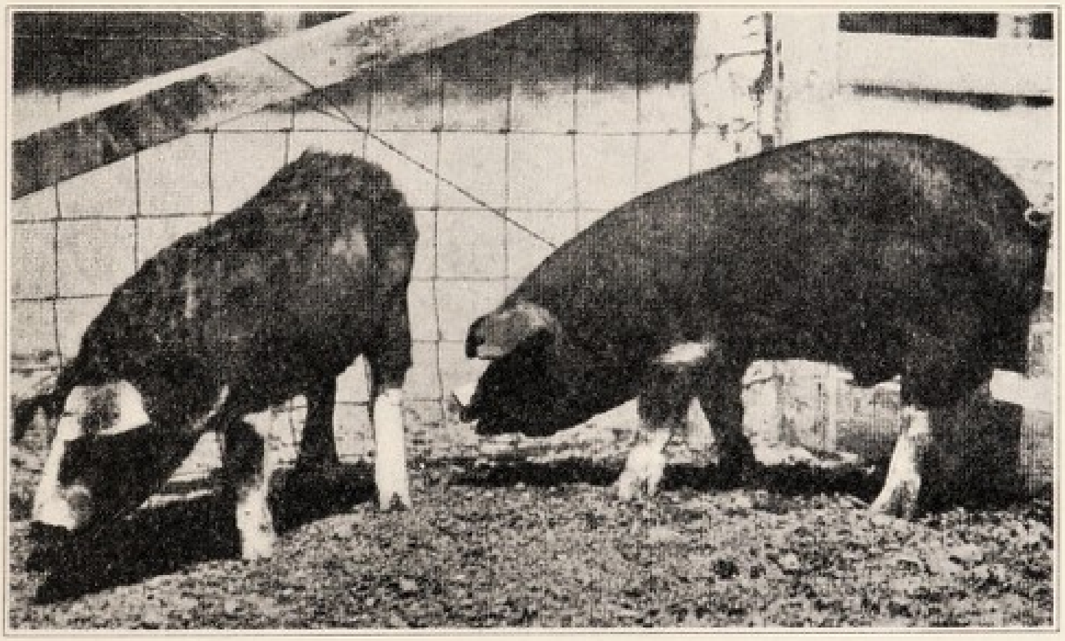


Fig. 4. The addition of one spoonful of butter fat daily to the ration of the pig on the right in Fig. 3, in four and one half months transformed him to the thrifty animal shown on the right here.

(From *Circular 73*, Iowa Agricultural Experiment Station, 1922.)

of isolated food substances containing artificial substitutes for "natural" protein-free milk) the special components of butter fat or cod-liver oil or egg fat induce only limited gains at best. Another "determinant" is furnished by these natural fats (or fractions more recently prepared therefrom by Osborne and myself or the saponification product of McCollum and Davis). Either of the determinants may become "curative"; both are essential for growth when the body's store of them (if such there be) becomes depleted.

Subsequently these "determinants" have been designated by a variety of names of which the most popular at present are the fat-soluble A (vitamine A) and water-soluble B (vitamine B), proposed by McCollum in this country and urged by Drummond in England.

That a still different factor plays an important nutritive rôle, in some species at least, is emphasized by the experimental study of scurvy. An antiscorbutic vitamine (vitamine C) is present in many natural foods. It is peculiarly thermolabile in the presence of oxygen, so that even the degree of heating employed in cooking may cause some foods to lose antiscorbutic potency.[8]

Not all species are equally sensitive to deprivation of the various types of essential factors thus far described. Thus the rat and the chick do not seem to suffer from a lack of antiscorbutic foods to which the guinea pig, monkey and man are particularly responsive. We have frequently seen rats grow vigorously in our laboratories on food which soon produces unmistakable symptoms of

[8] For a review of the subject consult Hess, A. F.: *Scurvy Past and Present,* Lippincott, Philadelphia, 1920; Sherman, H. C., and Smith, S. L.: *The Vitamins,* the Chemical Catalog Company, Inc., New York, 1922.

scurvy in guinea pigs. The reason for this is not entirely clear.

Sugiura and Benedict[9] have announced that pigeons on a diet of sufficient caloric value, even though it lacks fat and vitamine A, may maintain excellent condition, and may produce fertile eggs and rear healthy squabs. Hence, these investigators conclude, vitamine A is not essential in any stage of avian nutrition.[10]

All of the higher mammalian animals studied, however, are demonstrably affected by a lack of vitamine B. This factor has hitherto been the one most ardently studied. Experimental avian polyneuritis, the analogue of human beri beri, early attracted attention because its symptoms, produced by feeding a diet deficient in something other than the familiar foodstuffs and inorganic salts, can be relieved by very small doses of a great variety of natural food products. Whether the phenomena here concerned are strictly identical with the nutritive decline of mammals on comparable diets is by no means yet satisfactorily demonstrated. There are many indispensable variables in a diet; and most investigators in the past have failed to conduct their experiments so that only one shall be concerned in each test. The pigeon succumbs on a diet of polished rice. Why? Polished rice is obviously not a complete food. Its shortcomings may be manifold. The pathology of multiple dietary deficiencies is not easy to unravel. Many of the steps already taken in the study of

[9] Sugiura, K., and Benedict, S. R.: "A Study of the Adequacy of Certain Synthetic Diets for the Nutrition of Pigeons," *Jour. Biol. Chem.*, 1923, lv, 33; also Hoet, J.: *Biochem. Jour.*, 1923, xvii, 220.

[10] This has since been debated with reference to the hen by Emmett, A. D., and Peacock, G.: *Jour. Biol. Chem.*, 1923, lvi, 679.

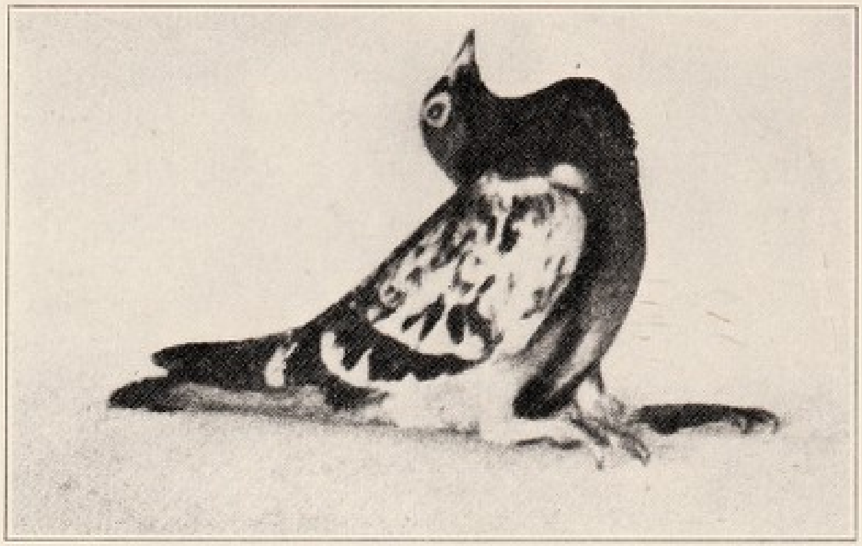


Fig. 7. Bird before injection of vitamine.

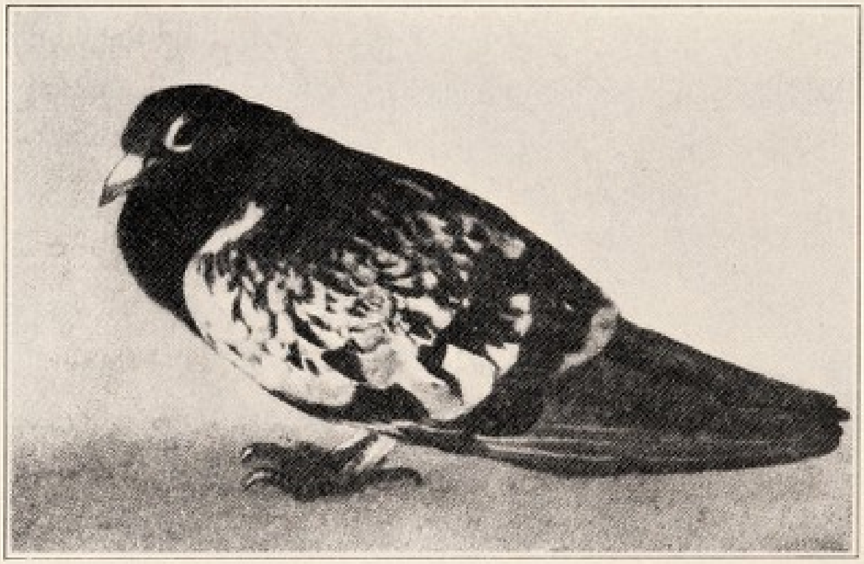


Fig. 8. Same bird as Fig. 7, after injection of vitamine.

The upper picture shows the development of typical symptoms in a pigeon on an exclusive diet of polished rice.

The lower picture shows the recovery from the symptoms.

(From the *British Medical Journal*, 1913.)

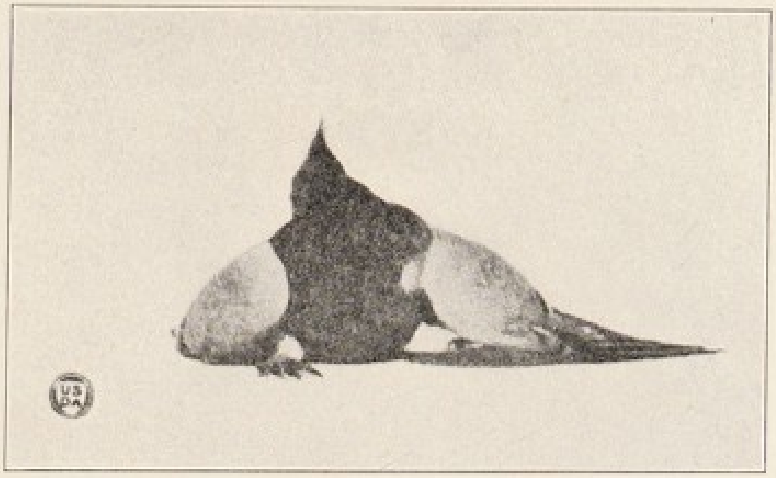


Fig. 2. Pigeon with acute polyneuritis, showing lack of control of muscles in the wings, legs, and neck.

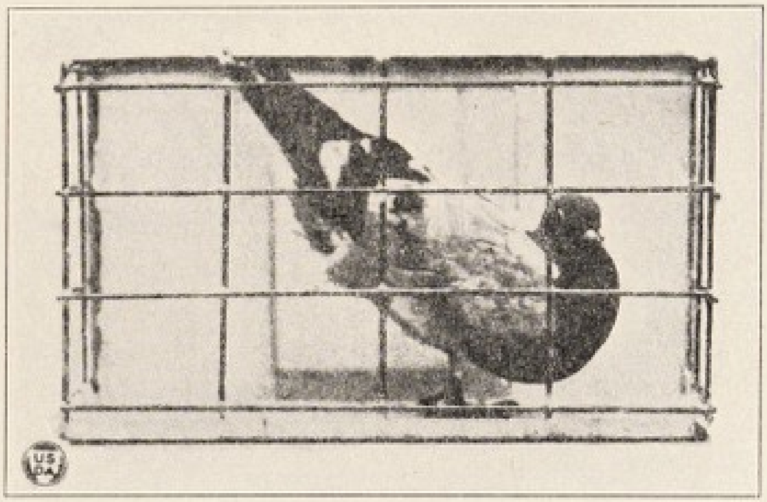


Fig. 3. The same pigeon as in Fig. 2, 24 hours later, after having been fed 15 grams of dried smoked ham. The bird is a little unsteady on its feet but shows no acute symptoms of the disease.

(From *Department Bulletin No. 1138,* United States Department of Agriculture, February 10, 1923.)

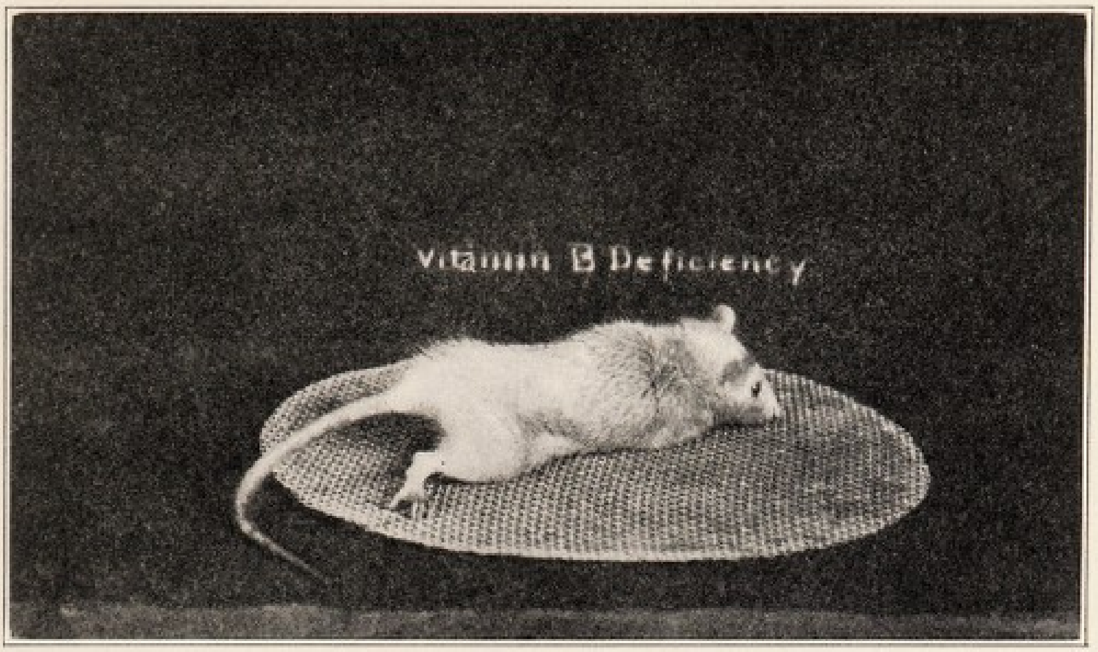
deficiency disorders therefore need to be retraced to find the answers to some of the vexed questions.

A more satisfactory procedure has been the current popular method of observing the nutritional condition of small animals kept on food mixtures presumed to be adequate in every respect except as to one of the essential vitamine components. Through supplying various supplements to such rations it can be determined whether the added substance prevents nutritive disaster (the prophylactic test) or produces a return to normal conditions (the curative test) in animals exhibiting nutritive disorders from lack of it. Usually the body weight is taken along with other obvious symptoms as the index of nutrition.

Experiments on growing animals are particularly striking because the failure to gain is readily detected. Yet there are many pitfalls in this field of study. Thus the presence of a toxic substance in food might simulate a deficiency in its effects; on the other hand vitamines may lurk in unsuspected places. Detrimental environmental conditions, unsuspected organic defects or infectious disease may mislead the investigator. Animals have individual capacities that cannot be foretold. Hence many trials are sometimes necessary before the vitamine problems can be answered with assurance.

Illustrations of the results of this mode of study are shown in the charts and photographs.

Some of the phenomena attributable to diets deficient in vitamines have an obvious importance for the well-being of man and animals. The earliest observable symptom of a lack of vitamine B—the most universally dis-

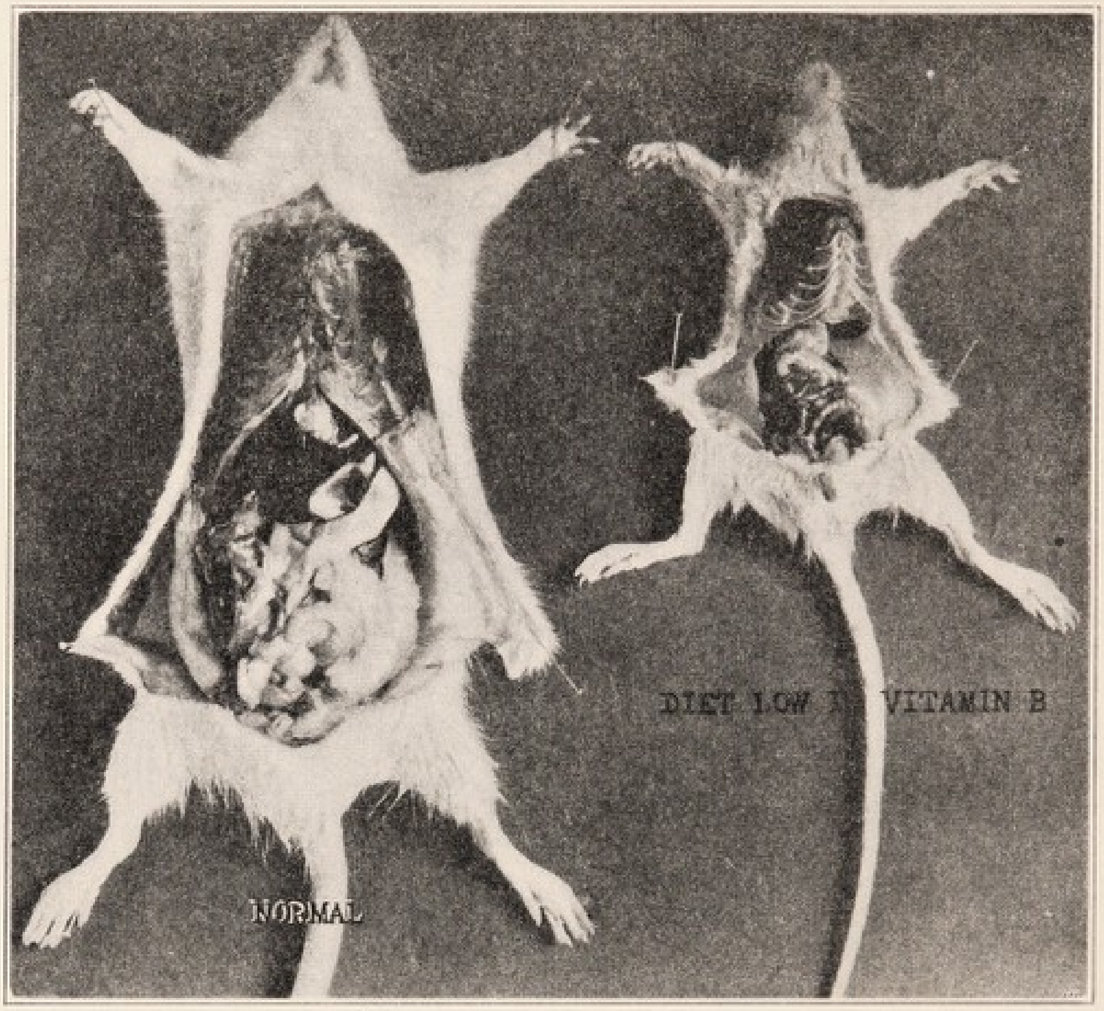


Showing typical symptoms in a rat fed on a diet deficient in vitamine B.

(From a photograph by Dr. Helen S. Mitchell.)

Showing the effects of diets rich and poor in vitamine B.

(From a photograph by Dr. Helen S. Mitchell.)



Showing dissections of the rats in the previous picture.

(From a photograph by Dr. Helen S. Mitchell.)

Fig. 1. Polyneuritic dog. This animal had been fed for 83 days on a diet lacking vitamine B. A very slight paralysis involving the hind limbs became evident on the 60th day; on the 74th day the paralysis became pronounced. Photograph was taken on the 83d day.

Fig. 2. Same animal as is shown in Fig. 1, photographed on the 83d day. Notice that the muscles of the hind limb are contracted even when the animal is lying down.

(From Cowgill, G. R.: *Am. Jour. Physiol.*, lvii, 1921, 420.)

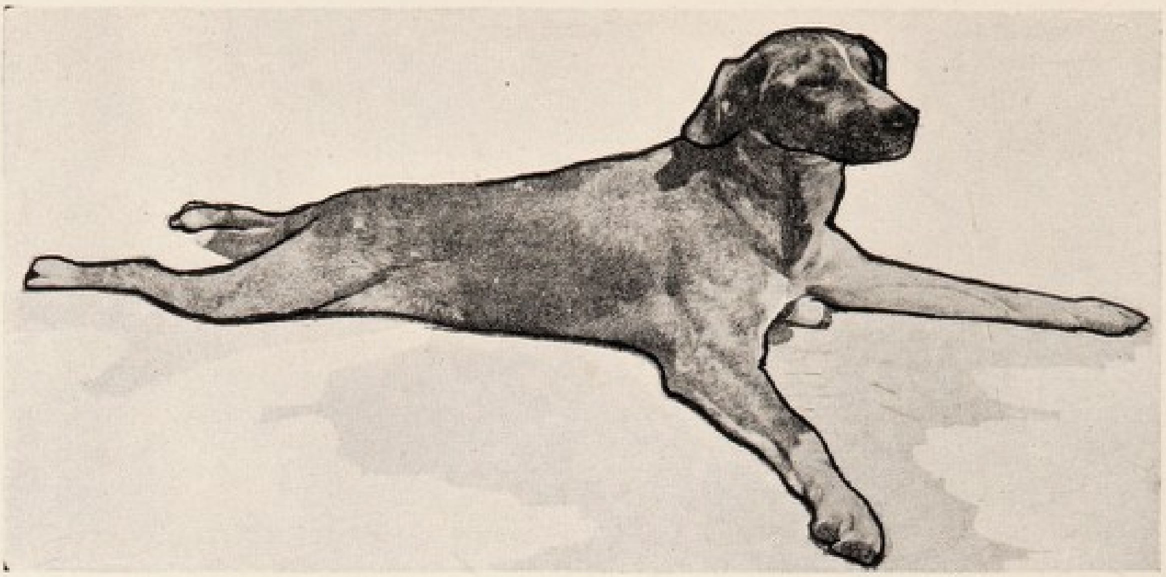


Fig. 3. Polyneuritic dog. The leg muscles were vigorously contracted, especially those of the hinder extremities, resulting in extension of all the limbs and inability of the animal to stand. If this dog was handled, severe clonic spasms resulted.

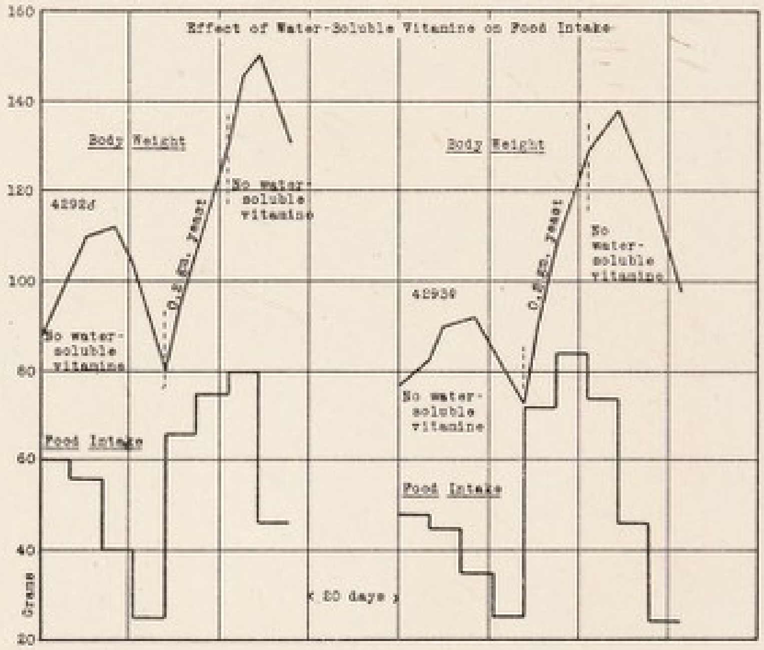
Fig. 4. Same dog as is shown in Fig. 3, 18 hours later and showing the effect of administering neutralized tomato juice. After such treatment the animal was able to walk although with a characteristic spastic or "steppage" gait. After repeated treatments extending over 4 days, the spasticity of the leg muscles and spastic gait almost entirely disappeared.

(From Cowgill, G. R.: *Am. Jour. Physiol.*, lvii, 1921, 420.)

The lower picture shows a rat which had been fed for one month on a diet deficient in water-soluble vitamine B. At this time the animal was so weak it was scarcely able to stand and would have died in a few hours if some source of this vitamine had not been furnished. After the picture was taken a small daily dose of yeast, which is very rich in the water-soluble vitamine, was given to the rat, the food remaining otherwise exactly as before. Twelve days later the upper picture was taken. The result is apparent.

(From photographs by Osborne and Mendel.)

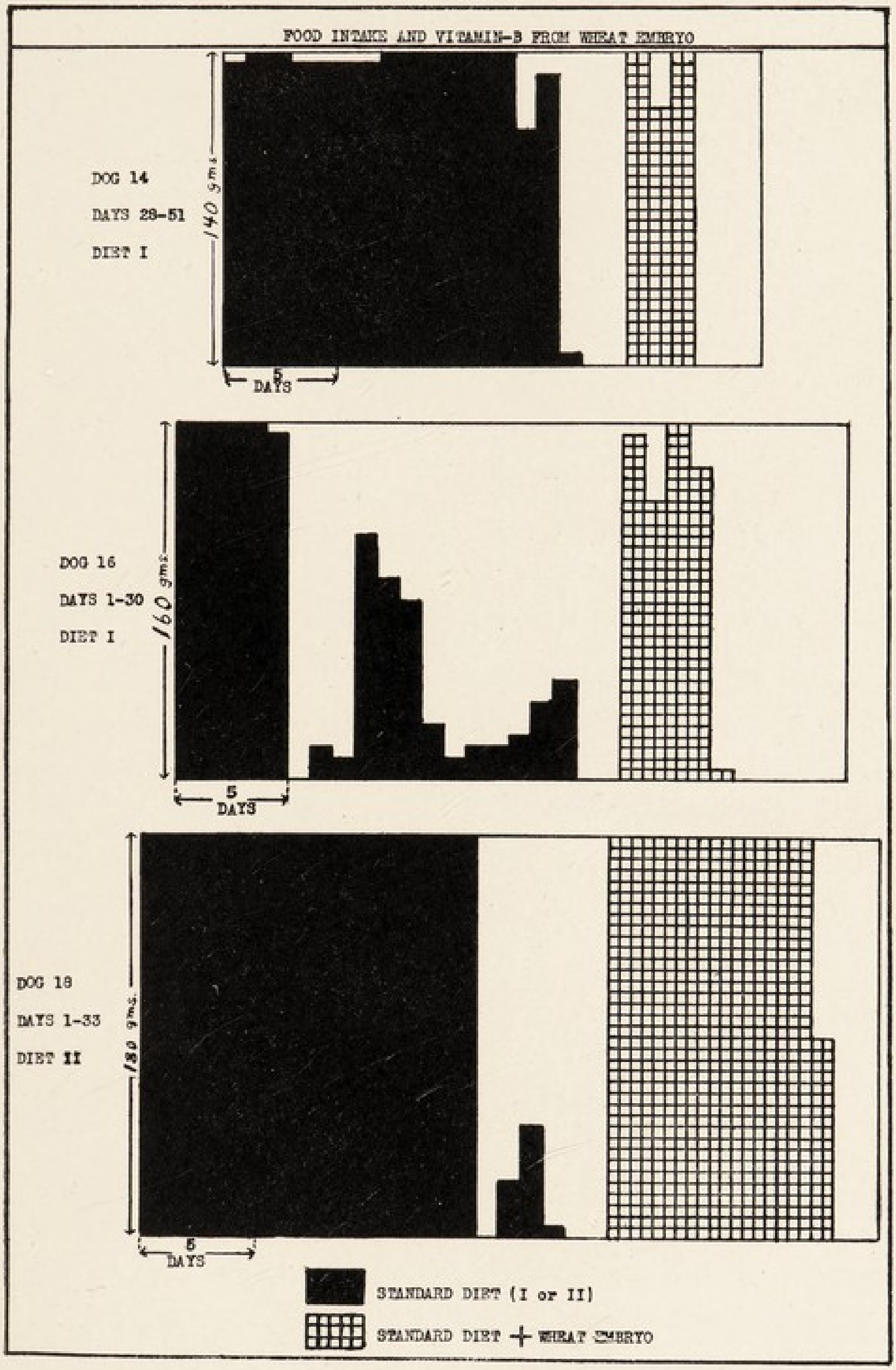
tributed of all these food factors—seems to be a failure to eat adequately. The administration of substances containing vitamine B soon brings about improved appetite and nutritive condition.



The lower line shows the grams of food eaten each week. During the first period, on a diet free from water-soluble vitamine B but otherwise adequate, food intake gradually fell to a very low level. When daily doses of 0.2 gram brewers' yeast were fed body weight and food intake increased with great rapidity. When the yeast was withheld body weight and food intake, after a few days, rapidly declined. Note that during the first week of the vitamine feeding Rat 4293 ate a quantity of water-free food equal to its own body at the beginning of the week.

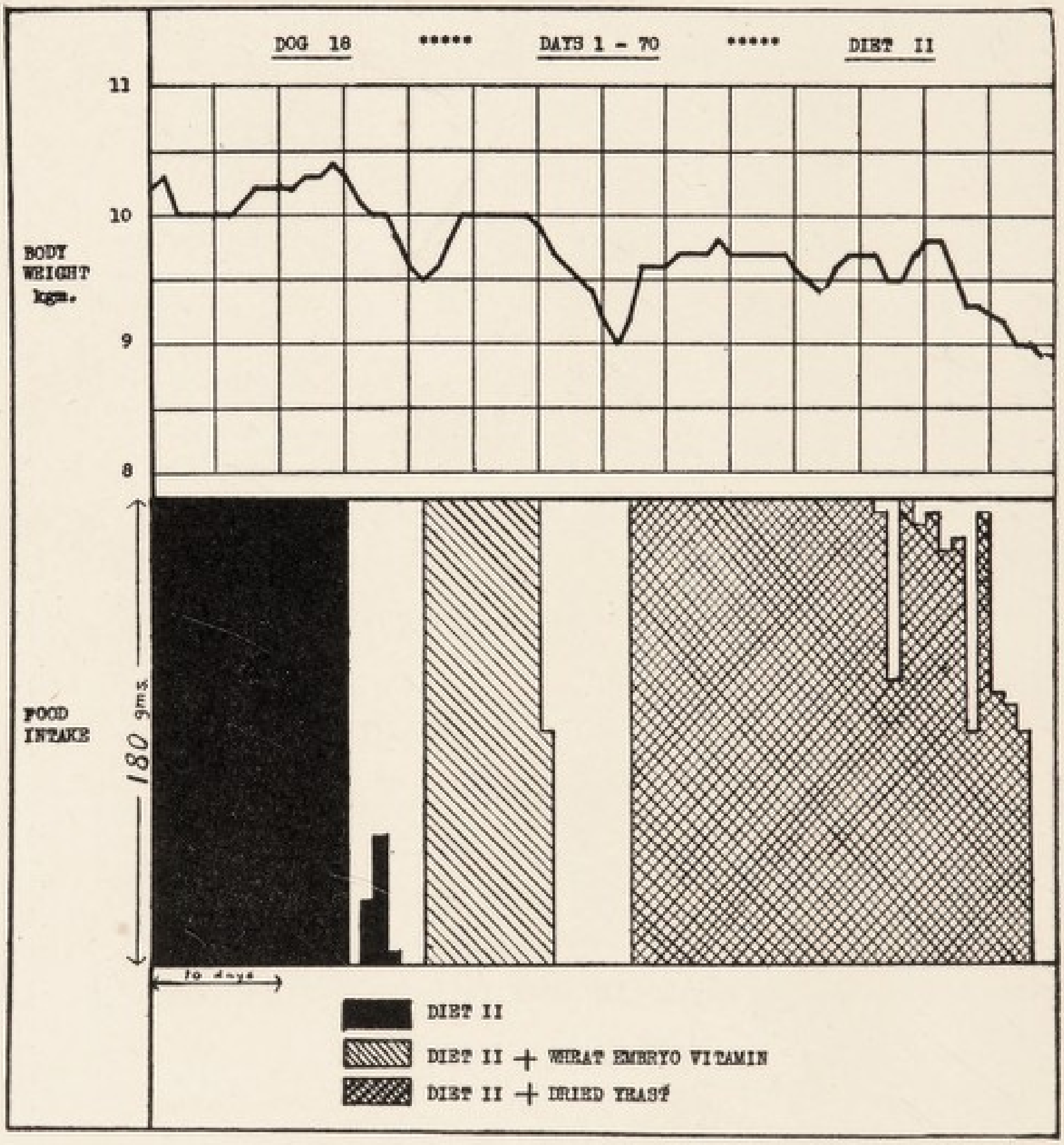
(Form *New York State Journal of Medicine*, July, 1920.)

The relation of cause and effect may perhaps be debated; but the end result is beneficial in any event. This vitamine does not act merely as a carminative or a gustatory stimulant, for the increased food intake can be secured even when the vitamine-bearing product is so administered that it cannot affect the senses of taste or smell.



(From Cowgill, G. R.: *Am. Jour. Physiol.*, lvii, 1921, 420.)

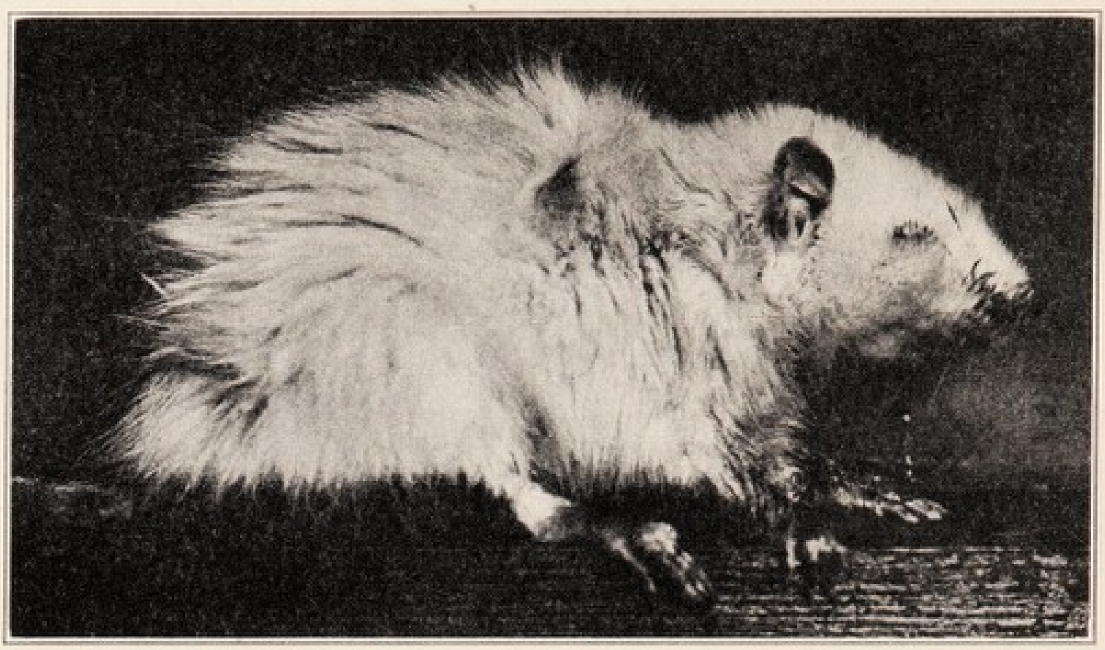
The benefit is apparently not due to any direct stimulation of alimentary secretions, for Dr. Cowgill has specifically investigated this point in my laboratory. How the vitamine acts—whether by promoting alimentary peristalsis, or by stimulating metabolic changes in cells as some drugs do, or by supplying an indispensable cellular ingredient as iodine does to the thyroid, or by some



(From Cowgill, G. R.: *Am. Jour. Physiol.*, lvii, 1921, 420.)

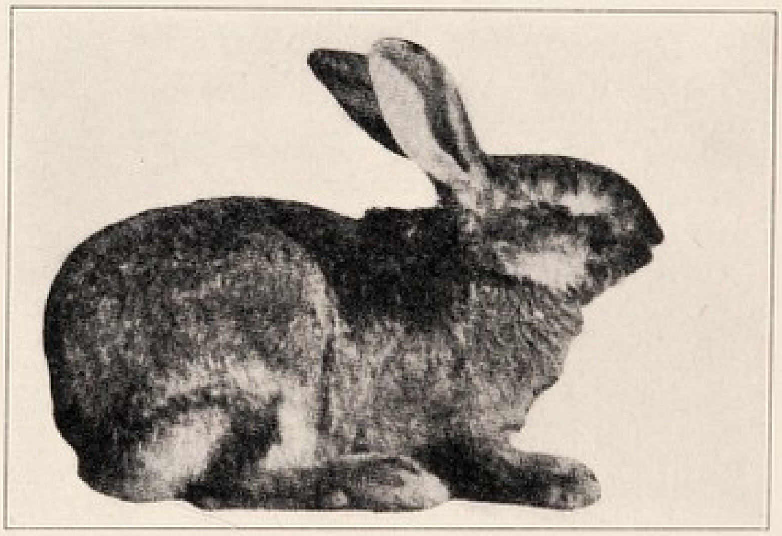
other undetermined procedure—has not yet been determined. The facts of experiment are striking by themselves apart from any theory; and when an animal is seen to recover in a few hours from severe prostration that is the direct or indirect consequence of vitamine deficiency, the phenomena may become almost dramatic in character. In watching a moribund animal grasp for a bit of some potent food product and recover within a few hours even when the diet offered and the hygienic environment remain unchanged, one stands before the seeming magic of the power of "little things" in nutrition.

The abnormalities just alluded to result from a lack of vitamine B in the diet. Among the extreme manifestations are the symptoms of beri beri and polyneuritis. Other aspects are doubtless concerned with the decrease in appetite or at any rate the diminished food intake observed when the supply of this vitamine is limited experimentally. When, on the other hand, the deficiency concerns vitamine A, the nutritive disturbance also brings about unsatisfactory growth to an extent depending on the degree of deficiency experienced. In this connection we discovered as early as 1913 that animals malnourished from lack of vitamine A may exhibit a peculiar ophthalmia. Although the malady does not yield to local treatment of the usual routine sort with antiseptic agents it almost always promptly disappears in a few days when some source of vitamine A is furnished. A single drop of good cod liver oil each day or a few milligrams of a suitable extract of green leaves will suffice to effect such cures in rats. When both vitamine A and B are present continuously in the diet this ophthalmia, which has already been detected



The effect of a diet deficient in fat-soluble vitamine A. Note the condition of the eye.

(From an experiment of Osborne and Mendel.)



This rabbit received a ration containing no vitamine A. The eyelids are swollen shut. This condition was quickly cured by adding butter fat to the ration.

(From *Circular* 73, Iowa Agricultural Experiment Station, 1922.)

in several species, does not arise. The statistics of 1000 rats representing essentially the entire group under study in our laboratory in one year are of interest in this connection.

RATS 5000-5999

	Total number of rats.	*Number with eye symptoms.*
On diets deficient in Vitamine A	136	69
On diets deficient in Vitamine B	225	0
On diets otherwise deficient	90	0
On diets experimental but presumably adequate	201	0
On mixed food (stock animals)	348	0
	1000	69

From this summary it will be seen that although nearly one-half of the thousand rats were on diets undoubtedly deficient, not a single case of the eye disease was observed in animals other than those experiencing a deficiency in the fat-soluble vitamine in the ration.

The ocular manifestations which appear in rats as the outcome of diets deficient in vitamine A have been studied by several of our collaborators, and have been described in detail by Yudkin[11] as follows:

[11] Yudkin, A. M.: "Ocular Manifestations of the Rat Which Result from Deficiency of Vitamin A in the Diet," *Jour. Am. Med. Assn.*, 1922, lxxix, 2206; see also Wason, I. M.: "Ophthalmia Associated with a Dietary Deficiency in Fat Soluble Vitamine (A)," *Jour. Am. Med. Assn.*, 1921, lxxvi, 908; and Mori, S.: "Primary Changes in Eyes of Rats Which Result from Deficiency of Fat-Soluble A in Diet," *Jour. Am. Med. Assn.*, 1922, lxxix, 197.

The first sign of an ocular complication is that the eyes water very freely, and the animals seem to dread the light more than a normal individual does. The normally prominent protruding eye of the rat gradually recedes into its bony orbital socket, and the photophobia increases. The animal facies assumes a sleepy appearance. Lacrimation increases and, instead of being watery, becomes more viscid. It is at this stage that the animal shows some signs of ocular irritation and rubs the lids with its front paws. A slight edema of the eyelids becomes manifest, and the viscid lacrimal secretion assumes a sort of serosanguineous character accumulating in the inner canthi in the form of crusts. The hair of the lids falls out, and the latter become thicker. When the swollen lids, which at this stage may be matted together with a dry secretion, are pushed back, accumulations of semisolid, fatlike, yellowish-white patches of secretion or perhaps exfoliated epithelium in the upper and lower fornices often appear.

In the early stages, the cornea shows no visible changes except for the marked congestion about its junction with the palpebral conjunctiva. There is no visible sclera in the albino eye. With the progress of the eye disturbance and following the swelling of the lids, the cornea shows some signs of haziness, particularly about the periphery. As the patches increase, the normal cornea reflex disappears. Frequently they are seen on the center of the cornea, but more often extend on to the corneal surface from the fornices. Thereupon the cornea becomes dry, lusterless and oily in appearance, losing its normal transparency. (P. 2207.)

Yudkin and Lambert[12] have pointed out, from a study of some of our affected animals, that the eye changes result-

[12] Yudkin, A. M., and Lambert, R. A.: "Location of the Earliest Changes in Experimental Xerophthalmia of Rats," *Proc. Soc. Exp. Biol. Med.*, 1922, xix, 375; "Lesions in the Lacrimal Glands of Rats in Experimental Xerophthalmia," *ibid.*, 376.

ing from deficiency in vitamine A and characterized by a widespread keratitis in the advanced stage, do not begin in the cornea but have their origin in the lids; and from their histological examinations it appeared that there is either a marked degenerative or an inflammatory change in the lacrimal gland. These alterations may account for some of the phenomena of so-called xerophthalmia. Yudkin believes that from the standpoint of a comparison of these ocular manifestations found in the albino rat with the somewhat similar clinical condition sometimes found in man, the early lesion resembles that described in the ophthalmic literature as xerosis of the conjunctiva and cornea; and the progressive changes of the cornea in the rat are like the condition known as human keratomalacia.

Another abnormality ascertained to be associated in many cases with lack of vitamine A is represented by phosphatic calculi which we have found deposited in the renal system of many animals subjected to a deficiency of vitamine A.[13]

The real significance and direct etiology of all these varied deviations from normal conditions of health remain to be ascertained. Bearing in mind that the pathological phenomena described are among the more obvious and unmistakable signs of disturbance one cannot avoid the suspicion that numerous less obvious yet equally detrimental defects or deteriorations as yet undetected and undetermined may also occur in so-called avitaminosis.[14]

[13] Osborne, T. B., and Mendel, L. B.: "The Incidence of Phosphatic Urinary Calculi in Rats Fed on Experimental Rations," *Jour. Am. Med. Assn.*, 1917, lxix, 32.

[14] McCarrison, Robert: "Studies in Deficiency Disease," *Oxford Medical Publications*, 1921; McCarrison, Robert: "Faulty Food in

Latterly both rickets and pellagra have been drawn into the category of vitamine-deficiency disorders. Doubtless multiple deficiencies often occur in which, as in rickets, the vitamine factor is only one of the contributory factors. In a critical essay on the etiology of rickets Professor Park[15] has defined the disease as follows:

> Rickets is a disturbance in the metabolism of the growing organism of such nature that the salt equilibrium, in particular as regards the calcium and phosphorus, in the circulating fluids is disturbed, and lime salts no longer deposit in the bones. Lime salts may not deposit because the ionized calcium in the blood is low, or because the ionized phosphate is low, or because both are low. When, however, the calcium in the blood is low, the formation of new bone and the destruction of old calcified bone (Umbau) is greatly accelerated, and the pathological process takes on a distinctive character. But no fundamental differences exist between the low calcium and the low phosphorus forms of the disease. Increasing knowledge concerning rickets has made it necessary to broaden the view in regard to the characteristic pathology and to admit to the disease all disturbances in metabolism in which lime salts cease to be deposited in the bones and cartilage. The first detectable signs of rickets are probably a diminution of the inorganic phosphorus or calcium of the blood.

Whether rickets is truly a so-called deficiency disease has been vigorously debated. The idea that it is merely a manifestation of a simultaneous lack of vitamine A and of an abundant calcium supply in the diet can no longer

Relation to Gastro-Intestinal Disorder," *Sixth Mellon Lecture*, delivered before the Society for Biological Research, University of Pittsburgh School of Medicine, November 18, 1921.

[15] Park, E. A.: "The Etiology of Rickets," *Physiol. Rev.*, 1923, iii, 106.

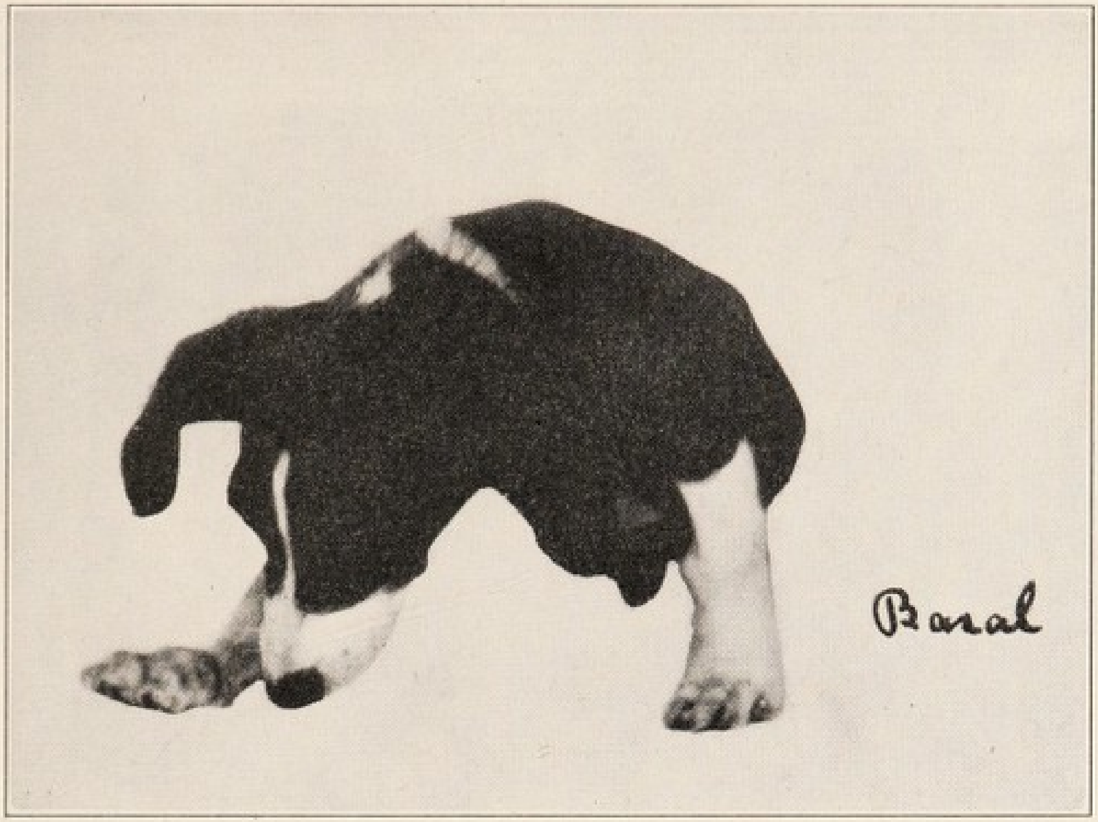
be strictly maintained. Cod liver oil, which Osborne and I found to be rich in vitamine A, is regarded by McCollum and others to contain an organic substance (X), distinct from the A factor, causing lime salts to deposit in the bones in rickets. Sunlight and other sources of radiant energy accomplish similar effects. Park has summarized the widely divergent suggestions in this conclusion:

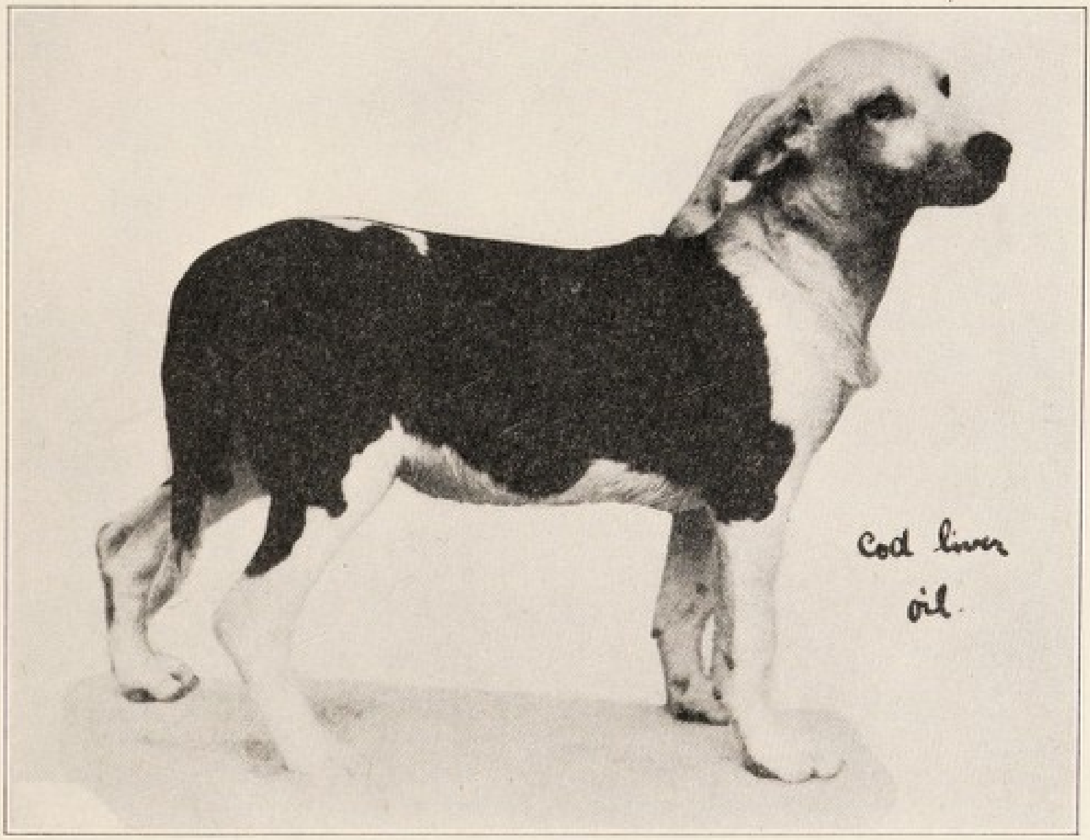
As the result of clinical observation and investigation it has become clear that two factors exist, the one in radiant energy, the other in an unknown form in certain foods, either of which is capable of preventing rickets from developing or from continuing, if already established. It has become equally clear, also, that only when the organism is deprived of the influences of radiant energy and of X, can rickets develop. Recent advances in knowledge have failed entirely to disclose the nature of vitamines, or their mode of operation in the organism or the mode of operation of the ultra-violet radiations of the environment. They have revealed, however, certain of the effects upon the organism of radiant energy and of X; both exercise a stimulatory or a regulatory influence on the metabolism of the body, in particular of the calcium and phosphorus. One at least of their functions appears to be the protection of the organism from the dangers attendant on the absorption and entrance into the blood of substances which might disturb its salt balance. Moreover, increased knowledge has indicated that the rôle played by radiant energy and X in the maintenance of the normal salt metabolism is of the utmost importance, and that the organism is dependent on the energy of the sun's rays or of their equivalent in the food to an extent little appreciated. The facts enumerated indicate beyond a doubt that rickets is a deficiency disease. Moreover, they settle for all time the differences of opinion between the English and the

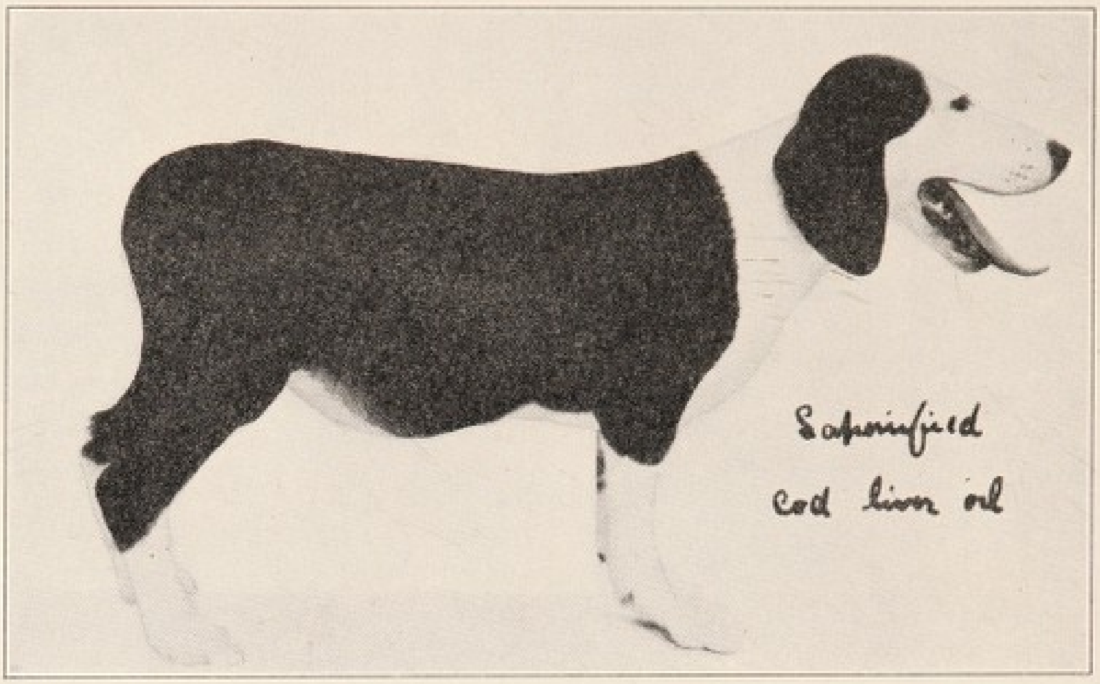
Scottish schools concerning the cause of rickets. Rickets is a dietetic disease, since, for its development the diet must be insufficiently supplied with the factor X. At the same time it is a disease of defective hygiene, since for its development there must be an insufficient supply in the environment of the radiant energy which exerts the protective action. The facts just mentioned also explain the disagreement among the students of rickets, the world over, concerning the causation of the disease. Obviously two factors have been concerned, but all investigators have proceeded on the assumption that only one factor was concerned, and have perceived so clearly the existence of the one that they have denied the possibility of the existence of the other. (P. 147.)

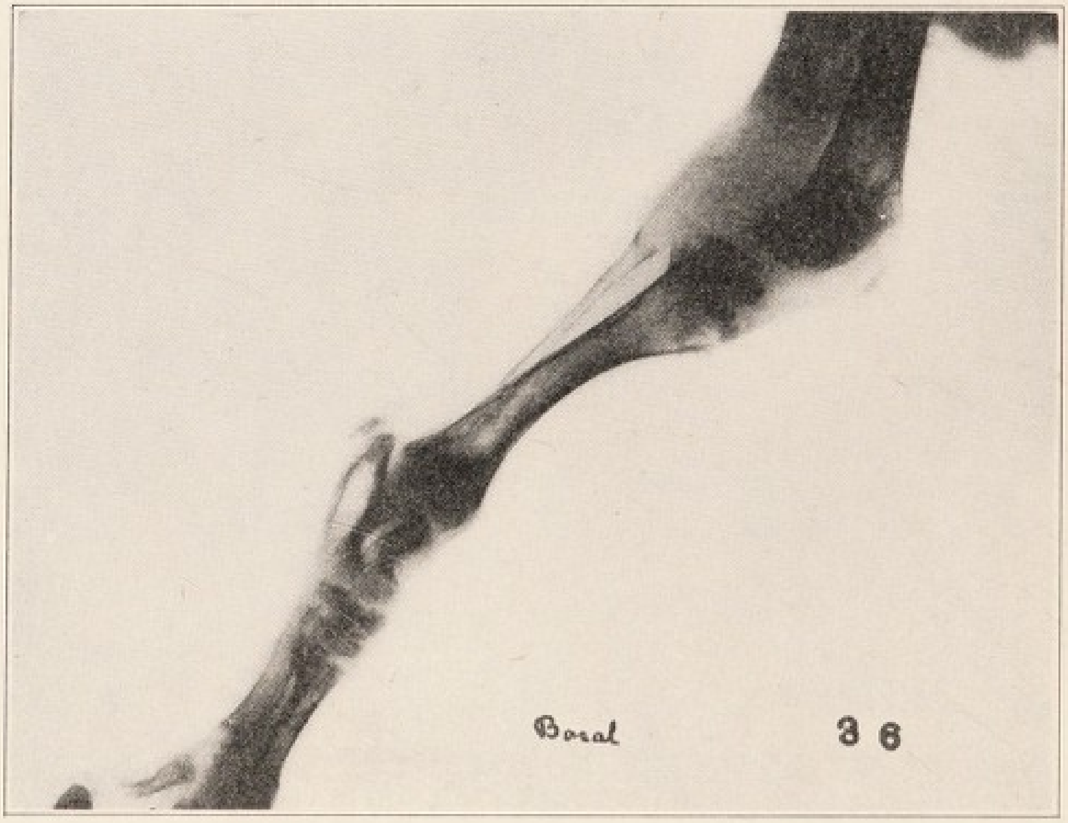
The untoward effects of the lack of the factor or factors supplied by cod liver oil have been demonstrated strikingly by Steenbock, Jones and Hart.[16] When puppies were given a ration of cooked white corn meal and oatmeal *ad libitum,* together with casein, common salt, calcium phosphate and skimmed milk—a ration poor in the factor which cod liver oil supplies—growth was inhibited, tetany resulted, the calcium and phosphorus content of the blood serum was much reduced, and the bones were poorly calcified, as shown by their ash content and the x-ray pictures. The addition of 5 c.c. cod liver oil per day, or the unsaponifiable material from the latter, changed the picture to that of successful growth, as the illustrations indicate.

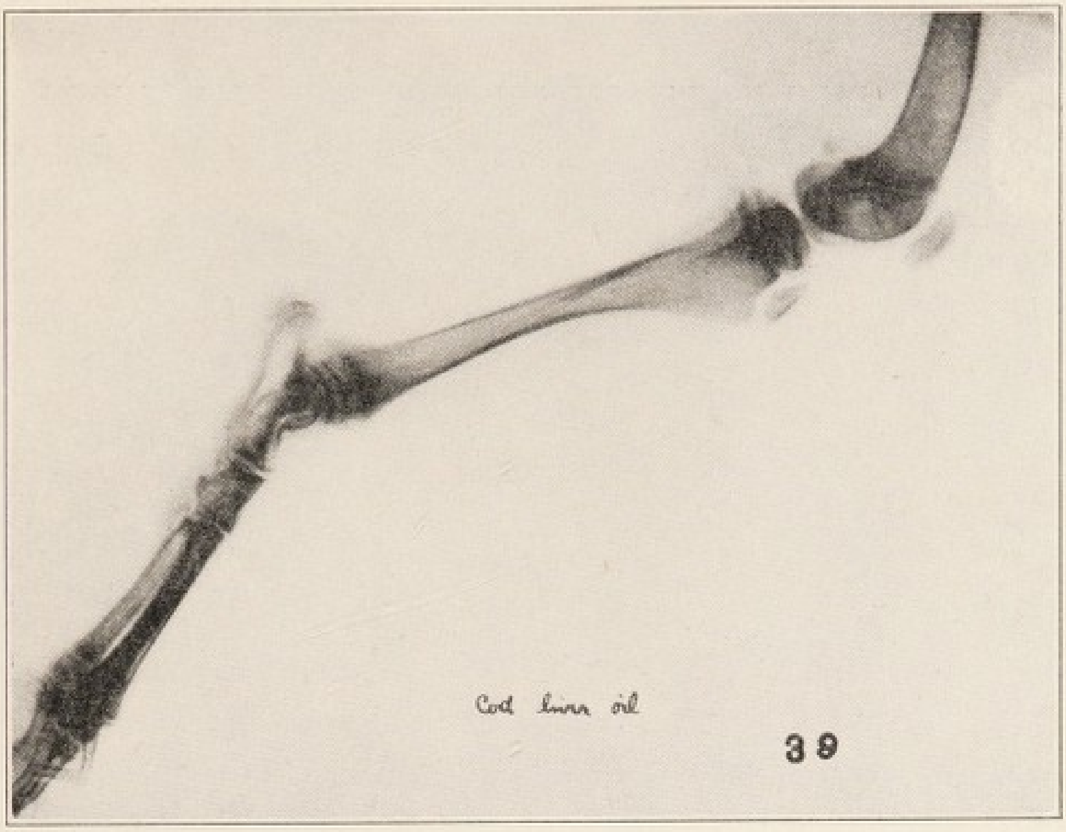
[16] Steenbock, H., Jones, J. H., and Hart, E. B.: "Stability of Vitamine in Cod Liver Oil," *Jour. Biol. Chem.,* 1923, lv, p. xxvi.

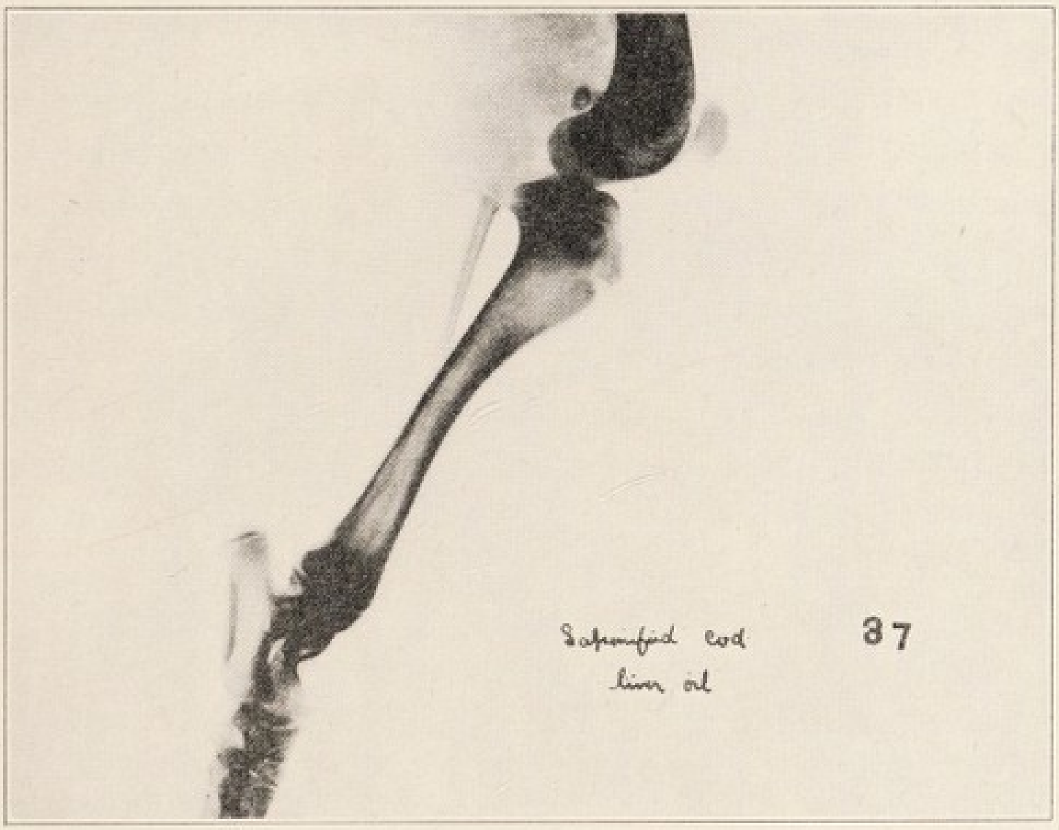

Basal


Cod liver
oil.


Saponified
cod liver oil


Boral
36


Cod liver oil
39


Saponified cod liver oil
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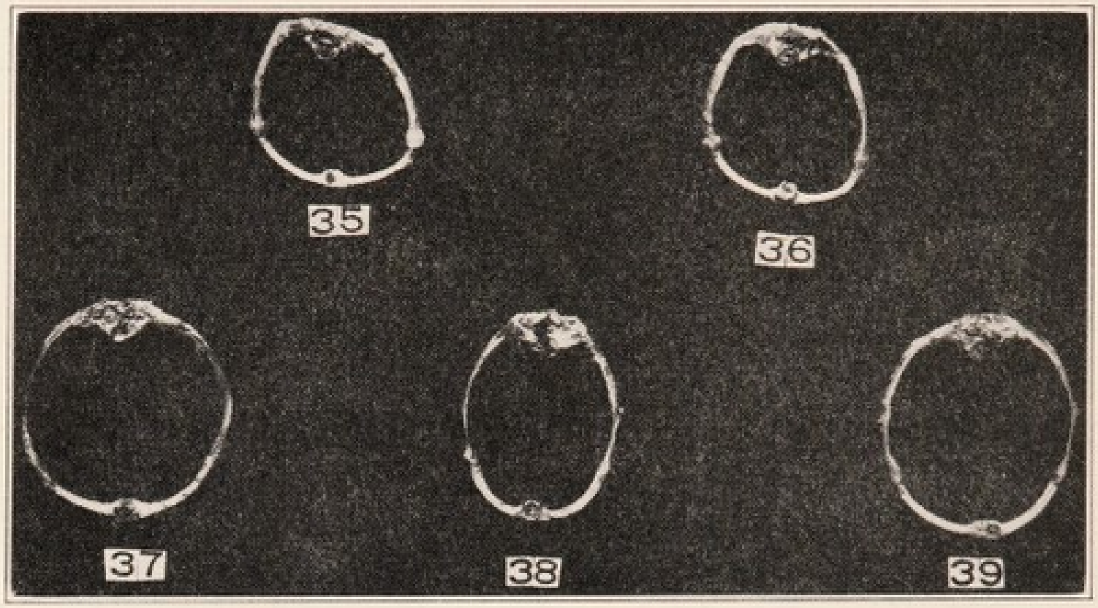


These pictures show the effect of a diet lacking the vitamine contained in cod liver oil on the growth of puppies. The basal ration consisted of cooked white cornmeal and oatmeal *ad libitum* and 5 grams of casein, 2 grams of sodium chloride, 5 grams of calcium phosphate, and 200 c.c. of skimmed milk per day. Some of the animals received daily in addition to this 5 c.c. of cod liver oil or the unsaponifiable material obtained from 5 grams of cod liver oil. Such dogs showed normal growth, normal Ca and P in the blood serum, normal ash content of the bones, and normal distribution of inorganic materials in bone as determined by x-ray examination.

Without the cod liver oil adjuvant, saponified or not, growth was inhibited, tetany resulted, Ca and P in serum were much reduced, and bones were poorly calcified as shown by ash content and x-ray examination.

The pictures of the ribs show the characteristic enlargements in dogs 35 and 36 on the basal diet.

These pictures are shown through the courtesy of Professor H. Steenbock.

Favorable observations on the effect of cod liver oil in promoting the use of calcium and phosphorus in rabbits also have lately been reported by Sjollema.[17]

What the chemical nature of these potent substances is, cannot yet be foretold. At present they are known only by their manifestations. The widespread assumption that the vitamines are easily destroyed by heat at such temperatures as food may be subjected to in cooking is only partly justified. Factors other than heat may modify the results. The current belief has doubtless had its origin in the comparative instability of the antiscorbutic property of many foods to heat. However, even the antiscorbutic vitamine can be preserved to some extent at least, notably in the case of acid fruits, milk or vegetables, after moist sterilization or desiccation under certain conditions. Vitamine A seems also to be deteriorated when products containing it are heated with free access of oxygen. It is apparently not identical with known lipoids, simple fats or fatty acids despite its comparable solubilities. We have steamed potent butter fat for hours without depriving it entirely of vitamine A. We have repeatedly fed green leaves dried in warm air and have found that the vitamine A which they contain was by no means entirely destroyed. Several investigators have reported that fats containing vitamine can be subjected to vigorous saponification without destroying the vitamine factor.[18] It seems

[17] Sjollema, B.: "L'Influence de L'Huile de Foie de Morue sur le Métabolisme du Calcium," *Archives Néerlandaises de Physiologie de l'Homme et des Animaux*, 1922, vii, 384.

[18] McCollum, E. V., and Davis, M.: "Observations on the Isolation of the Substance in Butter Fat Which Exerts a Stimulating Influence on Growth," *Jour. Biol. Chem.*, 1914, xix, 245 (butter fat); Zucker, T. F., Johnson, W. C., and Barnett, M.: "The Acid Base

to be associated with the unsaponifiable fractions, not with the fatty acids; and it is not identical with cholesterol. The resistant material obtained by saponifying cod liver oil with 20 per cent alcoholic potash for half an hour, extracting with ether and resaponifying the extracted product seems to be as potent as the oil from which it was obtained, in facilitating the proper deposition of bone constituents, according to the beautiful demonstrations of Steenbock, Jones and Hart already referred to. Zucker[19] has lately stated that a good yield of crude active product can be obtained by directly extracting cod liver oil with 95 per cent alcohol. This mixture of fatty acids, a small amount of oil, and other substances, is saponified with sodium hydroxide, and when the calcium soaps are precipitated from an aqueous solution, the unsaponifiable material, including the active substance, is precipitated with the soap. From this calcium soap, acetone will extract the active material. In this way he has obtained preparations of the active material which after a dilution of 1 : 1000, are as active as the original cod liver oil. With regard to the properties of the active material thus obtained Zucker states that it is not toxic in doses of more than 50 times the curative dose used in treating rickets. He found that a single large dose brings about healing at the same rate as a succession of smaller doses. The purified active material of Zucker is reported to be entirely free from fat-soluble A, as shown by the fact that it will not cure xerophthalmia in cases in which a

Ratio of the Diet in Rickets Production," *Proc. Soc. Exp. Biol. Med.*, 1922, xx, 20 (cod liver oil); also footnote 16.

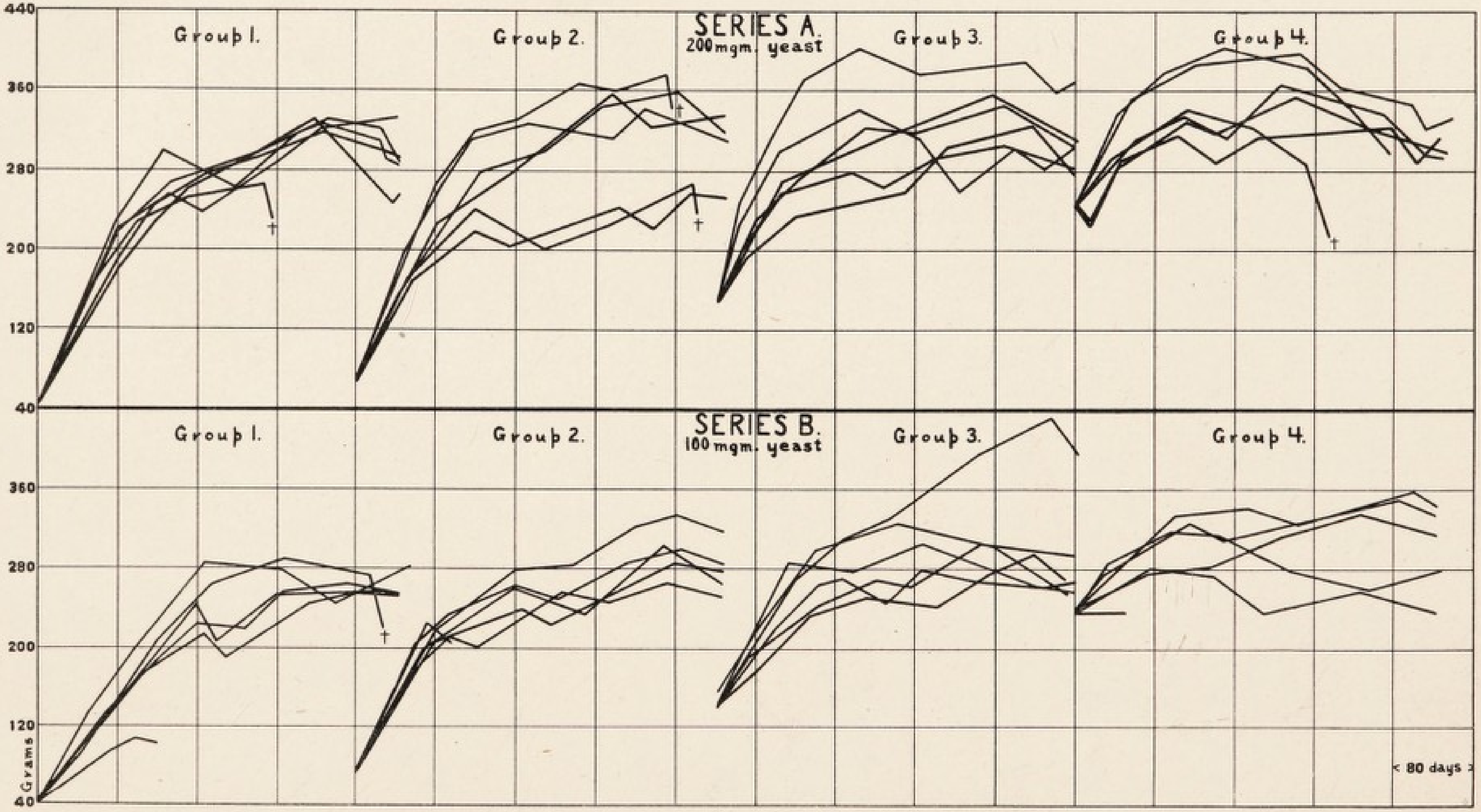
[19] Zucker, T. F.: "Further Observations on the Chemistry of Cod Liver Oil," *Proc. Soc. Exp. Biol. Med.*, 1922, xx, 136.

subsequent treatment with butter fat does relieve the condition.

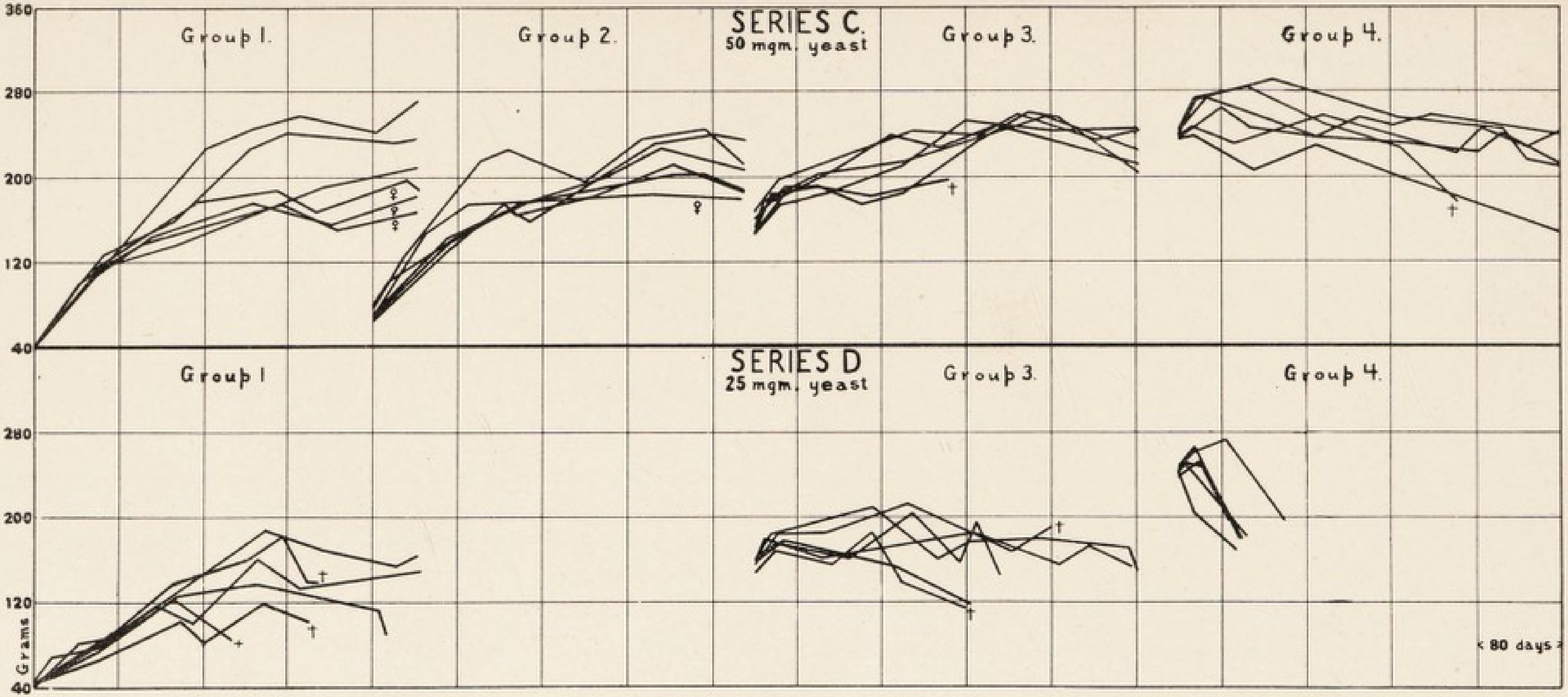
Vitamine B seems to be more resistant to destruction. Products containing it can be boiled with dilute acid without materially decreasing their potency. In alkaline media, however, the vitamine is unstable.

During the course of our investigations preparations containing a considerably higher concentration of the vitamines than the original sources exhibit have been prepared in the case of both vitamines A and B. For example, Osborne and Wakeman have separated from yeast a fraction of the cell content showing a vitamine B potency at least ten times as great as that of the mother substance furnishing it. Thus as little as 13 mgm. ($^{13}/_{1000}$ of a gram) of such preparations per day have sufficed to supply the needed vitamine B to young rats to which an otherwise adequate diet was furnished. If one considers that the greater part of such concentrates as have already been prepared consists of non-vitamine components, the minuteness of the requisite daily dose becomes impressive. It is probably represented by a few parts per million of the active body tissues.

That the vitamine requirement bears some quantitative relationship to the tissues of the animal concerned appears to follow clearly from many of our experiments. Thus in the following charts it will be noted that there is a minimum of daily requirement of vitamine B furnished in the form of dried yeast below which the food intake and consequent growth no longer are optimal in character. Furthermore a daily allowance of vitamine B which suffices for a small animal may no longer suffice when the latter has become larger in size.



(From Osborne and Mendel: *Jour. Biol. Chem.*, liv, 1922, 739.)



Charts 1 and 2. Representing the comparative effect produced by various daily doses of dried brewery yeast, offered apart from the rest of the ration as the sole source of vitamine B, on rats receiving an otherwise uniform food mixture. Each series represents, where possible, the results of a year's feeding period beginning with animals at different sizes (40, 70, 150, and 240 gm., respectively) in the different groups. It should be noted that with the continuance of growth the dose per unit of size decreases.

(From Osborne and Mendel: *Jour. Biol. Chem.*, liv, 1922, 739.)

The quantitative character of this need is further shown by tests of other sources of vitamine B. It is particularly evident in the case of milk, to which we have devoted considerable attention, because of the enormous practical importance of the subject.

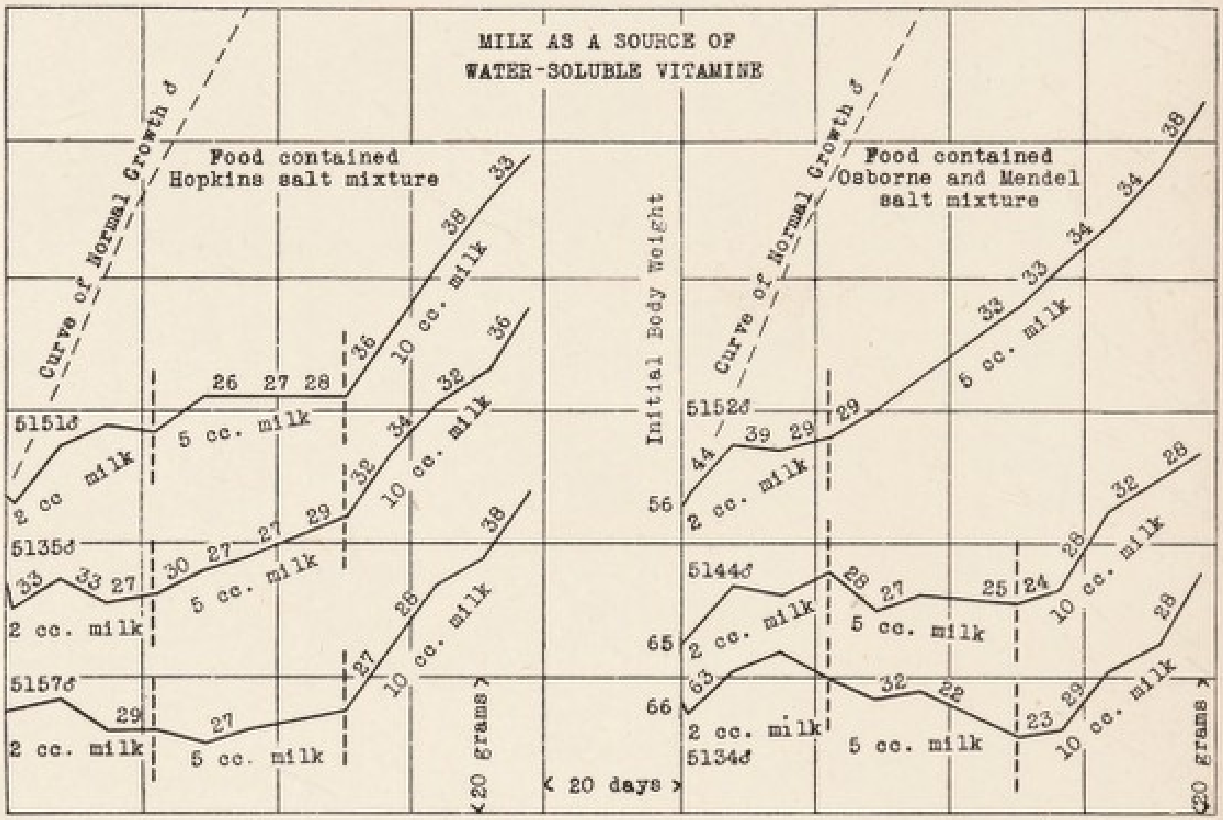


Chart showing that rats grow at approximately the same rate whether they receive a salt mixture similar to that used by Hopkins or the salt mixture used by ourselves, when like quantities of milk supply all the water-soluble vitamine. The weekly food intakes, expressed in gm. (exclusive of the milk solids), are indicated, where available, on the curve of growth.

(From Osborne and Mendel: *Jour. Biol. Chem.*, xli, 1920, 515.)

The quantitative data available regarding the requirement of vitamine A likewise show the absolute quantities involved to be surprisingly small. A few milligrams of

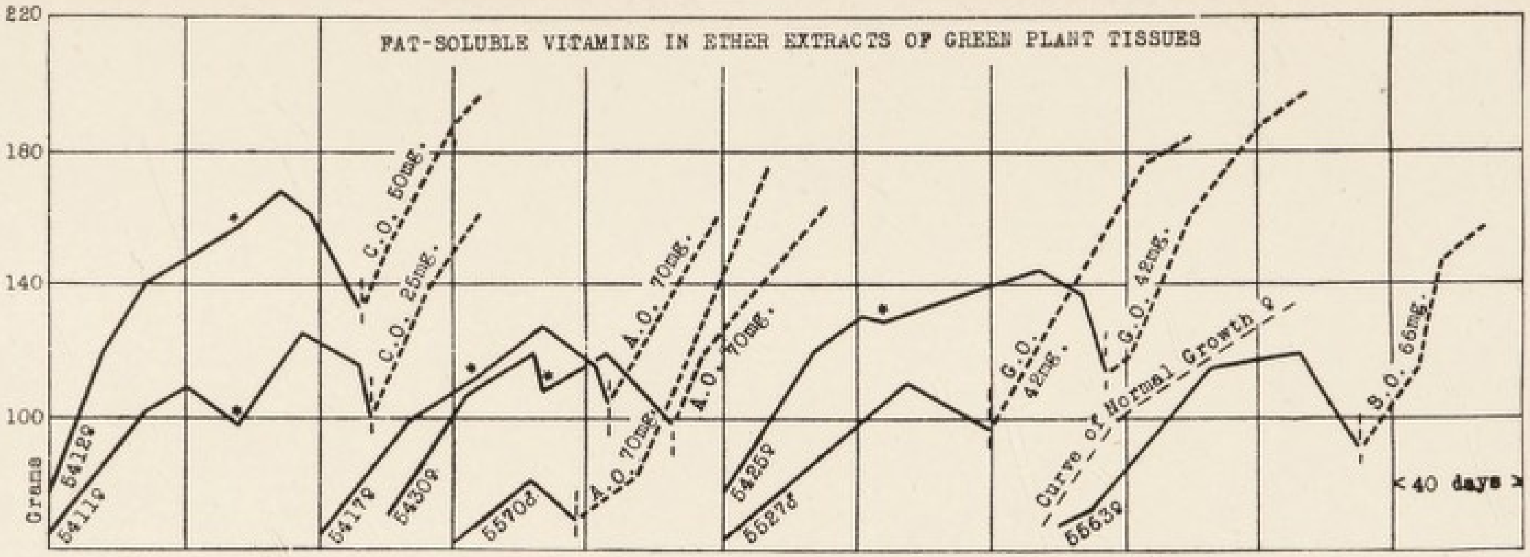


Chart showing the efficiency of U. S. P. ether extracts from clover, alfalfa, grass, and spinach respectively as sources of fat-soluble vitamine in promoting restoration of growth in rats that had begun to decline on diets otherwise adequate. An asterisk (*) marks the period at which the daily allowance of dried brewery yeast, fed apart from the rest of the food, was increased to 0.6 gm. Note that this addendum alone sufficed to promote the growth of the animals for a time in some instances, although decline ultimately ensued in every case. Rats 5417, 5570, 5425, and 5563 developed the characteristic eye disease, which in each case disappeared after the administration of the plant oil. Interrupted lines indicate the periods during which the plant oils were fed mixed with starch and apart from the rest of the ration. C.O. = clover oil; A.O. = alfalfa oil; G.O. = grass oil; S.O. = spinach oil. The daily dose is indicated on the chart.

(From Osborne and Mendel: *Jour. Biol. Chem.*, xli, 1920, 549.)

good cod liver oil per day suffice to furnish enough of this essential to a growing rat. Zilva and Miura[20] rated it at 1.7-5 mgm. for the oils they tested; Holmes'[21] figures for American products are of the same order of magnitude. If it is true that the active component is a non-saponifiable fraction the absolute quantity here involved must be very small, representing less than 0.02 per cent of the food. Osborne and Mendel[22] obtained potent oily extracts from the leaves of clover, spinach and alfalfa. (See p. 101.)

A comparison of the content of vitamine B, measured in terms of the quantity of the edible substance, required to promote growth on an otherwise adequate diet in 100-gram rats is shown for a few foods in tabular summary from our own experiments:

[20] Zilva, S. S., and Miura, M.: "The Quantitative Estimation of the Fat Soluble Factor," *Bioch. Jour.*, 1921, xv, 654.

[21] Personal communication from Dr. A. D. Holmes.

[22] Osborne, T. B., and Mendel, L. B.: "The Extraction of 'Fat-Soluble Vitamine' from Green Foods," *Proc. Soc. Exp. Biol. Med.*, 1919, xvi, 98.

COMPARISON OF CONTENT OF VITAMINE B
IN SOME EDIBLE SUBSTANCES

Measured in terms of requisite daily dosage for a 100-gram rat on an otherwise adequate diet free from vitamine B

	As served. grams	*Dry solids. grams*
Cow's milk	15	1.9
Human milk	15	1.8
Spinach	12	0.5
Lettuce	11	0.4
Cabbage	10	1.0
Orange juice	10	
Lemon juice	10	
Grapefruit juice	10	
Apples	>10	
Grape juice	>10	
Turnip	8.5	1.0
Carrot	8.5	1.0
Potato, skinned	8	2.0
Tomato	5	0.5
Okra	5	0.5
Whole egg	4	
Asparagus	2	0.2
Prunes	2	0.4
Egg yolk	1.5	0.8
Liver	<1.5	<0.5
Cereals		>3.0
Yeast		0.1
Avocado		0.5

Little is gained by attempting to convert these findings into terms of human dosage inasmuch as the multiplication factor for calculation is not known. Furthermore the relative needs of the human species may be quite different. Judged by comparative trials made by Osborne and Mendel on rats the juices of the orange, lemon and grapefruit are about as rich as is cow's milk or human milk in vitamine B. An ounce of fresh green vegetables like lettuce and spinach may be equivalent to one and a half ounces or more of fresh milk. The average-sized hen's egg is equivalent in vitamine B potency to about 150 c.c. of cow's milk; or a quart of milk and six or seven whole eggs of the average sort have approximately equivalent vitamine B values.

In the current discussions of food values considerable stress is being placed on the vitamine content. Only a few years ago the calorie aspect of the subject overshadowed all else in the comparisons of edible products. On that basis many of the fruits and vegetables secured a low rating. Today there is a tendency to emphasize or even overemphasize factors other than fuel values. The milling of grains, particularly wheat, has long furnished a question for vigorous debate, the loss of the embryo and cortical parts of the grain being stressed by the opponents of the popular patent flour and white bread. Part of this discussion now involves the possible location in the discarded offal not only of proteins and salts but also of vitamine. Cereal grain embryos are known to be rich in vitamine B; but the newer studies have demonstrated that by no means all of the vitamine of the wheat kernel is located in its embryo. Thus Bell ascertained the distribution in the milling products from one lot of wheat in my laboratory as follows:

DISTRIBUTION OF VITAMINE B IN MILLING PRODUCTS OF WHEAT

An attempted estimate of the distribution of the vitamine B in milling products of Minnesota winter wheat may be summarized in tabular form as follows:

Product	*Minimum percentage adequate in diet*	*Concentration of vitamine B referred to whole wheat*	*Percentage whole wheat milled into each part*	*Percentage vitamine B contained in each part*
Whole wheat	40	1	100	100
Patent flour	(?)	0-0.10(?)	50	0-5
First clear	40(?)	1-0.67(?)	15	15-10
Second clear	40	1	5	5
Low grade	20	2	8	16
Middlings	10	4.	10	40
Bran	20	2	12	24
Total			100	100

(From Bell and Mendel: *Am. Jour. Physiol.*, lxii, 1922, 145.)

At the present time there is considerable evidence that the ultimate source of the vitamines is to be sought in the plant kingdom; but the precise answer to the question of where, when and how the vitamines arise, still remains to be formulated.

That fertility and successful breeding may be modified by food has more than once been suspected. It is easy to imagine that a diet deficient in some respect may lead to impairment of the generative functions quite as well as it does to other abnormalities. When, however, animals which appear to grow up vigorously and be maintained in perfect health on certain foods nevertheless fail to produce young, we are face to face with some subtle factor. Can a diet adequate for somatic growth be inadequate in respect to the gonads or the functions of generation? Various investigators have pointed recently to this possibility which may concern mating instincts, the oestrus cycle, the testes, the ovaries, the uterus, placentation, etc. Stockard of New York and Evans and his associates at the University of California in particular have devoted much attention to this subject. The latter[23] have pointed out that:

> The sterility of dietary origin yields a highly characteristic picture. Animals suffering from it do not differ so profoundly from normal ones in their ovarian function as they do in placental behavior. Approximately the same number of Graafian follicles mature and rupture per ovulation and the ova are fertilized and implanted. The placentae are abnormal. They may persist almost throughout gestation but show as early as the second day of their establishment beginning blood extravasations which increase in extent. Resorption invariably overtakes the products of conception.
>
> Natural foodstuffs contain a substance, X, which prevents such a sterility or which cures the disorder occasioned by the purified dietary régime. We have thus been able to witness a comparatively sudden restoration of fertility to animals of proven sterility, and whose controls continued sterile, by the administration of fresh green leaves of lettuce. Even the dried leaves of alfalfa appear to possess a similar potency. The proven efficacy of leaves invites inquiry into the certainty of segregation of the new dietary factor from vitamines A and

[23] Evans, H. M., and Bishop, K. S.: "On the Existence of a Hitherto Unrecognized Dietary Factor Essential for Reproduction," *Science,* 1922, lvi, 650; also *Am. Jour. Physiol.,* 1923, lxiii, 396.

C. As regards A, it is conceivable that amounts of A adequate for normal growth, freedom from eye disease and, indeed, vigorous health might still be inadequate for the reproductive function. . . . It is perhaps also pertinent to point out that we have detected an invariable sign of inadequacy in the A factor of greater delicacy than those hitherto employed and may thus recognize such inadequacy long before growth impairment, for instance. The sign is constituted by a highly characteristic aberration of the oestrous cycle. . . .

The beneficial dietary factor can not be identical with the antiscorbutic vitamine C, for curative effects have been secured when ground whole wheat was added to our purified ration, and the cereals are, of course, notably deficient in C. Moreover, although some favorable influence on growth has been noted, it has been impossible for us to secure with orange juice the fertility effects so evident with lettuce. (P. 650.)

Osborne and I have observed the failure of rats to breed when kept on certain rations which permitted a seemingly excellent growth of both sexes to full adult size and therefore appeared to be adequate from the ordinary standpoint of successful nutrition. The problems here raised concern a large and important aspect of the relation of foods to the physiological functions. It is the desert of Evans and Scott Bishop to have demonstrated that although the conventional ration of isolated food substance together with sources of vitamines A and B permits normal growth in the rat, it produces sterility; and this effect ensues without upset of fecundity. Ovulation occurs and a normal number of ova are fertilized and implanted. The pathology of the sterility involves "a highly peculiar deficiency disease of the placenta cured by the administration of certain foods."

The effect of diet upon lactation has long been a subject for detailed consideration. Experiments conducted in my laboratory appear to be in harmony with the widespread belief that changes in diet are more liable to change the flow of milk than its composition. Reviewing the literature, Meigs[24] has stated, for cattle:

> Both the milk yield and the composition of the milk may be considerably influenced by changes in the ration. Of the three main organic constituents of the milk, the carbohydrate is by far the most constant; its concentration is not affected by any of the changes in ration so far studied. Reductions in the protein of the ration result very generally in reductions in the milk yield. The nitrogen content is usually either decreased or unaltered, and the fat content may be altered in either direction or may remain unchanged. Reductions in the fat of the ration have little or no effect on the composition and yield of milk until the amount of fat fed falls below 1 gram per kilogram of animal. When it falls below this level, the milk yield and the fat content of the milk are generally reduced, while the nitrogen content is increased. Small changes in the amount of carbohydrate fed, comparable in absolute magnitude with those which have been studied in the case of protein and fat have no immediate significant effect on either the yield or the composition of the milk. Large reductions, amounting to 50 per cent of the total nutrients contained in the ration, reduce the milk yield and the concentration of nitrogen in the milk, while leaving the fat and carbohydrate content practically unchanged. The effects of changes in the amounts of carbohydrate fed when the total quantity of this constituent in the basal ration is reduced to a minimum, have not been studied. . . .

There are numerous other experiments which show that

[24] Meigs, E. B.: "Milk Secretion as Related to Diet," *Physiol. Rev.*, 1922, ii, 204.

milking animals may remain for considerable periods in marked negative calcium and phosphorus balance without showing much drop in milk yield. (P. 208.)

With respect to the vitamines, however, there is more or less evidence tending to indicate that changes in the vitamine content of the diet influence directly the concentration of the vitamines in the milk. Apparently in this respect feed may be quite as important as breed for the quality of the milk secreted. Particularly does this seem to be true for the antiscorbutic potency and the content of vitamine A in cow's milk.

IV.

THE PROTEIN FACTOR IN NUTRITION

SINCE the days of Magendie, Boussingault and Liebig the pendulum of enthusiasm about the proteins has swung from one extreme to another. Liebig's doctrine of the superior rôle of proteins in the nutritive functions has already been cited; in contrast with it are the widely discussed views of Chittenden.[1] An illustrative statement by the latter may be quoted:

The peculiar position which proteid foods occupy in man's dietary naturally make them the central figure, around which the other foods are grouped. No other form of food can take the place of proteid; a certain amount is needed each day to make good the loss of tissue material broken down in endogenous katabolism, and consequently our choice and combination of the varied articles of diet made use of should be regulated by the amount of proteid they contain. But while proteid foods occupy this commanding position, it is not necessary or desirable that they should exceed the other foodstuffs in amount, or indeed approach them in quantity. We must be ever mindful of the fact, so many times expressed, that proteid does not undergo complete oxidation in the body to simple gaseous products like the non-nitrogenous foods, but that there is left behind a residue of non-combustible matter—solid oxidation products—which are not so easily disposed of. In the forceful language of another, "The combustion of proteid within the organism yields a solid ash which must be raked

[1] Chittenden, R. H.: *The Nutrition of Man*, F. A. Stokes Company, New York, 1907.

down by the liver and thrown out by the kidneys. Now when this task gets to be over-laborious, the laborers are likely to go on strike. The grate, then, is not properly raked; clinkers form, and slowly the smothered fire glows dull and dies" (Curtis).

Even though no such dire fate overtakes one, the penalties of excessive proteid consumption are found in many ills, for which perhaps the victim seeks in vain a logical explanation; gastro-intestinal disturbance, indigestion, intestinal toxaemia, liver troubles, bilious attacks, gout, rheumatism, to say nothing of many other ailments, some more and some less serious, are associated with the habitual overeating of proteid food. But excessive food consumption is by no means confined to the proteid foodstuffs; general overfeeding is a widespread evil, the marks of which are to be detected on all sides, and in no uncertain fashion. (P. 269.)

The controversy has continued. Thus McCay[2] subsequently remarked:

The general conclusion arrived at, from a broad consideration of all the facts available in the present state of our knowledge, is that the views held by the older writers on nutrition are sounder and more in accord with the findings of careful scientific study than are those of the newer school. Voit, who may be taken as a distinguished representative of the former, stands to-day absolutely vindicated; whilst the earnest plea put forward by Chittenden, for a lowering of the protein and caloric value of dietaries by large amounts, cannot be regarded as longer possible, in the light of the accumulated evidence of the ill-effects that follow in the train of chronic underfeeding. (P. vii.)

[2] McCay, D.: *The Protein Element in Nutrition,* Longmans, Green and Company, New York, 1912.

Within a year Hindhede[3] wrote in reply:

I have already said that it would seem to be practically impossible to avoid getting protein enough! Does it not appear to be quite in the order of things that, practically, we must always get enough protein for our needs if we eat as Nature dictates? How, otherwise, could mankind have progressed so well since some hundred thousand years before Christ until A.D. 1866, in which year Voit stepped on the stage with his standard? Nature makes such careful provision in all things that there could be nothing more certain than that a means of nourishment so indispensable to all animal organisms as protein actually is must be present in such generous measure in all our food-stuffs that there is not the slightest necessity to fear that we should be unable to get an adequate supply.

The first point is that much protein is useless; but the second is to discover to what extent and in what way a high intake of protein is harmful. The latter question is more difficult to handle than the first, and we must here content ourselves to consider probabilities as evidence; and probabilities can, in the end, become so very probable that with their help we may almost cross the boundary line into certainty. (P. 156.)

And still more recently he[4] has vigorously defended these views, paying his respects to the "older" beliefs as follows:

It was Liebig, who made the discovery at about the year 1840, that the foods are burned up in the blood. Since then Liebig is regarded as a great authority. His doctrines, right or wrong, were elevated to the rank of dogmas. Among the incorrect ones is the claim that protein is the sole source of

[3] Hindhede, M.: *Protein and Nutrition,* Ewart, Seymour and Company, London, 1913.

[4] Hindhede, M.: *Die Neue Ernährungslehre,* Emil Pahl, Dresden, 1922.

muscular work. Fat and carbohydrate were reputed to serve the purpose of maintaining the body temperature. The outcome of this teaching was an utter overrating of protein food, and above all of meat.

Following Liebig, Moleschott was the foremost to disseminate the belief in the "energizing" meat regimen,—in 1850 in his "Physiologie der Nahrungsmittel für Aerzte," and in his "Lehre der Nahrungsmittel für das Volk." With the manner of a propagandist he asserted that a liberal meat dietary gives rise to a strong musculature. On the other hand he warned against potatoes which were, at that time, the chief food product of the Germans. . . . Seventy years have gone by since Moleschott made these assertions; but the overestimation of meat and the underestimation of the potato were so firmly inculcated into the minds of the people that the error can be eradicated with difficulty only, and particularly so because it has been perpetuated by the successors of these older exponents of the physiology of nutrition, notably Voit and his pupil Rubner.

In so far as Voit is concerned one would have supposed that he would have discovered the error of overrating the importance of meat. For he had found in his own investigations that no more protein is broken down during work than during rest. This disposes of the doctrine that protein (meat) is the chief source of muscular activity. . . . After physiologists and physicians had with deep conviction been recommending the liberal use of meat for more than a generation, and the consumption of flesh foods had greatly increased among those groups of the population who could afford this relatively expensive food, the diet of various classes was investigated. The results show a large use of meat and consequently a high protein intake among the "well nourished" groups of the population, *i.e.,* among the well-to-do and the most successful urban workmen. This finding is accepted as a proof of the advantage of the high standard. In other words, the fact that science has succeeded in inducing the masses to adopt a doctrine—which will be seen to be incorrect—is taken to demonstrate the correctness of that doctrine.

Even in 1914, that is in recent times, Professor Max Rubner, reputed to be the leading authority on nutrition in Germany wrote: "One need merely glance at the poorest strata of the masses to see to what extent a diet preponderating in potatoes enervates the organism." Rubner identifies a comparatively high body weight and a robust, ruddy appearance, off hand, with correct nutrition. It does not seem to occur to him that such an appearance may also be a manifestation of damaging overnutrition.

No one can deny that Liebig and Voit were eminent investigators. But the errors of great men are a hundred times more dangerous than the nonsense of the multitude. Thus the agitation in favor of meat has been disseminated throughout the world. (P. 5.)

Meanwhile a new factor with a possible bearing upon the protein problem has come into play. The diversity of the proteins in nature has been clearly established. They are now recognized as differing not only in their physical and physico-chemical properties but also with respect to their organic make-up. What this may mean is best illustrated by the summary of some comparative analyses of the yield of different amino-acids from proteins:

QUANTITATIVE COMPARISON OF AMINO-ACIDS OBTAINED BY HYDROLYSIS FROM PROTEINS*

Compiled for the author by Dr. H. B. Vickery, 1923

	Casein	*Gelatin*	*Gliadin*	*Zein*	*Lactalbumin*	*Edestin*
Glycocoll	0.45	25.5	0.00	0.00	0.37	3.80
Alanine	1.85	8.7	2.00	9.79	2.41	3.60
Valine	7.93	0.0	3.34	1.88	3.30	6.20
Leucine	9.7	7.1	6.62	19.55	14.03	14.50
Proline	7.63	9.5	13.22	9.04	3.76	4.10
Oxyproline	0.23	14.1	?	?	?	?
Phenylalanine	3.88	1.4	2.35	6.55	1.25	3.09
Glutaminic acid	21.77	5.8	43.66	26.17	12.89	18.74
Oxyglutaminic acid	10.5	0.0	2.4	?	10.00	?
Aspartic acid	4.1	3.5	0.58	1.71	9.30	4.50
Serine	0.5	0.4	0.13	1.02	1.76	0.33
Tyrosine	4.5	0.01	1.61	3.55	1.95	2.13
Cystine	?	?	0.45	?	1.73	1.00
Histidine	2.5	0.9	1.49	0.82	2.61	2.19
Arginine	3.81	8.2	2.91	1.55	3.47	14.17
Lysine	7.62	5.9	0.63	0.00	9.87	1.65
Tryptophane	1.5	0.00	1.0	0.00	2.4	1.5
Ammonia	1.61	0.4	5.22	3.64	1.31	2.28
Total	90.17	91.31	87.61	85.27	83.41	83.78

* The analyses are combinations of what appear to be the best determinations by various chemists.

Owing to the disintegrating action of the alimentary digestive processes it is the liberated amino-acids rather than the proteins *per se* that are absorbed and represent the real contribution of the albuminous foods to the metabolism. The normal physiology of the protein has thus become largely a question of the behavior of the amino-acids in nutrition. As I have expressed it elsewhere:

Today we are concerned with the question whether this or that protein, whatever its biologic origin, will yield the characteristic desired amino-acids, such as tyrosine and tryptophane, leucine and lysine, glycocoll and cystine, histidine and arginine. Our attention is fixed on the building-stones or units out of which the great protein structures are put together. Instead of referring to the proteins in terms of their physical properties or empirical composition—their content of carbon, hydrogen, oxygen, nitrogen or sulphur—at least so far as the problems of nutrition are involved, the time has arrived for estimating their behavior in the organism on the basis of the quota of each of about eighteen well-defined amino-acids which the individual representatives of this group of foodstuffs can yield. Many, if not all, of these amino-acids are essential for the construction of tissue and the regeneration of cellular losses. In proportion as any specific protein can furnish these constructive units it may satisfy the nutritive needs of the body. The efficiency of the individual protein in this respect must depend on the minimum of any indispensable amino-acid that it will yield; for it is now known that some of them cannot be synthesized anew by the animal organism. If, for example, a protein or mixture of proteins comparatively deficient in their yield of the sulphur-containing amino-acid cystine be furnished alone to supply the body's nitrogenous requirements, the production of new, cystine-yielding molecules of protein will be limited by the amount which is available in the diet. An excess need not be wasted, for it can be burned up like sugar or fat to provide energy; but new construction or growth is limited by the minimum of the essential unit.

It has long been assumed that from the standpoint of nutrition there may be a "quality" factor in proteins although it was not always understood precisely wherein the differences in "assimilability" lay. Today, with the better knowledge of the amino-acid structure of many proteins it has become customary to speak of "complete" and "incomplete" proteins, of proteins of good or poor "biological quality," etc. The newer methods of investigation, which take into account the other known needs of the body,—calories, salts, vitamines,—have made it easier to formulate experiments in which the protein becomes the foremost limiting factor in each test. Contrast, for example, the outcome of feeding trials with comparable

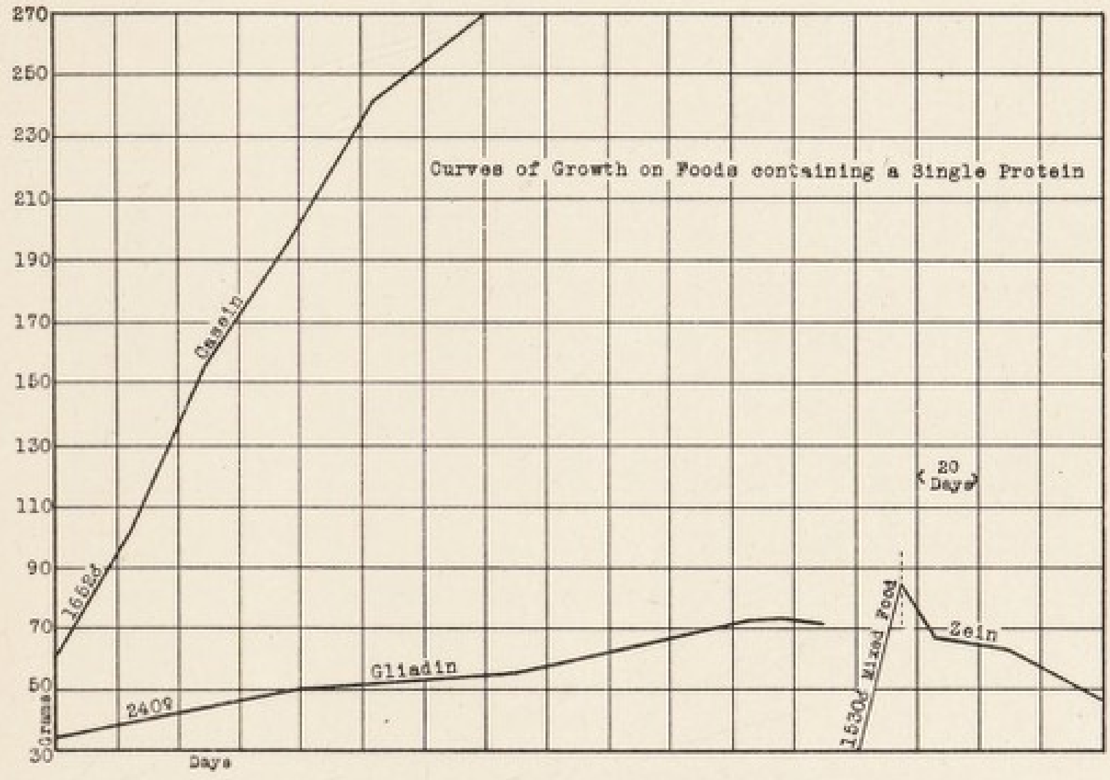


Chart 1. Showing typical curves of growth of rats maintained on diets containing a single protein. On the casein food (devoid of glycocoll) satisfactory growth is obtained; on the gliadin food (deficient in lysine) little more than maintenance of body weight is possible; on the zein food (devoid of glycocoll, lysine, and tryptophane) even maintenance of body weight is impossible.

(From Mendel, L. B.: "Nutrition and Growth," *Jour. Am. Med. Assn.*, lxiv, 1915, p. 1539.)

mixtures of food materials in which different purified proteins supplied all of the nitrogen except the small quantities included in the natural sources of the vitamines.

Several possibilities suggest themselves in the contemplation of such results. Are some of the proteins for which the unfavorable outcomes are shown perchance toxic; or are they poorly utilized because of resistance to digestion; or are the retardations of growth the chance consequence of failure to eat? These immediate questions have all been answered in the negative. The unsatisfactory rations in-

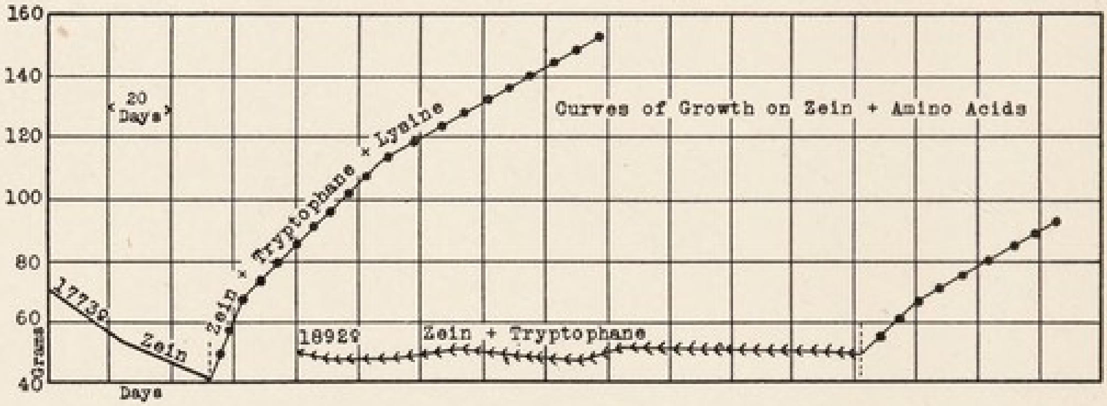


Chart 2. Showing the effect of the addition of the amino-acids tryptophane and lysine to zein which fails to yield them. With zein alone (Rat 1773) there is nutritive decline. The addition of tryptophane (Rat 1892) permits maintenance without growth on foods containing zein as the sole protein. The addition of tryptophane and lysine to zein enables the animals to make considerable growth. It is interesting to note, in relation to Rat 1892, that the growth of this animal was inhibited for six months without material change in its body weight. That the capacity to grow is not lost by prolonged dwarfing on imperfect food is shown by the subsequent growth of the animal when lysine was added to the food containing zein and tryptophane.

(From Mendel, L. B.: "Nutrition and Growth," *Jour. Am. Med. Assn.*, lxiv, 1915, p. 1539.)

dicated are not positively but negatively detrimental; they *lack* something essential. In the case of gliadin there was a shortage of the amino-acid represented by lysine; with zein the lack of both lysine and tryptophane groups was involved; in the case of phaseolin there was a deficiency of cystine. These proteins may possibly have

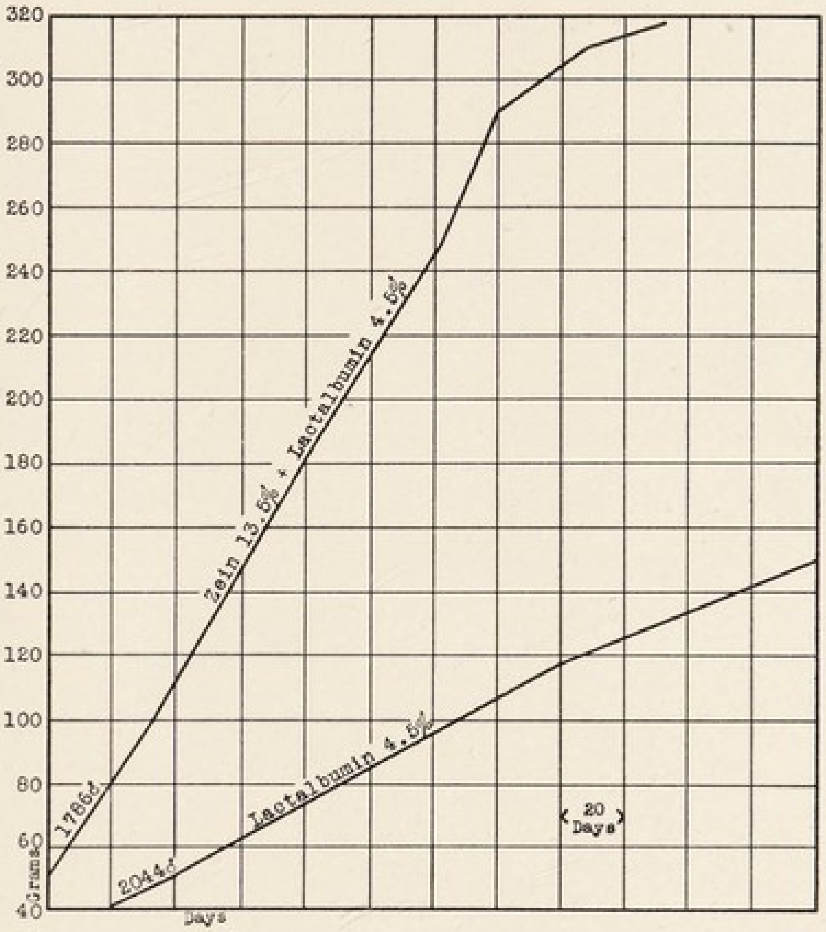


Chart 3. Showing the favorable effect on growth by supplementing a protein (zein) incapable of maintaining animals when it is the sole protein furnished in the diet with a more "perfect" protein (lactalbumin). The proportion of the lactalbumin used—4.5 per cent—was of itself insufficient to promote growth well. It evidently furnished the amino-acid groups lacking in the zein.

(From Mendel, L. B.: "Nutrition and Growth," *Jour. Am. Med. Assn.*, lxiv, 1915, p. 1539.)

additional deficiencies that were being made good by the vitamine preparations inevitably used; consequently until the latter are available in less contaminated forms it will be impossible to state positively that the amino-acids just referred to represent the *sole* deficiencies in the proteins named therewith.

It is not necessary to add the lacking amino-acids as such to the diet to insure success. They may be furnished in the form of proteins that yield them.

From what has been demonstrated it follows not only that certain amino-acids are indispensable for the organism in the long run but also that they are not synthesized *de novo* therein. In addition to cystine, lysine and tryptophane, regarding which there is fairly general agreement now, it has been suggested that either arginine or histidine represents an essential group. The evidence presented indicates that these two substances are interconvertible in the animal organism and that an adequate supply of sources of at least one of them in the diet is necessary for satisfactory nutrition. Ackroyd and Hopkins[5] state:

> When arginine and histidine are together removed from the diet of rats which have been previously growing on a complete amino-acid mixture there is a rapid loss of body weight. This is promptly succeeded by renewed growth when the missing diamino-acids are restored to the diet.
>
> When arginine alone, or histidine alone, is restored to the food there is no loss of weight and there may even be growth. Nutritional equilibrium is possible in the absence of one of

[5] Ackroyd, H., and Hopkins, F. G.: "Feeding Experiments with Deficiencies of the Amino Acid Supply: Arginine and Histidine as Possible Precursors of Purines," *Bioch. Jour.*, 1916, x, 551.

these related protein constituents though not in the absence of both. It is suggested that this is because each one of them can, in metabolism, be converted into the other. (P. 575.)

They believe that these amino-acids can furnish the starting point of purine synthesis in the animal body. Whether any amino-acids containing the benzene nucleus are necessary has been debated.[6]

Much of the earlier work of ourselves and others needs repetition when it shall be possible to prepare a diet free from the criticism of supplying unidentified nitrogenous supplements to the proteins in the sources of vitamine B necessarily in the food mixtures. Meanwhile it has marked a step in the direction of progress to realize wherein some, at least, of the deficiencies of individual proteins reside. The photographs show even better than charts of growth curves what the phenomena discussed may involve in living animals.

Some of the particular "inferior" proteins mentioned were derived from seeds. It does not follow, however, that all the proteins of each seed are inferior. In fact, they are not. In referring to a long list McCollum has remarked that current studies "leave no room for doubt that all the amino-acids necessary for the nutrition of an animal are contained in the proteins found in each of these foods. Certain of these are, however, present in such limited amounts as to restrict the extent to which the remaining ones, which are more abundant, can be utilized. It is for this reason that these proteins are of relatively low biological value unless supplemented by proteins from other

[6] Totani, G.: "Feeding Experiments with a Dietary in which Tyrosine is Reduced to a Minimum," *Bioch. Jour.*, 1916, x, 382.

A. Rat 238, female. Age 140 days, weight 144 grams, which is normal for a rat of same age as 240.

B. Rat 240, female. Age 140 days, weight 55 grams. Same brood as rat 238.

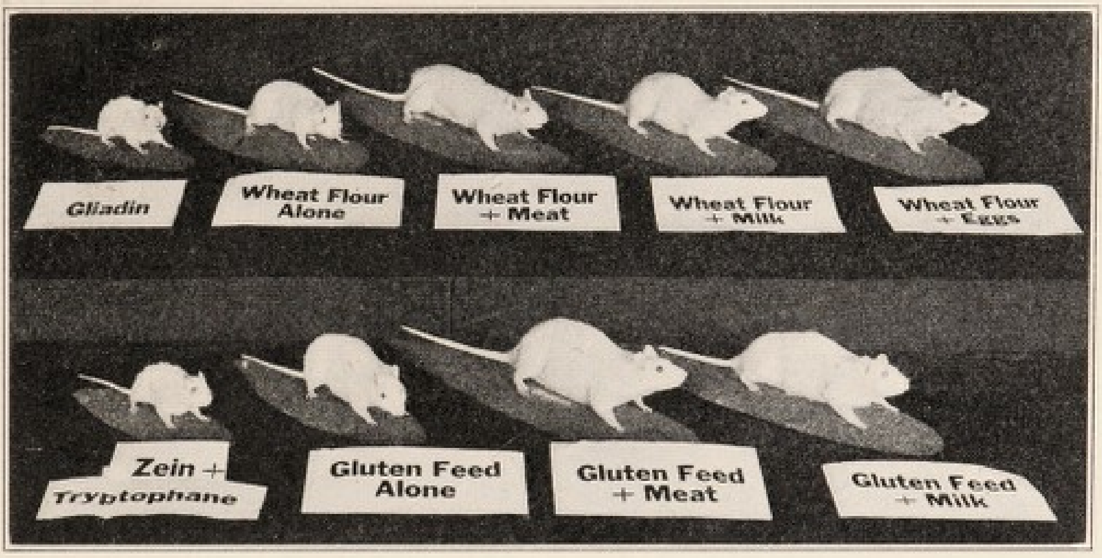
C. Rat 305. Age 36 days, weight 55 grams. Showing the appearance of a normal rat of same size as 240.

A and B show the contrast between two rats of the same age, kept on diets alike except for the protein which was casein for A and gliadin for B. The stunting effect of the "inferior" protein is clearly shown. The lower two pictures afford a comparison between two rats of the same weight, but widely differing in age. The older, stunted rat, B, has not lost the characteristic proportions of the younger animal, C.

(From experiments by Osborne and Mendel.)

sources, the constitution of which is such as to make good their deficiencies. The proteins of the cereal grains are of lower value than are those of milk and eggs, or than those of certain mixtures obtained by combining two or more of these seeds."

An illustration of the comparative value of cereal product mixtures respectively unsupplemented or supplemented with regard to the quality of the protein supplied is shown in the accompanying photograph.



These rats were all of the same age and fed for the same length of time on diets containing the same proportion of protein. The variation in size is due to differences in the chemical constitution of the proteins eaten.

(From experiments by Osborne and Mendel.)

The tests were conducted with rats of the same age and sex over the same period of time with mixtures comparable in respect to calorie value; an adequacy of salts and vitamines was supplied, the total content of protein (N x 6.25) also being the same. In some of the rations meat, milk, or eggs replaced the cereal products so that one-third of the unchanged total content of protein was derived from the supplement. Experience has shown that animals retarded in growth on the less advantageous mixtures promptly start to thrive better when the quality of the protein in the diet is improved.

It is still customary for agriculturalists to refer to the "nutritive ratio" of common fodders in relation to the feeding of domestic animals.[7] This means the proportion of protein-calories to the total energy value. In the experiments on rats just cited the nutritive ratio was essentially the same in all the rations, yet the outcome for tissue production was quite different. The limitation of the principle of nutritive ratios has been realized in agricultural practice before it seems to have been appreciated in scientific discussions. Quality as well as quantity may play a rôle in the proper selection of fodders.

I have already remarked elsewhere[8] that an apparent exception to the demonstrated need of supplying all nitrogenous essentials more or less ready-made to the animal organism has been recorded in certain ruminants. Sheep have been observed to gain many pounds over considerable periods of time on a diet of starch, denitrogenized straw, inorganic salts and urea, an exceedingly simple nitrogenous compound that readily disintegrates to form ammonia and carbon dioxide. A consideration of the peculiar anatomical arrangement of the alimentary tract of these animals serves to explain the possibility of

[7] See Wood, T. B.: An Agricultural War Problem, in *Science and the Nation,* edited by A. C. Seward, University Press, Cambridge, 1917.

[8] Mendel, L. B.: "Chemical Factors in Nutrition," *Jour. Franklin Institute,* July, 1921.

such an outcome. In the first stomach of the ruminants, the rumen or paunch, opportunity is afforded for micro-organisms to thrive in the warm reservoir where the food mixtures are temporarily incubated, so to speak. Bacteria can and do grow luxuriantly there. Subsequently, when the products of microbial activity, including an enormous increment of bacterial bodies, are moved along to the true, acid-secreting stomach, the bacteria, rich in newly synthesized protein-containing protoplasm, die and liberate the bacterial protein for use by the organism of the host. This is a unique instance of apparent protein synthesis by a higher animal, explicable however on the basis of the symbiotic action of bacteria. The same result could not be expected in man because his food passes directly into a chamber, the stomach, provided with bactericidal facilities in the acid gastric juice.

Inasmuch as the growth of the body can be retarded by a variety of influences among which are specific deficiencies in the diet such as are represented by a shortage of some essential amino-acid, it was hoped long ago that inhibition of tumor growth might also be secured by dietary deficiencies. The problem has been opened to experimental study by the discovery that tumors can be successfully transplanted at will in certain species. For certain types of such neoplasms it now appears that they have the conspicuous characteristics of parasites; that is, they possess "the power of commandeering what part of the food supply of the host they require for their own use." If the exogenous supply is unsatisfactory the tissues of the host are usually sacrificed to a considerable extent in order to provide the requirements of the parasitic cells.

Drummond,[9] who has carefully studied the effects of drastic dietary restrictions, has concluded:

> In the event of a deficiency arising in the diet of the host, the tumour, provided it possesses a satisfactory blood supply, will continue to grow, although the host may be quite unable to do so. There is evidence that this proliferation will proceed at the expense of the tissues of the host, until these are no longer able to supply the missing units.
>
> When the host is unable to make good the deficiency, by drawing upon its own reserves, the rate of tumour proliferation will decrease. This occurs at a comparatively early stage when the diet is deficient either in tryptophan or in the water-soluble accessory factor, B.
>
> There is no evidence that the cells of tumours possess powers of synthetical action which the normal cell of similar type does not possess.
>
> It does not appear possible to bring about an inhibition of tumour growth by an employment of dietary restriction, . . . without the nutritive condition of the host being very seriously impaired.
>
> There is, therefore, little hope of bringing about an alleviation of the disease in man by the imposition of dietary restrictions, such as are described. (P. 375.)

The proportion of protein in the diet may determine whether larger or smaller absolute amounts of the nitrogenous foodstuffs are consumed; but the actual intake of these is also modified by the character of the non-protein ingredients. The individual instinctively strives to satisfy its calorific needs. A diet rich in fats is consumed in smaller quantity than one poor in fats, consequently

[9] Drummond, J. C.: "A Comparative Study of Tumour and Normal Tissue Growth," *Bioch. Jour.*, 1917, xi, 325.

the absolute protein intake may vary independently of its concentration or percentage content in the food. When the absolute intake is small the "law of minimum" may come into play to limit the efficiency of the whole because of the relative shortage of some essential amino-acid. Thus the protein casein yields relatively little cystine. So long as casein appears in the diet in abundance no deficiency appears; but when the consumption of the protein is reduced a shortage of the least abundant essential may manifest itself, as the following chart shows:

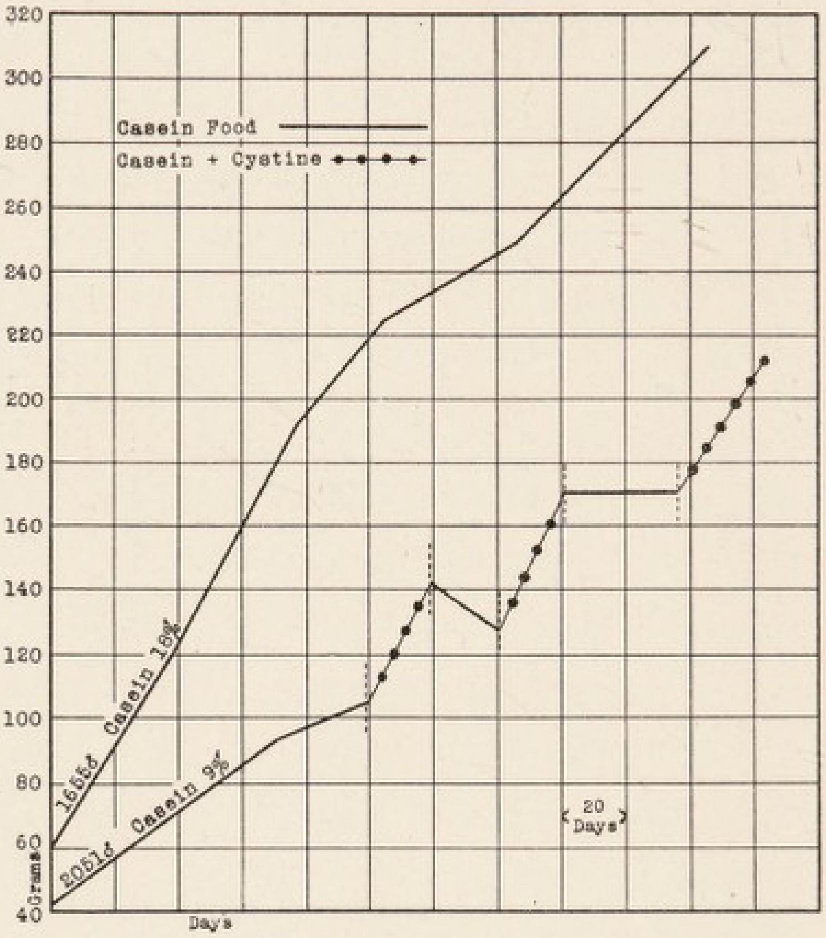


Chart 4. The curve for Rat 1655 shows the satisfactory growth obtained when 18 per cent of casein was present in the diet as the sole protein. With a smaller amount of casein (Rat 2051)—9 per cent—much less rapid growth ensued. That the insufficiency of the smaller amounts of casein is essentially due to its relative deficiency in cystine-yielding groups is shown by the marked accelerating influence on growth brought about by the addition of the amino-acid cystine to the food containing 9 per cent of casein and the prompt contrary effect when the cystine was withdrawn from the diet.

(From Mendel, L. B.: "Nutrition and Growth," *Jour. Am. Med. Assn.*, lxiv, 1915, p. 1539.)

Conversely, when an animal ingests a very large quantity of some protein poor in an essential unit, the absolute amount of the latter thereby available from the great abundance of its precursor may suffice to promote nutritive effects that fail to appear on a lower plane of protein intake.

It is not surprising that it should have been found possible to dispense with true fats from the diet, at least if one reserves the possible exception of the small quantities involved in the vitamine-bearing substances hitherto included in otherwise fat-free diets.[10] If fats can be formed from sugar in the body there is no evident theoretical reason for any exogenous source of these glycerides. The demonstration of nutrition on fat-free rations afforded by our experiments should, however, by no means be construed to minimize the great value of fats as a source of energy in the usual dietary of man, as well as their special advantages in culinary procedures.

It was more surprising to us to discover that animals can actually grow vigorously so as to make large gains in weight on diets in which nine-tenths of their energy is derived from proteins, appropriate salts and vitamines being furnished in addition. The earlier published surmises might well have led one to expect failure through breakdown of some vital organs—alimentary canal, liver, kidney, or what not—because of the "strain" occasioned in the disposal of the "nitrogenous waste." But urea is highly diffusible and very easily excreted ordinarily with-

[10] Osborne, T. B., and Mendel, L. B.: "Growth on Diets Poor in True Fats," *Jour. Biol. Chem.*, 1920, xlv, 145; Drummond, J. C.: "Nutrition on Diets Practically Devoid of Fat," *Jour. Physiol.*, 1920, liv, p. xxx.

out great "strain." At any rate, in some of our trials[11] in which the vitamine-bearing substances, representing less than 10 per cent of the food eaten, were the only note-worthy sources of non-protein foodstuffs, rats have made gains at essentially normal rates to more than 200 grams of body weight—a remarkable result.

In the absence of more than small proportions of pre-formed carbohydrate such animals must synthesize sugar from the great abundance of denitrogenized amino-acid "rests." As Osborne and I have pointed out, carbohydrates are ordinarily regarded as indispensable components of the food intake. This belief is based on the presence of more or less carbohydrate in the food mixtures consumed by man and the higher animals, and the fact that sugar is a constant constituent of the blood. It is almost universally taught that carbohydrate is essential for the proper metabolism of fats in addition to any other functions that it may perform in the body; for ketone substances may be excreted in diabetes when sugar fails to be burned up in the normal manner in the organism. On the other hand it is assumed that glucose can be formed from the protein molecule or its amino-acids under certain conditions in the metabolism so that one could conceive carbohydrate to become available for the special needs of fat metabolism and other purposes without being specifically furnished as *preformed* carbohydrate in the diet. The current opinion, summarized by one recent writer, maintains that "carbohydrates are the most economical of the foodstuffs, both physiologically and financially. They are the great-

[11] Osborne, T. B., and Mendel, L. B.: "Feeding Experiments with Mixtures of Foodstuffs in Unusual Proportions," *Proc. Nat. Acad. Sci.*, 1921, vii, 157.

est sparers of protein. Ingestion of fat has for its object the relieving of the intestine from excessive carbohydrate digestion and absorption. Ingestion of fat in too large quantities leads to digestive disturbances, and if carbohydrates are entirely abandoned, to acetonuria."

The animals which we have reared on the high protein diets (containing 75 per cent or more of protein) have not increased their calorie intake in any considerable measure above what is observed on the more customary types of rations. Consequently the nitrogen-free "rest"—the so-called "carbon moiety"—of the protein must have served their energy requirement almost as well as do sugar and fat. Incidentally it has been observed that rats on the high-protein diets show marked hypertrophy of the kidneys. Thus far full adult size, say 300 grams, has not been attained. Whether this is due to an inability of the animals to metabolize the quantity of protein required (when it is almost the sole source of energy) beyond a certain structural size, or whether the intake is limited by the limited capacities of even the hypertrophied excretory organs cannot yet be foretold. Newburgh[12] and his associates have attributed untoward results, arteriosclerosis and albuminuria, to high-protein feeding in rabbits and man. At present one is probably not justified in making too sweeping deductions as to the effects of proteins *per se* fed with great liberality.

[12] Squier, T. L., and Newburgh, L. H.: "Renal Irritation in Man from High Protein Diet," *Arch. Int. Med.*, 1921, xxviii, 1; Newburgh, L. H., and Clarkson, S.: "Production of Arteriosclerosis in Rabbits by Diets Rich in Animal Proteins," *Jour. Am. Med. Assn.*, 1922, lxxix, 1106.

V.

THE ENERGY PROBLEM IN NUTRITION

IN these days when one is no longer content to await the slow results of chance discovery unaided by special observation, or the "half-unconscious education which results from mere experience" the findings of the experimental sciences are as a rule quickly acclaimed. We are living in a period of hectic anticipation of novelties, when much is expected of science; and the momentary enthusiasm for the new is apt to bring about indifference to the old.

This has been true of such dramatic chapters in the healing art as modern surgery has written. And so the spectacular results which the more recent experimental studies of vitamines have afforded seem for the moment to have overshadowed much else in nutrition, not merely as judged in the public acclaim but also by the textbooks of recent months. Yet the problems of the transformation of energy in the body are probably the most fundamental of all considerations in the science of nutrition. All of us can remember the enormous importance attained by the food problem in the World War. The supply of food fuel was second to no other for the successful prosecution of the war.[1] The significance of energy to the body was taught everywhere: on billboards, on the printed page and by word of mouth. The word "calorie" lost its "high-

[1] See Kellogg, V., and Taylor, A. E.: *The Food Problem*, Macmillan Co., New York, 1917.

brow" reputation and at length became a part of the vocabulary of popular everyday science in the home.

The pioneer investigations of Voit and Pettenkofer in particular on the metabolism of energy have been continued through the lineage of two generations of research descendants from the Munich laboratories. The foremost recent developments in this field, in which the technique of investigation has already attained a high degree of perfection, have been concerned with human calorimetry. In this the determination of the "basal metabolism" of man, that is, the extent of the transformation of energy in the body at rest and without food, has received a large share of attention. The basal metabolism represents the "irreducible minimum" of the body's demand for energy. Upon the requirements of the basal metabolism are superimposed the needs for the energy represented in the functional activities, particularly muscular work. Here one is dealing directly with the highly important question: "*How much* food constitutes an adequate diet?"

Obviously some unit of measurement is essential, for the requirements of food fuel vary, among other factors, with the size of the individual. Shall it be expressed in terms of body surface with the implication that the metabolism or heat output of the human body depends on Newton's law of cooling and is therefore proportional to the surface area; or shall it be regarded as proportional to the "protoplasmic mass," the active tissues of the body? How is either of these factors to be measured?

Without attempting a critical discussion of this topic here it must suffice to refer to Boothby's recent conclusion that "the surface area is the most exact method at present available for estimating the active protoplasmic mass and in consequence the best method, in conjunction with appropriate standards of age and sex, for predicting the basal heat production."[2] Special height-weight formulas have been devised, notably by DuBois, whereby the calories required per square meter of body surface can be estimated. An enormous number of measurements made on adult man in recent years show the high percentage of persons who have normal basal metabolic rates according to the DuBois standard, unless they are suffering from some specific disease characterized by an alteration in the basal metabolism. The average normal heat output of adults approximates 40 calories per square meter of body surface per hour. On the basis of extensive experience Boothby and Sandiford[2] have remarked that the basal metabolic rate differentiates diseases into those with increased, normal and decreased metabolism as sharply as the temperature divides diseases into the febrile and afebrile groups. Little wonder, therefore, that clinical calorimetry has achieved prominence in the practice of medicine.

From the standpoint of nutrition one of the most significant features of the study of human calorimetry has been the demonstration of the relatively high basal metabolism of adolescent children. Such an outcome was not entirely expected. There is no difference in this respect between boys and girls up to about one year of age,

[2] Boothby, W. M., and Sandiford, I.: "A Comparison of the DuBois and the Harris and Benedict Normal Standards for the Estimation of the Basal Metabolic Rate," *Jour. Biol. Chem.*, 1922, liv, 767. A bibliography of the subject is given on page 802.

or about 10 kgms. of weight, after which there is a sex differentiation, boys of the same weight having a somewhat higher metabolism than girls until they reach 34 kgms. of body weight, when the metabolism of both sexes is the same; later the basal metabolism of girls is somewhat higher than that of boys.[3]

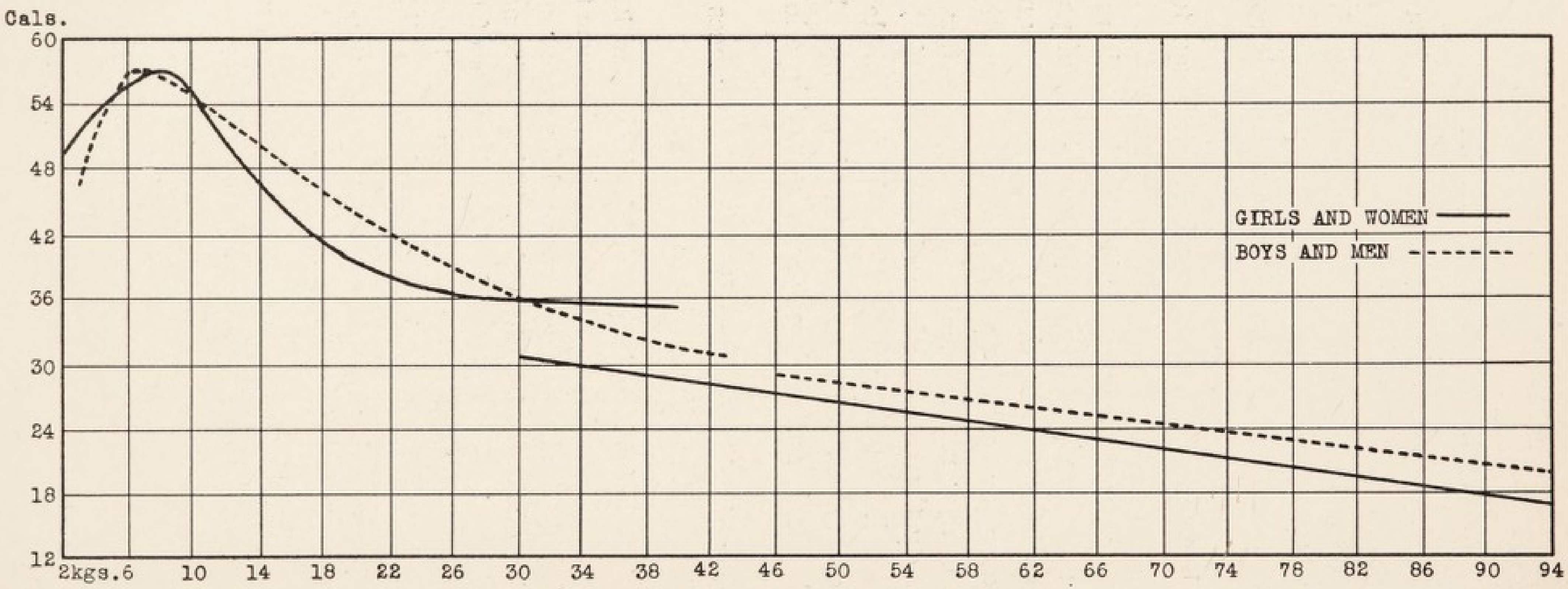
DuBois has shown the basal metabolism of boys to be one-quarter greater than that of adults. When to the high requirements at rest there are added the demands made by growth and the vigorous muscular activities of youth it is not surprising that the food fuel needs of a boy may amount to over 4000 calories per day and thus sometimes exceed the energy requirement of his father. After the age of puberty the rate or plane of metabolism falls to the adult level. Studies which Benedict has made on groups of girls show the same features of augmented or accelerated basal metabolism occurring with adolescence.[4]

In a survey of evidence regarding food allowances for healthy children it has been pointed out that:

> In computing the food requirements of family groups, it has been customary to regard the man as the unit and assume that the food of each child may be represented by some appropriate fraction of the food of the father. This practice naturally arose from the fact that the food requirements of men had been longer studied and were better known than those of children, few investigations having been made upon children

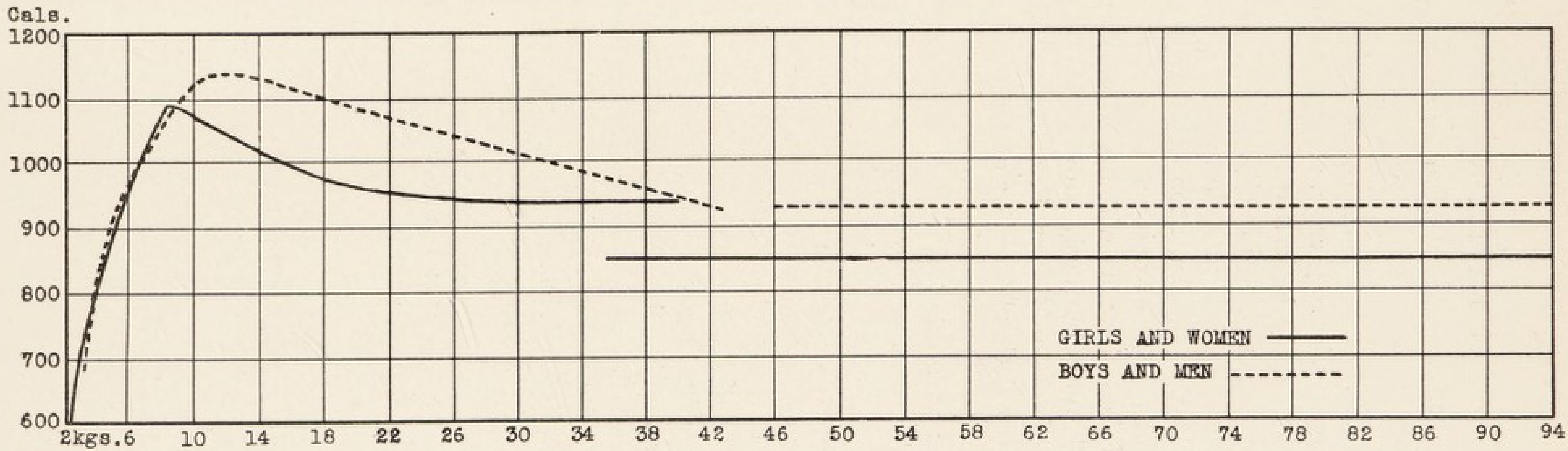
[3] Talbot, F.: "The Caloric Requirements of Normal Infants and Children from Birth to Puberty," *Am. Jour. Dis. Children,* 1919, xviii, 229.

[4] Benedict, F. G.: "Energy Requirements of Children from Birth to Puberty," *Boston Med. and Surg. Jour.,* 1919, clxxxi, 107.



Comparison of basal heat production of boys and men and girls and women per kilogram of body-weight per 24 hours referred to weight.

(From Benedict, F. G.: *Boston Med. and Surg. Jour.*, 1919, clxxxi, 107.)



Comparison of basal heat production of boys and men and girls and women per square meter of body-surface per 24 hours referred to weight.

(From Benedict, F. G.: *Boston Med. and Surg. Jour.*, 1919, clxxxi, 107.)

by accurate laboratory methods until within comparatively recent years.

But, as the writer has previously pointed out, the food requirement of a man varies so greatly, according to his occupation, that it seems hardly logical to make this the basis for estimating the dietary needs of a family. Thus a carpenter may require 3500 calories per day; a tailor, 2500; a fourteen year old son of either of these men, 2800 calories. With the carpenter as the unit, the boy's requirement would be represented by 0.8 of that of the father; but with the tailor as the unit, the allowance of 0.8 would obviously provide far too little food for the boy's needs. The Atwater dietary standards for children were stated as decimal fractions of the requirement of a man at moderately active muscular work such as a carpenter requiring 3400 or 3500 calories.

In practice, the dietitian who makes use of these decimal fractions in computing the food requirements of the family, finds it difficult to avoid the tendency to reckon the child's food requirement according to that of the father, which works serious injustice to the child if the father have a low food requirement because of being engaged in an occupation which does not involve active muscular work. Obviously, it is equally inaccurate to assume that the needs of all men are nearly the same, in order that the allowances for the children may approximate uniformity. In our opinion the food requirement of each member of the family should be determined on his own merits rather than in terms of the man's requirement.[5]

The compilations prepared in 1917 by Miss Gillett[5] afford further evidence of the changing basal energy expenditure during the period of adolescence, as shown in the tabular summary:

[5] Gillett, Lucy H.: "Food Allowances for Healthy Children," *Publication No. 115*, Bureau of Food Supply, The New York Association for Improving the Condition of the Poor, New York, 1917.

RESPIRATION EXPERIMENT AVERAGES

Basal Energy Expenditure per Man per Day, and per Kilogram

Age	No. of Expts.	Average Weight	Basal Energy Expenditure	
		kgms.	Total Calories	Per kgm. Calories
1st week	112	3.40	146	43
2d, 3d, 4th weeks	4	4.10	217	53
2d month	1	2.99	164	55
3d month	3	5.18	300	58
4th month	5	5.47	323	59
5th month	6	5.38	317	59
6th month	2	7.37	376	51
7th month	4	6.09	378	62
8th month	3	6.80	442	65
9th month	2	5.82	471	81
10th month	1	8.45	423	50
11th month	...	....	....	..
12th month	3	8.34	509	61
2d year	...	....	....	..
3d year	1	11.50	784	68
4th year	...	....	....	..
5th year	...	....	....	..
6th year	...	....	....	..
7th year	3	17.0	943	56
8th year	3	18.4	1030	56
9th year	...	....	....	..
10th year	1	21.8	1046	48
11th year	1	30.6	1346	44
12th year	3	34.5	1302	38
13th year	7	31.6	1261	40
14th year	5	32.5	1339	41
15th year	4	37.8	1362	36
16th year	...	....	....	..
17th year	3	51.4	1541	30
18th year	3	46.1	1418	31

The Interallied Scientific Food Commission which was created to advise the various allied governments regarding the ways and means of meeting the food exigencies created by the World War adopted the following ruling in its first report:[6]

FACTEURS DE CONVERSION EN "HOMME-MOYEN."

Pour déterminer ce nombre d' "hommes-moyens," la Commission décida d'adopter les coefficients, établis par le professeur Lusk, fixant les rapports qui existent entre les besoins alimentaires de l' "homme-moyen" pris comme base et ceux des différentes catégories de la population d'après l'âge et le sexe. Ces coefficients sont les suivants:

Age	*Coefficients de conversion en "hommes-moyens"*
0 à 6 ans	0,5
6 à 10 ans	0,7
10 à 14 ans	0,83
14 ans et au-dessus (femmes)	0,83
14 ans et au-dessus (hommes)	1,00

The now well-established indications of the fundamental augmentation of the basal metabolism in childhood together with the other factors that make towards a vigorous demand for energy in this period of life are in harmony with the dietary habits of the young. Their vigorous appetites sometimes become the occasion for comment unfavorable to the individuals involved. Children are chided occasionally for their tendency to supplement the traditional three meals a day with further

[6] *Commission Scientifique Interaliée du Ravitaillement, Rapport Général, Les Ressources et les Besoins Alimentaires des Pays Alliés.* (This report has not been distributed to the public.)

repasts. It should be borne in mind that in addition to having a high metabolic rate adolescents are as a rule intensely active. Muscular performance calls for energy in proportion to the amount of exercise indulged in. F. G. Benedict[7] has remarked in this connection:

> It is possible, of course, that when the activity is excessive, there should be some restriction, for there are those who believe that excess activity, even with children, ultimately shortens life. It is still, however, the best practice to give a most liberal diet to children, since the greater part of the evidence on underweight indicates that children usually receive too little rather than too much food. I feel that the question as to whether or not the active growing child can have too much food need not seriously trouble any one. Conservation of food as a war measure, is, happily, a thing of the past. Still, let the obese epicure save all the food he can. Let the over-fed dame of leisure curtail her supply. Both are justifiable on hygienic and, indeed, on real actuarial bases. But further evidence must be forthcoming before nutrition experts will agree on any curtailment of the food intake of active growing children, unless possibly (and God forbid) a new war-need should arise.

Benedict and Talbot[8] conclude their elaborate monograph on *Metabolism and Growth from Birth to Puberty* with this important statement:

> To explain the extraordinary needs of growing children solely upon the basis of activity is somewhat difficult. The

[7] Benedict, F. G.: "Energy Requirements of Children from Birth to Puberty," *Boston Med and Surg. Jour.*, 1919, clxxxi, 107.

[8] Benedict, F. G., and Talbot, F. B.: "Metabolism and Growth from Birth to Puberty," Published by the Carnegie Institution of Washington, 1921, *Publication No. 302.*

activities are, it is true, enormous. The food consumption is proportionately great. The deposition of tissue must be provided for from the food intake, and this, in turn, augmented above the true needs for simple physical activity. In all probability a factor by no means to be neglected is the stimulus to metabolism resulting from the ingestion of food. As has been shown in the report of an earlier research on mixed diets, especially when large amounts of food are taken, approximately 6 per cent of the total caloric intake is eliminated as extra heat, which has been technically termed the "cost of digestion."

The final computation of the total 24-hour food-needs or heat-output of a growing active child will require considerable research. The heat-output of children at play is entirely a matter of speculation. . . . In any event, it is clear that the caloric needs of growing children are very much greater than they are commonly supposed to be. The lesson to be drawn from our observations on private-school children is that outdoor life and physical activity contribute towards the development of a larger individual, so far as height, *i.e.,* skeletal growth, is concerned, with likewise a greater weight with children of the same age. But it is probable that even these children, with superior surroundings and presumably better medical examination, care, and dietetic supply, may advantageously be supplied with larger amounts of food than they at present take. One could infer, therefore, from these observations, that, aside from the possibilities of digestive derangements, it would be impossible to supply the growing child with an excessive amount of food. Every effort may legitimately be expended to secure a maximum skeletal growth and the development of children above so-called average weight. We believe that our investigation shows clearly that the average weight for children is distinctly below the ideal or physiologically desirable weight. (P. 213.)

The better appreciation of the nutritive needs of those destined to become the rank and file of our nation when they are grown up—an appreciation based alike upon experimental studies and statistical data as to food habits—is not the least of the contributions which the science of nutrition has made to public welfare during the past decade. The food dictators of the future will no longer be excused if they estimate the food needs of peoples in the once conventional terms of "man values" wherein the requirements of the child population were calculated as a fraction of the adult needs proportional to the smaller weight and stature of the young.

When the intake of energy is less than the output a loss in body weight is in due time bound to ensue. This is an obvious conclusion. Conversely, it is usually assumed and also stated in the generalizations on the subject of nutrition that when the food intake is in excess of the estimated requirement of energy a surplus is deposited in the body. Obesity is thus made an index or sign of overeating. If this conclusion is justifiable it follows that two persons of similar size, with similar basal metabolic rates and comparable activities should be similarly prone to gain in weight when their food intakes are very liberal. The gain thus becomes a question of the balance of energy—of physiological bookkeeping in which intake and output are charged against each other. Experience tends to lead one to question whether the body always responds with such a nicety of regulation. It is often remarked that certain persons remain lean despite a liberal appetite and unimpaired digestion, whereas others deposit fat with apparent ease. Such differences are seen in various breeds of animals, among which some fatten more readily than others. This aspect of temperament or tendency to obesity or the reverse has been "explained" in various ways.

Is it not possible that certain individuals actually "burn up" a surplus of intake by an increased metabolism in order to rid the organism of the unnecessary food rather than to store it as fat? This suggestion recalls the older theories of "luxus consumption." In this connection reference may be made to Gulick's[9] attempt to ascertain whether the body can vary its destruction of fats and carbohydrates in accordance with their fluctuating intake, somewhat after the manner in which it varies its nitrogen exchange. A person of the difficultly fattening type was investigated, first, to determine the minimum food required for maintenance of weight at the customary level; second, to ascertain whether and to what extent an excess of starchy food would be stored by this type of person as adipose in a long period of superabundant measured diet; and third, to learn whether after the body was returned to the initial weight with the least possible loss of nitrogen, any change had occurred in the minimum requirement of food. The person was found to owe his resistance against fattening to an extravagant calorie requirement which persisted at all times, despite a moderate daily round of activities. This extravagance increased during the course of the excessive carbohydrate diet, and stayed above the initial level even after the return to normal weight. Gulick remarks:

> The general results of these experiments are that this example of a person belonging to the difficultly fattening

[9] Gulick, A.: "A Study of Weight Regulation in the Adult Human Body during Over-Nutrition," *Am. Jour. Physiol.*, 1922, lx, 371.

type was found to show a wasteful rate of oxidation during all the feeding experiments, including both the periods in which the diet was moderate or low and those in which a large excess of starch was superposed upon the normal diet. During the prolonged periods of high diet this wasteful oxidation became more pronounced, and it continued so throughout the following periods of under-nutrition, so that even after the body had been brought down again to its original weight, it required more food to keep it at steady weight than had been necessary at the start. . . .

The basal rate of metabolism as determined in a reclining position before breakfast did not rise above the average expectation for the subject's age, weight and height. Pulse and blood pressure were also entirely normal.

It seems clear that throughout the entire experimental series there was some factor at work which caused fuel food to be burned more freely than in the average individual. This factor was not an over-active thyroid as attested by the entirely normal basal metabolism.

It is possible that a part of the waste is attributable to neuromuscular factors. During all the experimental periods the greater part of the daily activities were of the less intense variety, the calorific cost of which is always problematical, because it can never be predicted how much will be wasted in the increased tone of the unemployed muscles. This undeterminable expenditure may easily have varied from the average expectation, and may be responsible for some of the unexplained energy expenditure. But if this were the whole explanation, we ought to find a lessened wastefulness and not an increase during the months of overfeeding when there was a continued stuffed feeling and a disinclination to exertion. For this reason it seems more probable that the main factor is not to be sought in neuromuscular habits, but in some factor in the chemistry of nutrition. (P. 392.)

The development of the conception that foodstuffs may under certain conditions replace each other in accordance with their heat-producing values is largely due to Rubner. According to the "isodynamic law," as it is sometimes called, the body can secure its heat and the energy for external work from either fat or carbohydrate, these foodstuffs being equivalent to each other in the energy balance approximately in proportion to their calculated heat equivalents or physiological calorie values. This means that, calorie for calorie, fat and protein are substantially of the same nutritive significance; in terms of matter 100 grams of fat should be isodynamic with 232 grams of starch or 234 grams of sucrose.

In a critique of this hypothesis Cathcart[10] has questioned the thesis that the basis of nutrition is the exchange of energy and not the exchange of material. His own experiments indicate that under otherwise comparable conditions isodynamic quantities of fat and glucose exhibit unlike potencies in protecting the body from loss of protein and in determining the type of nitrogenous metabolism. Carbohydrate is regarded as the more effective protein-sparer. Cathcart remarks:

> No one will of course seriously maintain that nutrition can ultimately be reduced merely to the satisfying of the energy demands: the calorie factor may be regarded as strictly secondary to the supply of material. We do not live on calories, yet all our general estimates of food requirements are quite properly for the most part made in terms of calories. Calorie value is simply a very convenient physical standard for the assessment of diets, but merely because such a standard has

[10] Cathcart, E. P.: "The Influence of Fat and Carbohydrate on the Nitrogen Distribution in the Urine," *Bioch. Jour.*, 1922, xvi, 747.

proved of great utilitarian value there is no real justification for placing this standard as the foundation stone of hypotheses framed to offer an explanation of cellular activity. Many writers are obsessed with the idea of the calorie, forgetting that the organism is certainly not a heat engine. It is perfectly true that calories are a measure of heat, but it must not be forgotten that we do not consume actual heat units but only potential heat-giving substances which can eventually be degraded to the form of heat and be measured as such. The thermal aspect of nutrition is unduly stressed, for, while heat may be a necessary product of tissue activity, it is, after all, a by-product. (P. 752.)

Accordingly, Cathcart argues that the use of the term isodynamic in connection with problems of nutrition should be strictly limited. One can undoubtedly speak of isodynamic quantities of various substances but it does not follow that they are of equal, or indeed of any, value to the organism. When dealing with foodstuffs we ought to keep constantly in view that the material side is fully as important as the energy side. Therefore, Cathcart adds, one ought not to stress so much the equality in energy as the equality in sparing or preventing tissue breakdown, the isoeconomic or, as he prefers to call it, the *isotamieutic* (ταμιευο = to husband or to spare) value. Such a value is more physiological than isodynamic as it covers all phases of cellular activity.

Investigations conducted by Krogh[11] in recent years have likewise pointed to the inadequacy of the "isodynamic law" when it is too strictly interpreted. The assumption that every food can be utilized in the contractile

[11] Krogh, A.: "Energy Exchange in Man," *Proc. Physiol. Soc.*, 1919, *J. Physiol.*, lii, p. lxxiv.

functions of muscles in proportion to its isodynamic equivalent value has not met the test of actual experiment. The carbohydrates are evidently superior. According to Krogh when fat is utilized for muscular work, a loss of energy of 8 to 12 per cent of the fat katabolised occurs. Some people on a fat diet become very tired; this does not occur with carbohydrate; perhaps, as Hill, Hopkins and Fletcher think, fat must first be converted into some substance allied to carbohydrate which can be directly used by muscle. Similarly Durig has shown that despite its high calorie value alcohol is used less economically than fat and protein as a source of energy in muscular work.

Notwithstanding the great advances which recent years have witnessed in the science of nutrition almost innumerable problems still confront the critical investigator. The fundamental chemistry of the nutritive processes is scarcely understood in a single detail. The energetics of the organism have as yet been sketched in broadest outlines only. Although the significance of the "little things" in nutrition is becoming better appreciated their function is by no means completely explained. Instinct is not always an unerring guide in the selection of food. Although it may lead along the paths of nutritive safety under the unhampered conditions of nature, it has been found undependable in more than one instance where the food choices of the highly artificial civilized world are concerned. In any event the history of science should warn us against the dangers of dogmatism in the presence of so much that remains unknown or unexplained or unapproachable. Particularly when experience and science seem to be in conflict is it well to keep an open mind. *Noblesse oblige!* It becomes the duty of those who by training or natural endowment or unique opportunity are exceptionally equipped for investigation to beware of an attitude of finality where knowledge is incomplete and deductions are at best hypotheses. In an address entitled "First Get the Facts" Secretary Redfield[12] reminded his hearers that prejudice and half truths and narrowness of view and obstinacy of thought are all weights that men carry in the race of life; expensive things, bringing at times both pain and poverty into his lot who tolerates them. Secretary Redfield proceeds:

The mind of science is one of high ideals. It is a modest mind, for it recognizes that there are many things it does not know. It is a discriminating mind, for it tests and selects or rejects as the test may tell. It is a practical mind, for it aims to find the hidden things of nature and put them to use. It is an honest mind, for it seeks neither to deceive nor to be deceived. It is an open mind, ready to reject the truth which seems to be in favor of that which is proven to be. The scientific mind, if it be true to itself, knows no passion nor prejudice nor predilection, unless it be the passion for the truth that is not yet known, a judgment given in advance in favor of that truth when it shall be known and a preference for any form of truth whatever, and a distaste for shams. . . . In the business world facts are stubborn things and insist upon being respected. They have a way of bowling one over if one does not respect them. Enter a great mill and look about you. The machine which is nearest at hand is itself the illustration we seek. It is the embodiment of ascertained fact. As you stand and look at it and think of how it came to be you will find your mind running back through a long series of facts which one by one were gathered often through many years and which have ended in

[12] Redfield, W. C.: "First Get the Facts," *Science*, July 9, 1915, xlii, 39.

the mechanism which you see. If it were not made in accord with the facts out of which it grew it would cease to work and become a helpless thing. If it is not used in accordance with the facts which control its service it ceases to be useful and again becomes a helpless thing. It is made up out of past facts. It is working out present facts, and its product often points toward the development of facts which are to be. . . . The relation men hold to truth, their respect for facts, their use of facts, largely determines their place and power in life. We make progress in the business world not necessarily by research for facts but at least by outreach for them and by respectful treatment of them when they are found. . . . The amount of success will depend a good deal upon how far your vision goes in seeing the facts that surround you and on the extent to which your practice goes in using those facts. The man of broad mind sees more facts than he who has a narrower vision. Mental nearsight is usually not profitable. To be farsighted is at times physically inconvenient but commercially has much in its favor. It is more essential, however, that the sight, whether it be far or near, shall know a fact when it sees it and be ready to abandon a pseudo fact for a real one and to abide by the latter till further facts are found. (P. 40.)

The science of nutrition is in the midst of a continual evolution of facts and development of truth. For the present, therefore, we should "first get the facts."