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THE VITAMINS

AND THEIR

CLINICAL APPLICATIONS

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A Brief Manual

by

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FOREWORD

In recent years perhaps no other branch of medical research has survived such tempestuous development as has vitaminology. To-day we recognize in these substances not only vital components of nutrition indispensable for the living processes in the human and animal organism to every living cell, and for the cooperation of organs and organic systems, but beyond that, they are substances bound up with the events of the living world in general. If it is permitted to put along side of the saying of Pflueger "Without albumen no life" another "Without vitamin no life", it may be appreciated, what it means, that during late years progress has been successfully made in clearing up the chemical composition of the vitamins. The advantage of being enabled to work with pure substances now is very evident. The possibility of their pharmacological and toxicological investigation is at hand. The question of dosage can be answered directly. Furthermore we are in a position to examine the vitamins as to their curative effects reaching beyond their properties as merely accessory materials.

The questions just indicated hold the center of investigation at present. There is no doubting their importance for the practitioner desiring to use vitamins for curative purposes. Sensing the want of the busy man, in general or hospital practice, of a chance to inform himself in vitaminology by means of a lucid presentation with special regard to the purely practical, the idea arose to write a concise review of the new expanding field of science. Unwilling to lose sight of our problem, it is necessary to strictly limit ourselves as well in regard to actual experimental material as to observations and experiences with patients. Only the most important could be submitted, and of the investigators of merit only some few could be cited. If we have reported our own rather large experience with the metabolism of A and D, purposely in greater detail, it has been done, because we have been engaged in these questions with special intensity. We are firmly convinced that vitamin therapy is still in its incipiency. May this little booklet be of aid in the evolution of it. Uncritical optimism has to be avoided the same as fruitless resignation.

Munich—Wiesbaden, early 1936.

STEPP, KÜHNAU, SCHROEDER

TRANSLATOR'S PREFACE

When pioneers and settlers enter into and then extend scientific fields, they soon reach areas posted with question marks. It is in these regions where new sciences form, as, for instance, "Vitaminology" since 1929.

In this respect there are enormous reaches of land under experimentation and not the least portion under American cultivation. The news of the discoveries in pernicious anemia flashed like chain lightning across the medical firmament.

The man in practice finds the literature bewildering, the plethora of facts and reports are difficult to assemble and clinically to apply. It is with alacrity therefore, that we hail the little book, "Clinical Application of Vitamins." Seasoned veterans guide us through blocks of experimentation; we seem to grasp it all, and do not tire. With masters of medicine we are clearly viewing clinical situations formerly enshrouded in fog.

That a medical man should become desirous of making an effort to enlarge the circle of readers is only natural. In doing so, the translator must acknowledge his indebtedness to Dr. Royal Lee for his generosity in arranging publication of this translation, and especially to Alfred William Hubbard for bringing the book to my attention, and for the inspiration, assistance and kind courtesies he has given me throughout the work. Also to Mrs. R. A. Glaser, thanks for her untiring work at the manuscript preparation and indexing.

HERMAN A. H. BOUMAN, M. D.

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SURVEY OF THE VITAMINS KNOWN TO-DAY

In the following table all vitamins where existence has been established at present are set up. In the text only those are discussed which are of proven importance to man.

Letter designation of the vitamin	Functional designation of the vitamin	Remarks
	I. *Fat-soluble vitamins*	
Vitamin A	Antixerophthalmic vitamin	
Vitamin D	Antirachitic vitamin	
Vitamin E	Antisterility vitamin	not uniform
Vitamin K	Antihemorrhagic vitamin (Dam, Schönheyder)	indispensable for the chicken.
.....	Fat-soluble growth vitamin (Coward-Key-Morgan)	*
	II. *Water-soluble vitamins*	
Vitamin B_1 (B in America)	Antineuritic vitamin	
Vitamin B_2	Thermostable growth vitamin (lactoflavin)	**
Vitamin B_3	Thermolabile growth factor (Williams-Waterman; O'Brien)	indispensable for pigeon*
Vitamin B_4	Thermolabile growth factor (Reades; Keenan)	indispensable for chicken, rat and other mammals. not uniform.
Vitamin B_5	Thermostable growth factor (Carter-Kinnersley-Peters)	indispensable for pigeon*
Vitamin B_6	Pellagra preventive (Györgyi)	identical with factor Y of Chick-Copping**
Vitamin B_7	Enteral vitamin (Centanni-Montevecchi)	not uniform
Vitamin C	Antiscorbutic vitamin (ascorbic acid)	
Vitamin H	Skin-antiseborrheic vitamin (Györgyi)	probably ident. with factor R of Huntu, Williams and factor X of Boas Fixen
Vitamin J	Antipneumonic vitamin (v. Euler)	*
.....	Antianemic vitamin; extrinsic factor (Castle)	**

* Significance for man unknown.

**The growth factor B_2 (lactoflavin) the pellagra factor B_6 and the anemia factor of Castle form a functional unity and are comprehended as vitamin B_2-complex. Under this designation the three substances are discussed in the text together. In America the vitamin B_2-complex is generally called vitamin G.

As vitamin F Evans (1928) and Oncken (1935) signify a mixture of vital, not synthesizable in the body, highly unsaturated fatty acids, the lack of which produce in rats necroses of the skin, sterility and uremia.

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HISTORICAL INTRODUCTION

Max von Rubner developed the energetics of metabolism, allowing the presentation of the nutritional processes with a lucidity never approached before, so that the physiology of nutrition, evolved by C. von Voigt and his school, seemed to be put upon a firm basis for all time. Some few experimental facts of the last decades of the past century, which could not be made to harmonize with the teachings of Voigt and Rubner, signal among them the investigations of Lunin of Bunge's laboratory in Bale, had either remained little noticed or had been forgotten. They began to be reminded of them again when physicians in the tropics, on the basis of newer studies, conceived the beriberi disease as a disturbance of nutrition, resulting from food consisting preponderately of polished rice. This viewpoint was decidedly confirmed by the discovery of experimental polyneuritis by Eijkman in 1897 and in sequence by the studies of G. Grijns, Axel Holst and numerous other investigators. All of them contributed to prepare the ground for the growing changes of our ideas about nutrition ensuing in the following decades. To be sure the firm conviction that there were, beside the main foodstuffs, still other unknown substances indispensable to growth, maintenance and reproduction of the human and animal world prevailed quite generally only, when, in comprehensive new and systematic alimentary tests in which stipulations were formulated with increasing precision, the total results despite entirely different methods pointed in the same direction. Diets were used which were in part freed from lipoids by extraction with alcohol and ether and in part artificially composed of the purest nutriments. All test animals (mice, rats, pigeons, etc.), showed consistently the same behavior: Cessation of growth, stationary weight or loss of it, collapse and death. Supplementing the food with the substances removed from it, that is, certain extracts, even in very small quantities, proved their power to correct the nutritional deficiency; animals already ill recovered rapidly, while the healthy upon timely administration of extracts could be maintained in health. Of the work which adduced convincing experimental proof, may be named that of Stepp, Schaumann, Hopkins, Casimir Funk, Osborne and Mendel and others. The work of recent years, in particular the clearing up of the chemical composition of several vitamins, has vastly extended the new field. The close connection of vitamins and hormones has even at this time adduced decidedly new aspects in the study of the pathogenesis of many disease conditions. No less benefit of this research has the physician received in his practice, and will surely continue to do so. The vitamins are not only of great consequence as accessory substances, but curative

effects have been recognized in them, which they may render independent of the tasks assigned to them in the food-stuffs.

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TERMINOLOGY OF THE VITAMINS AVITAMINOSES AND HYPOVITAMINOSES

The vitamins are components of the plant body sharing in very small quantities in the regulation of the processes of the plant. They are, therefore, also considered as hormones of the plant world. After they have been taken up by the animal body in the food, they incur important tasks, partly in regard to vital phenomena in the cell itself (affecting permeability, catalyzing fermentative action), and partly to regulating remote processes. From the standpoint of quantity they can hardly be considered as energy producers. In general, since it is not able to synthesize them, the animal body is obliged to ingest the vitamins with the nourishment—directly in vegetable food and indirectly in animal nutriment—either in ready form or as provitamins (out of which the specific substance is produced in part by radiant energy or in part by catalytic cooperation of other diet factors). If too little of these vital substances is taken up (for reasons of lack in the food, of deranged resorption in pathological conditions or of their destruction by bacteria in the gastrointestinal tract) when the reserves of the body's own are depleted, the functions pertaining to them are disturbed, and manifestations of more or less sharply defined syndromes of deficiency designated as avitaminoses or hypovitaminoses develop.

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RELATIONS BETWEEN VITAMINS AND HORMONES

The vitamins must be ascribed to the primitive substances of all organic life, since they are found in the lowest forms of life (bacteria, algae, etc.). They play a decisive role in the animal, even in the organisms possessing neither hormonal glands nor hormones. In higher animals where internal secretion appears first as a physiological arrangement, there are at once close reciprocations established with the vitamins. As they grow, the vitamins affect, generally, development of the hormonal glands and their function, and enter into reciprocations with the hormones by turns in a sense of a co- and counter play. Because of the close connection indicated between both of these groups of substances, it is often practically impossible to carry out a strict separation of their effects. A lack of as well as "too much" of vitamins may become manifest as hormone activity.

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THE VITAMINS AS FOOD-STUFFS AND AS CURATIVE SUBSTANCES

The animal world, subsisting upon plant food essentially, takes up plant tissues or parts of them (the carnivores of animal nutriment in a roundabout way) usually containing albumen and besides in varying quantity then more carbohydrates and then more fats, but always minerals and also vitamins. Therefore, a multiplicity of substances received with the foodstuffs (i.e. catabolic products) comes to bear upon metabolism almost exclusively. How much the principal foods—proteins, carbohydrates and fats—in regard to their absolute and relative quantity and their reciprocal quantitative relations influence the specific functions of each vitamin and thereby of each hormone in detail is beyond our knowledge. (The direct effect upon hormonal glands and hormones themselves must not be left out of consideration.) It is only certain that such reciprocations do exist. Of great practical importance is the discovery made in recent years that the actions of the individual vitamins are closely linked together and this in the sense of a co- and counter play. The lack of a vitamin in a particular diet is followed of necessity by a change of effect of other vitamins. The deficiency symptoms resulting from removal of a vitamin from the nourishment do not in a strict sense give positive information of the function of the particular vitamin in the organism. If, nevertheless, the symptoms of deficiency (phenomena of loss or lack) are described as characteristic of the individual clinical syndromes designated as avitaminoses, it has been done, because, under certain conditions upon removal of one or another vitamin they come to be observed ever in a like manner. It is necessary however to keep constantly in mind that the direct functional loss of the respective vitamin participates equally in the development of the morbid disturbances as well as resulting in the changed effect of the vitamins remaining in the nutriment under these conditions, and in that of the function of the hormones regulated by them. The conception that the investigation of the pure vitamin might possibly disclose new and so far unknown effects has proven especially productive with Vitamin C. It appears that this vitamin given in pure form may influence disease conditions, which (so much may be said today) have nothing to do with states of avitaminoses or hypovitaminoses. Thus the vitamins, beyond the service they render as accessory substances, possess the properties of curative-stuffs.

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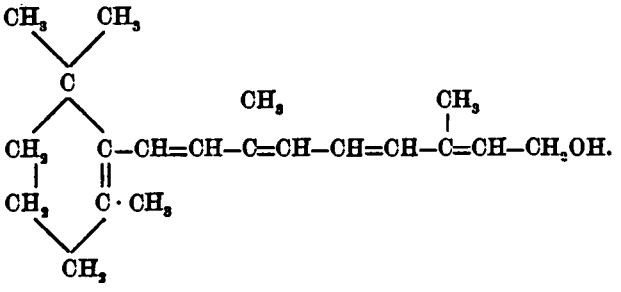
CHAPTER ONE

VITAMIN A

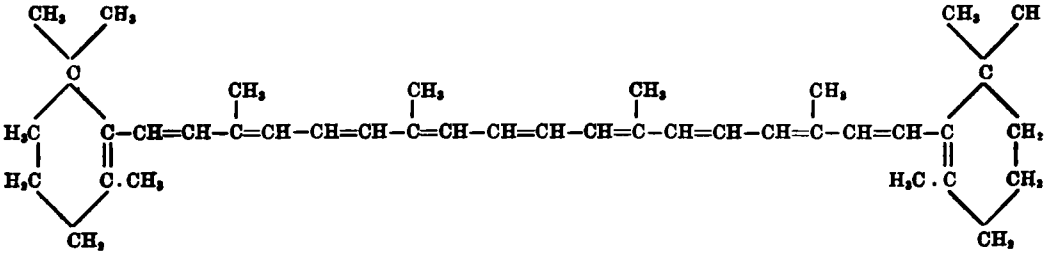
History. In 1909 W. Stepp reported that white mice fed on a diet deprived of its alcohol- and ether-soluble substances, but otherwise sufficient, could not be kept alive. He drew the conclusion, therefore, that the principal aliments (proteins, carbohydrates, fats and minerals) did not suffice to sustain life, and that aside from them there were still other materials, unknown as yet, assigned to lipoids because of their solubility in ether and alcohol, which were equally indispensable. The conjecture that the neutral fats, so easily formed from carbohydrates, were not the decisive factors could soon be confirmed, when, during continued feeding experiments, additions of the purest neutral fats failed to save the animals. These and further experimental feedings under different schemes of investigation in rats by F. G. Hopkins confirmed the work of Stepp completely. This was the starting point for the extensive experiments carried on chiefly in English-speaking countries, mostly in rats, during the World War, which established the fact that deficiency of a fat-soluble substance would lead to a disease of the eyes, later recognized as xerophthalmia or keratomalacia. We mention the names of Osborne and Mendel, McCollum and his school, Davis, Sherman, Drummond, Mellanby and the German investigators Freise, Goldschmidt and Frank. In the light of this knowledge one could understand the reports of Japanese eye clinicians of 1896 about the occurrence of a grave epidemic of xerophthalmia and keratomalacia in Japanese children. The disease had appeared chiefly in children of Mid-Japan where the food was principally of vegetable origin. Among the population of the coast, where fish was plentiful, the disease was scarcely ever seen. Ten years later Mori described a similar eye affection in 1400 children from the ages of 2 to 5 years. This malady, known in Japan as hikan was eminently improved by chicken livers, eel fat and cod liver oil. At that time, when the vitamin researchers had already taken notice of the existence of an antixerophthalmic vitamin, Bloch in Denmark reported numerous observations of keratomalacia in children, fed with skimmed milk and margarine instead of whole milk and butter. Continued search then led to the important recognition that a so-called fat-soluble vitamin, aside from the antixerophthalmic, an antirachitic factor, must be distinguished. By the laborious and admirable efforts of English and German investigators (Windaus, Pohl, Linsert, Rosenheim, Webster, et al) the latter was isolated and its chemical constitution determined. Not less successful were the efforts aiming at the clarification of the antixerophthalmic Vitamin A. The

work of Steenbock, H. von Euler, and Karrer deserves emphasis since they could prove the activation of Vitamin A by pure carotin. Relying upon the work of R. Kuhn and Winterstein relating to polyemia P. Karrer and H. von Euler were jointly enabled to isolate the Vitamin A and to establish its chemical structure.

Chemistry. The Vitamin A is an alcohol of the following formula:



Its accuracy was verified by comparing the compound gained by hydration with the product* obtained by synthesis. Complete identity of both bodies became evident. The Vitamin A stands in closest relationship with the carotin dye-stuffs. They are the red, orange-red and yellow dyes, hydrocarbons with 40 carbon atoms, in which single and double joined hydrocarbon atoms follow each other with regularity. Among them the β-carotin has a separate position in so far as theoretically one molecule may give rise to two molecules of Vitamin A, as may be seen in the following formula. The splitting up occurs in the middle, taking up two molecules of water.



Because of the conversion of carotin into Vitamin A in the animal body it has also been designated as Provitamin A. The conversion occurs in the liver, aided by a ferment, the so-called carotinase and for its efficacy

* Of the perhydrovitamin; both were carried over the ketone into the semicarbon.

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thyroxin of the thyroid is indispensable. Carotin, delta and gamma, both comprising only one hydrate ring, the so-called "ionon ring", furnish correspondingly less Vitamin A. The activity of Vitamin A is connected as well with the β-ionon ring as with the presence of the double compounds. And so it is only a restricted number of carotin dyestuffs which activate provitamin effect.

As carotinoids* carotins are definitely related to dye-stuffs with 40 or less carbon atoms. Closely connected are the oxygen-containing xanthophylls, which like carotin dye-stuffs have 40 carbon atoms. They occur in the green parts of vegetables always associated with carotin. The carotin dye-stuffs as well as the carotinoids are built up by bacteria.

Most of the xanthophylls are Vitamin A inactive like many others not containing the intact ionon ring carotinoids. The practically important dye-stuff of the tomato, the carotinoid lycopin,** displays, for example, just as little Vitamin A effect as does the dye-stuff of the egg yolk, the lutein, belonging to the xanthophylls.

The only xanthophyll so far known to be Vitamin A active is the kryptoxanthin (caricaxanthin). Upon the occurrence of kryptoxanthin in yellow corn and egg yolk especially depends the Vitamin A activity of these foodstuffs.

The precursors of Vitamin A in Nature are the following: α- β- γ- and (probably) δ-carotin, kryptoxanthin and retinin (in the retina).

Determination. Detection of Vitamin A is possible by biological as well as by chemical and spectrophotometric methods. A separation by biological means of carotin and Vitamin A is not feasible, since the carotins within the organism, as mentioned, are converted into Vitamin A. The so-called xerophthalmia test much used formerly has given way to the growth test. This can be carried out by the prophylactic, or better, by the curative method. Rats serve as experimental animals. They are fed a Vitamin A-free diet until cessation of growth sets in (depleted reserves). About 7 days later additions of the substance to be investigated are started. Resumption of growth with an average increase of 3 gm. per week in 60% of the animals proves the presence of Vitamin A. An observation lasting three weeks suffices.

> Merck & Company proceed with the biological investigation as follows: That dose of the substance to be tested, given daily, which in 80% of the test rats kept on a vitamin-free diet, produces after 35 days an increase in weight of at least 15 gm., preventing xerophthalmia at the same time, is considered a biological unit.

Of β-carotin the rats need per diem about 2.5 γ, of α- and γ-carotin 5. (1 γ equals 0.000001 gm.). It has been found recently that a lack of Vitamin A in the feed of rats develops a sort of continued estrus, which indeed may be safely distinguished from the true estrus histologically. This condition, removable in three days even by Vitamin A, is designated as Kopokeratosis (Kopokeratosis=rest). Less closely corroborated as yet has been the re-

* Of general biological interest is the fact that by the oxidation splitting of the carotin dye-stuffs partly new dye-stuffs and partly taste and scent substances arise in the plants.

** Adverse newer reports need confirmation.

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sistance test; in rats fed a Vitamin A-free diet for four weeks, an otherwise harmless saprophyte, the bacteria mucos. capsul. proves pathogenic.

Chemically the presence of carotinoids as well as Vitamin A may be detected by the reaction of Carr-Price with trichloride of antimony. For quantitative determination of the carotin and Vitamin A, sera and organs are extracted with alcohol and benzol. The extract (organs are previously saponified) is concentrated and from that the carotin is determined. The residue is taken up with chloroform and therefrom the Vitamin A is determined. The index of carotin ensues by comparing the yellow color in the extracted fluid due to carotin with the graduated yellow glasses in the Lovibond tintometer; the content is expressed in yellow units. The Vitamin A is ascertained by adding trichloride of antimony. The resulting blue color is compared with the blue of the graduated blue glasses in the Lovibond tintometer and is expressed in blue units. Since trichloride of antimony and carotin show also a blue tinge (Vitamin A reacting, to be sure, about 20 times stronger), it is necessary to subtract the value of the blue, due to carotin, from that found at the determination of Vitamin A. The former is obtained by converting the yellow units found for carotin by means of a gauged curve in the blue units.

In performing the reaction it is to be remembered that certain, also Vitamin-A active carotinoids, yield positive results. On the other hand there are certain substances known as checking bodies which may hinder the success of the reaction.

Recently the spectrophotometric method has proved of great value for the determination of Vitamin A. It has a typical band of absorption at 328 μμ. Very recently the method used hitherto has been replaced by employing shorter periods of exposure, since the mercury light destroys a part of the vitamin even on short exposure.

Furthermore, the blue solutions obtained by the Carr-Price reaction are examined spectrophotometrically. There appear two typical absorption bands, one at 606 μμ and one at 572 μμ. They are based, as has been demonstrated recently, upon two chromogens, and the other the hepaxanthin equals 580 μμ-chromogen. The structure of the latter has not yet been fixed. A vitamin unit has been proposed by the Section on Hygiene of the League of Nations as the vitamin activity of 0.6 γ (γ equals 0.001 mg.) of the β-carotin.

Occurrence. The source of Vitamin A is the vegetable kingdom. Very soon it was recognized that it was widely distributed there and at that usually together with the chlorophyll. These correlations are clarified today insofar as the statement may be made that the formation of chlorophyll and that of the carotinoids runs parallel; a direct dependence of origin of one upon the other could not be proven. The extent of the Vitamin A activity in vegetable products is due to the carotin content they possess; indeed it is questionable if the complete Vitamin A occurs in plants at all. The respective decision is not obtainable by biological, but only by chemical or spectrophotometric means. Since comprehensive investigations with these methods have not been submitted, the

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question cannot be definitely answered. The high Vitamin A efficacy of many plant products is frequently marked at once by their yellow color, thus, for example, white corn is almost Vitamin A inactive, while the yellow is strongly active. Of great interest is the fact that the carotin content of plants is dependent upon the kind of soil in which they grow. A soil rich in copper, manganese, zinc, nickel and chromium guarantees high carotin content. The green parts of plants are rich in carotin; when they turn yellow in the Fall their content of it is reduced to $\frac{1}{20}$ of the original quantity. Subterranean plants contain but little carotin. Mushrooms contain little or no Vitamin A. Algae such as Nitschia closterium, for example, have an abundance.

Fruit is, generally speaking, a poor source of Vitamin A; berries may be excepted; but dried pumpkin contains generous quantities.

The animal body, as stated, converts carotin easily into Vitamin A, providing they contain the β-ionon ring and the double combinations in proper form (c.f. chemistry above), but for itself it is not able to produce it. Not all animals have the power to convert carotin into Vitamin A. Thus, for example, the cat and many kinds of fish are continuously supplied in their food with the complete vitamin.

The formed or the complete Vitamin A taken with the nutriment is stored throughout the body, especially in the liver. In women the storing is greater than in men. The liver of the human fetus holds little Vitamin A; it is also percentually less than in the adult and it is still more diminished towards the end of pregnancy. In the fetal liver carotin is deficient. During pregnancy the liver is particularly rich in Vitamin A; it contains 95% of the entire stored amount; the rest is chiefly distributed in lung and kidney. Besides Vitamin A carotin is found in milk. Yellow butter (very rich in carotin) is a particularly good source of the vitamin. The richest source of Vitamin A is liver oil. Holding first place are the liver oils of the fish Soombresox saurus, Rhombus maximus, Stereolepsis ischiagni and then that of the liver of the sea bird Larus marinus. According to very recent investigations halibut oil excels all others. The content of carotin and Vitamin A expressed in milligrams of carotin in 100 grams of various foods is given in the following table.

Stepp-Kühnau, neue Dtsch. Klinik, Erg.—Bd., 1, 43, 1933.

Cod Liver Oil	4 - 200	Carrots	.8
Butter	2 - 20	Tomatoes	1.6
Egg Yolk	4 - 20	Green Beans	1.4
Milk	0.2 - 0.8	Watercress	.4
Cheese	1.6 - 3.2	Black Berries	0.8
Liver, Summer	40	Black Cherries	0.6
Liver, Winter	7 - 12	Green Kale	.4
		Spinach	8 - 24

Manifestations of Deficiency of Vitamin A. The effects of Vitamin A, which seemed formerly to be definitely designated as "antixerophthalmic" and "fat-soluble growth vitamin", have been very much broadened by

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our present knowledge. Essentially they may be summarized in four groups. Lack of Vitamin A factor causes:

1. Degenerative changes of the structures of the skin and the mucosa. The epithelium, especially of the mucosae, begins to proliferate showing a tendency to keratinize, a process particularly plain in the vagina. In sequence there appears an increasing permeability of the superficial epithelial strata, resulting in a lowering of the natural resistance to infections of all sorts. Vitamin A has, therefore, been designated as the antiinfectious vitamin. Alveolar pyorrhea, mastoiditis, otitis media, sinusitis, bronchitis, puerperal sepsis, and urethritis are very frequently observed in animal experiments with lack of Vitamin A. The glands cease their secretory activity; in and around the salivary glands there develops a stasis of secretion and a tendency to abscess formation; analogous processes about the tear glands lead to decomposition and infection of the conjunctival secretion, formation of exudates and desiccation of the cornea—xerophthalmia and keratomalacia.

   Also the over-present abnormal increase of enamel and cement formation with disturbance of dental growth is nothing else but an expression of the changed epithelial structure. In like manner the formation of stones in the biliary and urinary ducts and further the intestinal gout of chickens, attributable to uric acid deposits in the gut, must be explained.
2. Insufficient supply of Vitamin A or its precursor produces disturbances in the central nervous system, which also need further study in animal experimentation. First, a sort of tract degeneration of the spinal cord and then a condition approaching ergotism seems to develop. The nervous manifestations of lathyrism, pellagra and pernicious anemia used to be linked with lack of Vitamin A. The cord symptoms especially of the latter disease are said to respond favorably only to fresh liver preparations, but not to liver substance alone. It is worthy of note that a pellagra-like disease among dogs—"black tongue", not rare in America, —is cured by carotin, but not by Vitamin A. That is information deserving of notice, because, though standing out for itself alone, it may admit a biological activity of carotin.
3. The importance of Vitamin A for the regeneration of visual purple has received in very recent time close attention only by students and has advanced appreciation of non-hereditary hemeralopia as being a specific symptom of deficiency. The retina is the organ of the body richest in Vitamin A. The visual purple is an albuminous compound of Vitamin A. Failing supply of Vitamin A endangers the anabolism of the pigment indispensable to vision. In addition attention may be called to the Bitot spots of the cornea as prodromal, and the brown scaly pigmentation of the conjunctival epithelium as signs of recovery from xerophthalmia or keratomalacia.
4. The comparatively high content of Vitamin A in the sexual glands has been known and appreciated for a long time. The question of closer relationships between Vitamin A and the sexual sphere has been more

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accurately investigated only since Vitamin E was discovered. It was astonishing to see that the symptoms of Vitamin A deficiency almost completely resembled those of avitaminosis E in regard to their effect upon the sexual organs. In male animals appear changes in the seminal tubules and destruction of the germ cells, in the females absorption sterility; and in addition—something not seen with lack of Vitamin E—an extinction of the sexual impulse and disturbance of fertilization and implantation of the ovum.

Absorption and Cell Effect of Vitamin A. For the absorption of Vitamin A the presence of neutral fats but not that of bile is an essential presumption.

The statement that the Vitamin A substance was found in the thoracic duct could be confirmed from personal observations at the First clinic of Munich in a patient with chyluria. Perorally administered fat-dissolved Vitamin A (carotin as well) soon became demonstrable in the urine. If larger quantities of carotin are taken in, they are in a preponderate measure converted into Vitamin A and stored as such. The conversion, however, never ensues to 100%, but always so that a small quantity of carotin itself is stored.

It is regrettable that the information as to how Vitamin A affects the cells is still incomplete, but recent investigations indicate the direction in which search must be made. In animals receiving a sufficent supply of the vital substance, as compared to others, a relatively high content of purines has been demonstrated in their tissues. If the presence of abundant purines enhances the formation of the nucleus, this finding would point to the fact that the regenerative ability of the cells were benefited by Vitamin A. Pursuant to investigations of respiratory processes in the liver (from sections of liver of normal animals and those Vitamin A deficient after the method of Warburg) the vitamin seems to facilitate the processes of oxidation within the cell itself. In a like sense observations speak for the catalytic activities of Vitamin A (and the carotinoids) in the auto-oxidation of unsaturated fatty acids. As important as these findings may be respecting obvious conclusions, a certain reserve is commendable, because many carotinoids without Vitamin A effect behave in quite a similar manner.

The Vitamin A effect is tied, however, to the presence of iron, and indeed for that purpose small quantities of hemin-iron, which is available in every cell, suffice.

Requirement of Man. The daily requirement of man may be appraised to be about 3-5 milligrams of carotin. The minimum is about 1 milligram and the optimum about 5 milligrams. The spread between minimum and optimum is apparently particularly large. That is of great significance for the important question of a latent relative lack of Vitamin A, i. e. the question of an hypovitaminosis A. In this connection it will certainly be possible to progress by comprehensive examinations of the blood as to its content of carotin and Vitamin A in a large number of healthy and sick individuals.

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Mechanism of Action of the Pure, Isolated Vitamin A, and Its Relation to Metabolism. While the most essential manifestations of insufficiency arising from lack of Vitamin A had been thoroughly studied (at this time the isolation of the vitamin or its precursors, the carotins, had not met with success), the investigations of the working mechanism could only be started when the pure substances were at hand. The most important fact was the finding that Vitamin A proved a direct antagonist of thyroxin. The growth effect of Vitamin A is suspended, and its storage in the liver prevented by thyroxin. Conversely, the toxic action of thyroid substance is retarded by Vitamin A, as well as the tadpole metamorphosis is accelerated by thyroxin. The disease condition ensuing from oversupply of Vitamin A (hypervitaminosis A) is relieved or arrested by thyroxin. Moreover, the important observation was made that thyroidectomized goats are unable to convert carotin into Vitamin A. Lactating thyroidectomized goats eliminate not as usual, a white, but a yellow milk.

These briefly sketched relations between thyroid and Vitamin A, which are evident at present, are surely of great import therapeutically in practice, particularly in view of liver pathology. At this point some few remarkable results of the experimental research may be adduced. Following administration of thyroxin or thyreotropic anterior hypophysis hormone the consumption of Vitamin A rises and it causes a depletion of the Vitamin A depots in the liver. It appears, however, that the ability of the liver to retain Vitamin A is in nowise disturbed. On the contrary with a very abundant supply of the vitamin more is stored in a liver damaged by thyroid substance or thyreotropic hormone than under normal conditions. It is said that there is eight times more Vitamin A stored than carotin. If there exists a thyreogenic liver damage for an extended period of time, the conversion of carotin into Vitamin A is not complete.

The relations of Vitamin A to protein metabolism have been investigated many times. A clear perception, however, is as yet impossible.

The relative connections of Vitamin A and carbohydrate and fat metabolism are likewise not fully surveyed at present. It has been suggested that fixed proportions of carotin and Vitamin A were necessary to form methylglyoxal in sugar metabolism. Moreover certain experimental investigations have led to the idea that Vitamin A was needed for the formation of fat from carbohydrates, as well as for the synthesis of fat from fatty acids and glycerine. It is possible that Vitamin A plays a role, also, in the oxidation of unsaturated fatty acids. Since they are chiefly found in phospholipoid compounds, the relation of Vitamin A to phospholipoid metabolism must be thought of. Cholesterin metabolism seems likewise to be related to Vitamin A. Upon supplying considerable quantities of Vitamin A there appears temporarily an increase of cholesterin, the ether-soluble phosphorus and fatty acids in the blood, which after some time again disappear (Wendt, Klin. Wschr., 14, 9, 1935). A strict coupling of Vitamin A with cholesterin metabolism is not evident, as investigations of hypercholesteremia in man have demonstrated.

For the preservation of a certain state of equilibrium between Vitamin

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A and carotin in the blood as well as in the liver the facts seem to indicate that Vitamin A may be converted into carotin.

About the elimination of Vitamin A or carotin in urine, bile, semen, feces, etc. nothing certain is known.

Hypervitaminosis A. An oversupply of Vitamin A encourages the development of a grave clinical syndrome, which is evidenced in rats and mice by emaciation, loss of hair, fatty degeneration of the liver, pulmonary and intestinal hemorrhages and thyroid hypertrophy. With overdoses of carotin it does not seem possible to produce such a hypervitaminosis. More recent experimental efforts clearly emphasize the important bearing Vitamin A has upon the fat and lipoid metabolism. Histological examinations revealed fatty changes of the von Küpfer star cells in the liver, of the interstitial cells of the testicle, heavy lipoid accumulations in the horn cells of the skin, and recently also the appearance of exophthalmus and a tendency to spontaneous fractures, all of which have been described as manifestations of the hypervitaminosis. In man hypervitaminoses have not been observed so far. According to experiences gained from experiments on animals the doses employed for functional tests and therapeutic purposes are insufficient to cause damages in man in the sense of a hypervitaminosis.

Vitamin A in the Synergism and Antagonism of the Vitamins. As has been briefly set forth in a previous chapter, the withdrawal of a vitamin from the food means an alteration of effect of the other vitamins still remaining in the nutriment. Thus the phenomena resulting from a lack of Vitamin A correspond in a certain degree to those produced by an oversupply of Vitamin D, and conversely those resulting from an oversupply of Vitamin A correspond to a Vitamin D deficiency. There seems to be, then, for Vitamins A and D a condition of equilibrium which is indispensable for the maintenance of normal cell formation. However, there exists relations not only between the fat-soluble Vitamins A and D, but also between A and the components of the water-soluble B complex and Vitamin C. In respect to the former (A and D) the evidence is not yet clear, since the results of the examinations with pure Vitamin B_1 and B_2 extracts have not been submitted. Antagonism between Vitamin A and Vitamin C, however, may be discussed with some assurance. Thus it happened that at the First Clinic in Munich a hypervitaminosis A produced in guinea pigs by large doses of Vitamin A could be relieved by heavy doses of Vitamin C fed at the same time. The accumulation of Vitamin A in the liver due to abundant Vitamin A supply is diminished by concomitant additions in the food of Vitamin C (Wendt, Schroeder, Zschr. Vitamin f., 4, 206, 1935.).

Clinical Observations Relating to Physiology, Pathology and Therapy of Vitamin A in Man. Large series of investigations of the carotin and Vitamin A content of the blood in healthy individuals have resulted in considerable fluctuations in the medium average of value of 8.6 LEG* for carotin and of 1.4 of Vitamin A LEB** (calculated to 10 cc). The labilities

* Lovibund Einheit Galle—L. Units Yellow.
** Lovibund Einheit Blau—L. Units Blue.

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of the carotin and Vitamin A contents in the serum are so marked that values even double the figures indicated are found in healthy men. Fluctuations of carotin and Vitamin A contents in serum are equally great downward, but zero values for Vitamin A and carotin have never been found in healthy men. It was previously mentioned that the liver is not only the organ of storage for carotin and Vitamin A, but also that the conversion of carotin into Vitamin A occurs principally in the liver. This faculty of the liver for conversion seems to gradually decrease with progressing years, for higher carotin and lower Vitamin A serum values are met with in advanced age. During prolonged feeding tests with pure carotin the carotin level of the blood is abundantly increased and the Vitamin A level rises simultaneously, though not nearly so much as the carotin (Wendt). If the administration of carotin is continued long enough there develops, even in healthy men, the picture of xanthosis, a yellow tinged skin due to deposits most evident in the palms of the hand and in the mucous membranes, but particularly not in the sclera. Transmission of carotin into the spinal fluid, urine, perspiration and bile could not be observed nor was there evidence of any elimination in the feces. If Vitamin A (in form of Vogan) is provided during long continued feeding tests, the Vitamin A level rises to a manifold degree without the carotin level being influenced appreciably. During feeding tests with carotin as well as with ready Vitamin A it is noteworthy that a maximum of the carotin or Vitamin A levels once reached after a long time are not exceeded any more in spite of continued supply. Upon prolonged intake of Vitamin A a marked increase of fatty acids and blood lipoids (cholesterin, ether-soluble phosphorus, etc.) is observed, which gradually reverts after some time, though the Vitamin A supply is continued. A positive explanation of this strange observation has not been submitted. It is remarkable on the other hand that in lipemias or lipoidemias seen in man in pathological conditions neither carotin nor Vitamin A appear in increased quantities in the blood. Thus in lipemia of the lipoid nephrosis the Vitamin A figures are within normal limits. The diabetic lipemia is an exception, the carotin and the Vitamin A being regularly found markedly augmented. Just what these connections signify is still obscure. At any rate it is certain that it is not explained by the quantity taken with the food, since it never exceeded the usual amount. Insulin has no influence whatever upon the Vitamin A level. The whole question is yet to be clarified.

Lowering of the carotin and Vitamin A levels in the blood is far more frequently encountered under pathological conditions. Thus we observed in disturbances of the fat absorption, specifically in chronic diseases of the pancreas and in patients with grave gastroenteritis, a reduction of the carotin and Vitamin A values. Likewise in cases of jaundice with retention of bile from the bowel there occur grave disorders of absorption, so that in these patients the blood values for carotin and Vitamin A cannot be successfully raised by providing both of the substances. Whether the sinking levels, however, should be solely attributed to disturbances of absorption in liver disease associated with icterus or in cirrhosis of the liver, or whether the liver pathology as such should be blamed, needs further

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exploration. Depletion of the Vitamin A of the organism may reach so high a degree that neither in the serum nor in the liver of patients with cirrhosis may Vitamin A be demonstrated. The manifestations of lack of Vitamin A (keratomalacia, etc.) repeatedly seen in chronic liver diseases with jaundice, liver cirrhoses and in atrophies of the pancreas, find their explanation in the above observations.

The carotin-Vitamin A levels are notably lowered in serious cases of Biermer's anemia. After treatment with fresh liver, by reason of the abundance of Vitamin A in the liver employed, the level of Vitamin A rises perceptibly. However, the idea that there might exist etiological relations between Vitamin A and the incidence of the anemia, must be declined. The preparations so excellent for the successful treatment of Biermer's anemia, like Campolon, are free of Vitamin A. An ascent of the Vitamin A level following successful Campolon treatment does not obtain, and a remission cannot be established by giving Vitamin A (Vogan) alone.

Of greater import, as mentioned above, are the connections between carotin, Vitamin A metabolism and the thyroid gland. Corresponding to experimental investigations, there being an antagonistic behavior between thyroid incretion and Vitamin A, in cases of grave hyperthyroidism with a high rate of basal metabolism, a marked decrease or even a complete absence of Vitamin A could be demonstrated in the serum. Following successful iodine treatment of Basedow patients, or operation, the Vitamin A level resumes its ascent spontaneously. Pursuant with our present knowledge it must be accepted that a rising thyroid activity increases consumption of Vitamin A. In the opposite condition—that of hypofunction of the thyroid (myxodema and cretinism) the consumption of Vitamin A is markedly decreased. It must be assumed at the same time that there exists in these diseases a disturbance of conversion of carotin into Vitamin A and perhaps as in many cases an inability of the liver to store carotin and Vitamin A. Thus, in the serum of cretins no Vitamin A at all nor any trace of it was found, (Wendt, Muench, med. Wschr., 1679, 1935.) These entirely different processes and changes in the carotin and Vitamin A metabolism at first sight lead seemingly to the notable results that hyperthyroidism as well as athyroidism present the same picture respecting carotin and Vitamin A in the blood. The recognition of the increased consumption of Vitamin A in hyperthyroidism has led to an attempt to treat this condition with Vitamin A (Wendt, Muench. med. Wschr., 1160, 1935.) In the First Clinic of Munich they succeeded with large doses of Vogan (three times daily—30 drops) to achieve appreciable gains in weight and in many cases even a reduction of the basal metabolism to normal rates. The iodine Basedow in particular seems to react favorably. Further investigations are necessary to determine the importance of the Vitamin A treatment of hyperthyroidism as compared to other therapeutic measures.

Excellent results have been obtained in the treatment of diseases of the eyes with Vitamin A. Nyctalopia, an early symptom of Vitamin A deficiency, was treated with liver in Egypt (papyrus Ebers) as early as

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1000 years before Hippocrates. The French physician Despont treated numerous cases of night blindness (1850-1857) successfully with cod liver oil, whereby he properly surmised that a specific highly active component of the oil was responsible for the curative effect.

That the avitaminotic keratomalacia reacts surprisingly has also been known for a long time. These successes have been materially improved upon since Vitamin A has been provided in the form of concentrates rich in Vitamin A (Vogan). In many other ulcerations of the cornea, however, which off-hand were deemed unrelated to a lack of Vitamin A, local application, instillation of Vogan in the conjunctival sac, has brought about recovery. Thus an extensive ulcer of the cornea in a nursing mother was cured by applying Vogan locally. Such a success becomes evident at once if one is mindful of the fact that the growing of fat during pregnancy and the nursing of the child later force the organism to be deprived of great quantities of Vitamin A. In cases of gravidity, in which the vitamin reserves are small because of a previously deficient nutritional state, and when the nutrition during and after treatment of pregnancy continues insufficient, the manifestations of the avitaminosis may result in disaster. Ulcers of the cornea in cases of hyperthyroidism, in which hypovitaminosis appears in sequence of increased consumption of Vitamin A, are cured with Vogan.

Since animals fed on a Vitamin A-poor diet are especially sensitive toward the most varying infections, the vitamin has been drawn upon to combat them. Investigations have demonstrated, however, that the state of immunity, i. e. the formation of antibodies and of bacteriocidal forces, is not influenced by administration of Vitamin A. The effect of the Vitamin A seems to be limited to those infections, in which a relative or absolute deficiency of Vitamin A in the mucous membranes gives rise to changes in them, allowing the irritants to enter the organism. There are numerous observations, reported in this and other countries, of catarrhal infections, pneumonias, la grippe, puerperal fever, etc. having been improved by Vitamin A. In children, whose skin is very sensitive toward infections, pediatrists have treated this susceptibility with excellent results by enriching the food with Vitamin A. First and foremost the effect of Vitamin A as an anti-infectious vitamin lies in its faculty to prevent or cure the epithelial defects in skin or mucosa. It has been proposed therefore to change the term "anti-infectious vitamin" to that of "epithelium-protecting" vitamin. Attention may be called in this connection to skin changes which come to be seen as prodromal signs of an A deficiency before the typical eye symptoms are yet manifest in the form of an unusual dryness and roughness, reminding one of "goose flesh", known among the blacks as "toad skin". The cause is a keratinization of the epithelial cells due to a lack of Vitamin A. Upon treatment with Vitamin A it disappears promptly just like the most varying inflammatory and suppurating skin affections due to epithelial changes (v. Drigalski. Zschr. f. Vitamin f., 3, 37, 1934). Furthermore connected with the described effect of Vitamin A upon skin and mucous membranes is its beneficial influence upon the granulations of wounds by local application. The beneficial effect of cod liver salves and dressings may

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be held as assured, and surgically it is being made use of extensively (Loehr).

Vitamin A Preparations and Their Dosage. 1. Vogan (E. Merck, Darmstadt). The most potent German preparation of Vitamin A represents a Vitamin A concentrate prepared from fish liver oils of high potency. Free from carotin, it contains very small quantities of Vitamin D. One cc. of the substance corresponds to 40,000 biological (rat) units or 120,000 International units.

(a) Fluid form in dropper bottles of 10 cc. each. Average dose per day—5-10 drops (8,000-16,000 units), either in a single dose or divided in smaller doses per diem. Best taken in warm milk, soup or the like.

(b) Tablet form in boxes of 50 (1 tablet contains 4,000 units). Two to four tablets a day, masticated or not.

2. Detavit. (I. G. Farben and E. Merck). A combination of Vitamins A and D, containing about double the Vitamin A of the normal medicinal cod liver oil. Detavit neither smells nor tastes of oil. Children take one-half to one teaspoonful and adults one-half to one tablespoonful daily.

3. Other reliable Vitamin A preparations:

A vitamin Degewob (Berlin)
Avoleum (British Drug Houses, London)
Essegen (Lever Brothers, Port Sunlight, England).

Besides there are numerous preparations obtainable in other countries combining Vitamins A and D.

Clinical Application of Vitamin A and Its Dosage. To start with, a few preliminary remarks. It is self-evident that Vitamin A is to be applied primarily to the specific deficiency of Vitamin A, the classic syndrome of avitaminosis. More difficult to analyze is the problem of hypovitaminosis A. There are surely conditions of latent lack of Vitamin A, which are not at once so clearly apparent; for the spread between the minimum and the maximum is very large with Vitamin A. During pregnancy and lactation, in particular, the vitamin requirement is great and deficiency may exist without it being easily recognized. It is the problem of research to study this question most intensively, so that an uncritical application of Vitamin A may not discredit the proper treatment. In our opinion only a few directions may be pointed out for research to start from.

1. Hemeralopia, xerophthalmia, keratomalacia:
Generally speaking Vitamin A is given perorally, unless contraindicated by disturbances of the gastrointestinal tract, liver, biliary passages or pancreas (absorption interfered with). Excellent cures with this method have been observed not only in animal experiments but also in man. In most cases of adults ten drops of Vogan three times a day suffice. In children and nursing infants five drops three times daily are sufficient for the treatment of xerophthalmia; in older children a little more is given.

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In cases where the absorption of Vitamin A (gastrointestinal-liver-pancreas diseases and jaundice) is not quite reliable, subcutaneous or intramuscular administration must be resorted to. E. Merck and Company have put up a sterile Vogan preparation, which will be on the market in the near future. Ampules of 1 cc. are offered containing as much Vitamin A as the Vogan and are sterile. In accord with our personal experiences a dose of 0.5 cc. is advised to start with. In nursing infants and small children keratomalacia is treated at first with this dose (0.5 cc.) for several days, or with a single dose of 2 cc., which has been deemed adequate. Outstanding successes have been described and observed by ourselves with local instillation of Vogan in the conjunctival sacs. The dose amounts to a few drops daily.

2. Hyperthyroidism, and specifically the iodine Basedow.
   In most cases thirty drops of Vogan three times daily will suffice. It is recommended, however, that the Vitamin A blood-level be checked from time to time. As to dosage, we have been careful to keep the level at 5-10 blue units. To obtain this goal a larger quantity of Vogan of forty, even fifty drops, three times daily seems necessary in rare cases (Wendt).

3. Wounds.
   For the treatment of serious, deeply penetrating wounds, following injuries, cod liver oil salve in the form of the so-called Unguentolan (Loehr, Chirurg., 6, 5, 1934) has been recommended. The results obtained are excellent. In burns of all sorts (Roentgen included) this therapy seems to do astonishingly well. The question of whether this effect is solely due to Vitamin A has not been decided as yet. Salves containing pure Vitamin A do not seem to render the same service. It is possible that we are dealing with a complex effect in the action of the cod liver oil and that it depends upon the combination of Vitamin A and Vitamin D.

   Perhaps there are still other components of the cod liver oil participating—unsaturated fatty acids and the like. At any rate Vitamin A plays an important role, because irradiated cod liver oil, in which the vitamin is destroyed, is not active. As it seems the local application cannot be displaced by the peroral use. Essentially a local effect appears to be the deciding factor.

4. The various skin diseases.
   Those associated with suppuration, specifically in small children, are often rapidly improved by adding Vogan to the food. It is to be desired that experiences be recorded in such cases to learn, if (based upon blood examinations) a real deficiency of Vitamin A in the blood might be ascertained. The same holds true in patients susceptible to diseases of the numerous membranes of the respiratory apparatus. And further Vitamin A may be given to patients showing symptoms of the so-called "toad skin", a blood examination indicating a deficiency.

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5. General Infections.

In general infections, originating in the skin or mucous membranes, Vitamin A has been repeatedly given with good success. The relative connections are not fully clarified in this respect, so that continued investigations are urgently desired.

BIBLIOGRAPHY FOR VITAMIN A

Abelin, Biochem. Zeitschr., 198, 228, 1930.
Abelin, Biochem. Zeitschr., 242, 385, 1931.
Abelin, Klin. Wschr., 2205, 1931.
Abelin, Zeitschr. Vitaminforsch., 4, 120, 1935.
Abelin, Schweiz. med. Wschr. Nr. 46, 1936.
Aykroyd and Krishnan, Ind. med. Gaz. Bd. 71, 1936.
Anschütz, Nordwestdeutscher Chirurgenkongress, Dexembersitzung, Hannover, 1933.
Anschütz, Verhandl. Dtsch. Chirurgenkongress, Berlin, 1934.
Barenberg-Lewis, Journal of the American Medical Association, 98, 199, 1932.
Bezssonoff, Bullet. d'hygiène alim. 11, 14.
Binet and Ungar, Arch. des Mal. Apparat. digest., 23.
Birger Rössiö, Hoppe-Seylers Zeitschr., 182, 1929.
Birnbacher, Münch. med. Wschr., 1114, 1928.
Boller, Z. klin. Med. Bd. 130, S. 163, 1936.
Boller, Klin. Wschr. Nr. 19, S. 685, 1936.
Bomskov and Seemann, Zeitschr. exp. Med., 89, 771, 1933.
Breusch and Scalabrino, Zeitschr. exp. Med., 94, 569, 1934.
Brockmann and Tecklenburg, Hoppe-Seylers Zeitschr., 221, H. 3/4.
Brugsch, Dtsch. med. Wschr., 325, 1933.
Busson and Simonet, Compt. rend. Soc. biol., 109, 1253, 1932.
Collazo and Rodriguez, Klin. Wschr., 1732 and 1768, 1933.
Collazo, Torres and Rodriguez, Klin. Wschr. II, 1934.
Dann, Biochem. Journ. 27, 1998, 1933.
Davies and Moore, Biochem. Journ. 28, 288, 1934.
Debré and Busson, Compt. rend. Soc. Biol. 114, 1164 & 1297, 1933.
Debré and Busson, Presse médicale 31, 1934.
Dietrich, Münch. med. Wschr. Nr. 8, 1936.
Dominici and Oliva, Dtsch. med. Wschr., 1955, 1934.
v. Drigalski, Klin. Wschr., 308, 1933.
v. Drigalski, Zeitschr. Vitaminforsch., 3, 37, 1934.
v. Drigalski, Zeitschr. Vitaminforsch., 3, 260, 1934.
v. Drigalski and Laubman, Klin. Wschr., 1171, 1933.
Edmund and Clemmesen, Act. med. Scand., Nr. 89, S. 69, 1936.
Edmund and Clemmesen, Chem. Zbl., II, Nr. 6, S. 1014, 1936.
van Eekelen, Klin. Wschr., Nr. 23, 1935.
van Eekelen and de Haas, Acta brevia neerlandica, Bd. 14, Nr. 2/3, S. 52.
Ender, Zeitschr. Vitaminforsch., 3, 247, 1934.
Erben, Dtsch. med. Wschr., 954, 1933.
v. Euler, Arkiv. für kemi, mineral. geol., 1933.
v. Euler, Ergebn. Physiol., 34, 360, 1933.
v. Euler and Klussmann, Hoppe-Seylers Zeitschr., 21, 213, 1932.
v. Euler Zondek and Klussmann, Svenska Vet. Akad. Arkiv. f. kemi, 11B, 1, 1932.
Falta, Dtsch. med. Wschr., Nr. 29, 1936.
Falta, Wien. klin. Wschr., Nr. 8, 1936.
Fasold, Zeitschr. exp. Med., 94, 35, 1934.
Fasold and Heidemann, Ztschr. exp. Med., 92, 53, 1933.
Fasold and Peters, Münch. med. Wschr., 1427, 1933.
Fasold and Peters, Zeitschr. exp. Med., 57, 92, 1933.
v. Fellenberg, Biochem. Zeitschr., 42, 253, 1932.
Frank, A., Monatsschr. Kinderheilk., 25, 147, 1923.
Fromme, Verhandl. Dtsch. Chirurgenkongress, Berlin 1934.
Gaehtgens, Kl. Wschr. Nr. 2, 1937.

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Gerstenberger, s. b. Claussen, Journal of the American Medical Association 101, 1384, 1933.
Gierhake, Klin. Wschr. Nr. 20, 1936.
Gierhake, Münch. med. Wschr. Nr. 42, 1936.
Goodwin, British Medical Journal, 3837, 113/114, 1934.
Greaves and Schmidt, American Journal of Physiology, 111, 502, 1935.
Gross-Selbek, Klin. Wschr. 61, 1935.
Halban, Zbl. f. Gynäkol. Nr. 44, 1935.
Higgins, Therap. Berichte, H. 7/8, 1936.
Hoff and Jeddeloh, Zeitschr. exp. Med., 15, 67, 1934.
Hohlweg and Fischl, Klin. Wschr. 1139, 1933.
Hubel, Fortschr. d. Therap. Nr. 2, 1935.
Jusatz, Klin. Wschr. 95, 1934.
Jusatz, Zeitschr. exp. Med., 87, 529, 1933.
Justaz, Zeitschr. Vitaminforsch., 3, 268, 1934.
Jusatz, Dtsch. med. Wschr., 573, 1934.
Kauffmann and v. Drigalski, Klin. Wschr., 306, 1933.
Klages, Verhandl. Dtsch. Chirurgenkongress, Berlin 1934.
König and Sebesta, Arch. Kinderheilk., Bd. 106, Nr. 3, 1935.
Krüger, Therap. Ber. Nr. 9, 1935.
Lasch, Klin. Wschr., 1534, 1934.
Lasch, Klin. Wschr., 1070, 1935.
Lauber, Zschr. f. d. ges. exper. Medizin Bd. 98, H. 4, 1936.
Lauber and Rocholl, Klin. Wschr. Nr. 32, 1935.
Lineweh, Med. Klin. Nr. 14, 1936.
Loewenthal and Nicholls, Lancer, 709, September 29, 1934.
Lohr, W., Arch. klin. Chir., 179, 312, 1934.
Lohr, W., Der Chirurg., 5, 6, and 263, 1934.
Lohr, W., Zbl. Chir. 31, 1934.
Lundborg, Biochem. Zeitschr., 258, 325, 1933.
Marx, Arch. klin. Chir., 181, 575 (zit. nach Schneider), 1935.
Mellanby, British Medical Journal, 1, 515, 1926.
Mellanby, British Medical Journal, 1, 677, 1930.
Mellanby, Journal of the American Medical Association, 96, 325, 1931.
Menken, Dtsch. med. Wschr., 1484, 1932.
Moll, Dallmer, v. Dobeneck, Domagk and Laqueur, Arch. exp. Path., 170, 176, 1933.
Moore, Lancet, 223, 669, 1932.
Mouriquand and Michel, Compt. rend. Soc. de Biol., 7, 1170.
Oelrichs, Z. Hyg. Bd. 117, S. 684, 1936.
Pfannenstiel s. b. Jusatz.
Pillat, Mercks Jahresbericht, 1936.
Poulssen, Arch. exp. Path. and Pharm., 157, 84, 1930.
Pranken, Ned. Tydschr. v. Genneesk., 76, 4521, 1932.
Proto, Münch. med. Wschr. Nr. 41, 1935.
Ralli, Flamm, Joffee and Stueck, American Journal of Physiology, 107, 157, 1934.
Rehn, Dtsch. med. Wschr., Nr. 23, 1935.
Rohmer, Bezssonoff and Stoerr, Compt. rend. Soc. Biol. 118, 56, 1935.
Schneider, Arch. klin. Chir., 181, 575, 1935.
Schneider and Widmann, Klin. Wschr., 670, 1935.
Schneider and Widmann, Klin. Wschr., 1497, 1934.
Schneider and Widmann, Klin. Wschr., 1786, 1935.
Semb, Baumann and Steenbock, Journal of Biological Chemistry, 107, 697, 1934.
Simola, Acta Soc. Med. Fennicae "Duodecim", Helsingfors, Ser. A, 16, 1932.
Skarzynski, Bullet. internat. trad. poln. Sci. 2, 1-5.
Stepp and Kühnau, Neue D. Klin., Erg. Bd. 1, S. 41, 1933.
Stepp, Die Ernahrung 1, 1 (1936).
Stepp and Schroeder, Klin. Wschr. Nr. 16, 1936.
Stepp, Kühnau, Schroeder and Wendt, Klin. Fortbildung, Ergänz. Bd., 1936.
Stocker, Schweiz. med. Wschr. Nr. 13 and Nr. 42, 1936.
Stepp and Wendt, Z. f. exp. Path. and Pharm., i. Dr., 1937.
Sure, Kite and Church, Proc. Soc. Exp. Biol. Med., 30, 620, 1933.
Thoenes, Verhandl. Ges. Kinderheilk., 129, Wiesbaden 1930.
Thoenes, Monatsschr. Kinderheilk., 48, 1, 1931.
Thoenes, Jahrb. Kinderheilk., 1, 131, 1931.

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Thoenes, Jahrb. Kinderheilk., 139, 200, 1933.
Vogt, Münch. med. Wochenschr., 79, 1570, 1931.
Vogt, Dtsch. med. Wschr., 26, 1110, 1931.
Walb, Therap. Ber., Heft 6, 1936.
Wald, Nature (Lond.) II, 65, 1934.
Wendt, Klin. Wschr., 9, 1935.
Wendt, Klin. Wschr., 222, 1936.
Wendt, Münch. med. Wschr., 1160, 1935.
Wendt, Münch. med. Wschr., 1679, 1935.
Wendt, Münch, med. Wschr., 808, 1936.
Wendt, Med. Klinik 1, 1936.
Wendt, Dtsch. Med. Wschr., S. 1213, 1936.
Wendt, Verhandl. d. Kongresses d. Dtsch. Ges. f. inn. Med. in Wiesbad., i. Dr., 1937.
Wendt and Schroeder, Zeitschr. Vitaminforsch., 4, 206, 1935.
Willstaedt, Harry, Die Vitamine., Klin. Wschr., 24, 1935.
Wolff, Lancer, 617, 1932.

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CHAPTER TWO

THE VITAMIN B GROUP

Introduction. The history of the vitamins, at most, dates from the discovery of Eijkman that the polyneuritis of poultry was caused by an inadequate supply of a specific food substance. This opened a new field, and much later (1911) the beriberi preventive factor was found. It was called "Vitamine" because C. Funk, the discoverer, desired to designate it as a basic protein and therefore a "vital amine". When still other vital diet factors, effective in small quantities, became known, the name was carried over as a group designation and as such retained, though the newly discovered substances proved free of protein. In the series of vitamins, which were differentiated by assigning a letter, the classic vitamin contained in yeast, the beriberi preventive, received the mark B. That two decades had to pass from Funk's discovery until Windaus succeeded in finding the exact chemical formula, was because, in the case of Vitamin B, conditions were more complicated than was assumed to be originally. With increasing refinement of biological and chemical methods of investigation it was successfully ascertained that Vitamin B, demonstrated in yeast and green plants, was not a uniform substance, but a mixture of water-soluble, proteinic active materials, difficult of separation from one another. And so the necessity arose for indicating these substances, by the addition of index figures, retaining the letter B. Thus, for the first time, in 1925 the pellagra-preventive B_2 was separated from the real, now called B_1, the beriberi-preventive factor which in time failed again to prove uniform. Later, a whole series of biologically similar (growth-promoting) factors were discovered associated with these substances. They differed in their behavior toward heat and alkali and in that they were needed to a varying extent by certain species of animals. Their significance for man is, as yet, entirely unknown. Finally it has recently been possible to demonstrate an enterotropic B-factor (B_1) (perhaps not uniform). The vitamins known to date are listed in the table on page viii. In the following only those will be discussed which play a proven role in human pathology and therapy.

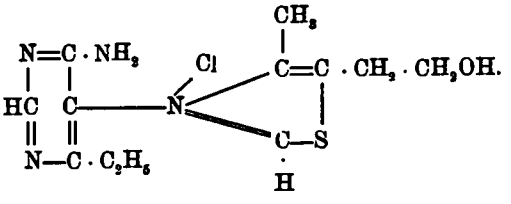
VITAMIN B_1 (Antineuritic vitamin).

A. General part

Historic Introduction. Though C. Funk as early as 1911 worked with highly effective preparations of the antineuritic vitamin (beriberi-pre-

ventive), production of this vitamin in pure form was held up for years because of its sensitivity to heat and alkali. The Dutchmen, Jansen and Donath, who perhaps first succeeded in producing crystalline Vitamin B_1 (only slightly contaminated with B_4) did not recognize its chemical constitution. It was reserved for Windaus (about simultaneously with van Veen in Batavia and Ohdaka in Tokio) to set up the correct gross formula of Vitamin B_1 and prove that of the known vitamins it alone contained sulphur.

Chemistry. Pure Vitamin B_1 has the formula $C_{12}H_{16}N_4OS$, which forms as a base beautiful crystalline salts, for example the chlorhydrate (melting point 250°) and two sulphates (melting points of 203° and 264° respectively). It is optically inactive, and is easily soluble in water and alcohol. In the purest state it shows a selective absorption at 247 μμ (Holiday). From the properties of the waste products in all probability the following structural formula results (Williams). Instead of the ethyl group there are possibly 2 methyl groups at the pyrimidin ring (Windaus).



The sulphur combination in Vitamin B_1 presents a form (thiazol ring), which so far has not been found in nature. By careful oxidizing, the colorless, non-fluorescent Vitamin B_1 is changed to a yellow, intensively blue fluorescing dye-stuff, not uniform chemically, but having at least the equivalent vitamin effect of B_1 itself. Thus there exist several substances of Vitamin B_1 character (Kinnersley-O'Brien-Peters). This dye-stuff seems to exist in several isomeric forms, comprised under the name of chinochromes; they are co-responsible for the blue fluorescence of animal organs. One of the chinochromes, the beautifully crystallizing thiochrome $C_{12}H_{14}N_4OS$ occurs in yeast (Kuhn), and by means of ferric cyanide may be produced from Vitamin B_1, from which it differs only by a deficit of 2 H atoms (Barger-Bengel-Todd). The oxidation of Vitamin B_1 proceeds apparently in several steps, the first being reversible, and finally ends up in biologically inert products. The chinochromes, possibly like the flavins, which they also resemble in a physical respect, contain a Pyrimidazin ring. As a result it would follow that Vitamins B_1 and B_2 are chemically related, built up by the plant perhaps from kindred basal substances.

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Occurrence. Vitamin B_1 is widely distributed in the plant world. As as been known for a long time, it occurs abundantly in yeast and rice ran, while the decorticated rice is nearly B_1-free. This is the explanation or the frequent appearance of avitaminosis B_1 among oriental people ating rice preponderously. In bread of fully milled white flour it is bsent, but is present in bread made of whole grain flour (gray or black read). The ability to synthesize Vitamin B_1 may be seen in the plant world t the earliest stages of evolution (in bacteria and schizomycetes). Vitamin B_1 is also present in animal organs, especially abundant in liver, heart nuscle and kidney, less in brain and skeletal musculature, scarcely in lood, spleen and lung (Brodie-Macleod). The Vitamin B_1 in the organs riginates from the nutriment. When the supply of Vitamin B_1 is deficient, he content of it in the organs is likewise diminished, but it never disap- ears entirely, even in beriberi (Abderhalden-Westenbrink). Thus the issues are retaining tenaciously the last indispensable residue of Vitamin B_1. It is a noteworthy fact that rats fed Vitamin B_1-free, but carbohy- rate-rich diets, do not come down with beriberi, providing they can get t their own feces (refection). The intestinal bacteria and yeasts of rats ed in this way are apparently able to synthesize Vitamin B_1, which thus resent in the feces, is again taken up by coprophagy of the rats. The acterial synthesis of Vitamin B_1 obtains in the cecum (Guerrant-Dutcher- omey). Upon resection of it refection ceases. In cattle, which can get long for a long time without Vitamin B_1 supply, the bacteria of the rumen re able to metabolize Vitamin B_1 (Bechdel-Schieblich). The Vitamin B_1 enerated by the bacterial metabolism is absorbed directly in the stomach nd passes, for example into the milk, the Vitamin B_1 content of which s therefore quite independent of the feed. The Vitamin B_1 content of uman milk varies, however, with the kind of nourishment, sinking to othing if the food is Vitamin B_1-free (Sure; Fasold-Peters). The content f Vitamin B_1 in some of the foods is listed in the chart (by Baker- Wright) on page 36. The customary household cooking diminishes the Vitamin B_1 content of raw materials 50% on the average (Hoff).

Determination. The determination of Vitamin B_1 in foodstuff is gen- rally done biologically, and recently also chemically (colorimetrically). erving with the biological methods as tests are: growth-promoting, reventing or curing polyneuritis and bradycardia. All of these methods re applicable in restorative and prophylactic form. Generally the former roduces more accurate values. The method employed mostly is the urative pigeon test (Kinnersley-Peters). After pigeons, fed polished ice for 2 or 3 weeks, have become ill with manifest beriberi, they receive ne injection of the substance to be investigated. The weight of the dose ivided by the number of days before the spasms reappear, result in the "pigeon daily dose". It is equal to 1.54 γ of free B_1 base or 1.96 γ of B_1 ydrochloride (Kinnersley-O'Brien-Peters). It has been shown recently hat the "heart-test" in rats, held for a time as nonspecific, being simpler echnically, gives more uniform results (Birch-Harris). Young rats fed Vitamin B_1-free diets develop in about 2 weeks the syndrome of a grave inus bradycardia, which by adding Vitamin-B_1-containing material is

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relieved just so much longer as the given substance is rich in Vitamin B_1. The Vitamin B_1 content of it may be calculated, if compared with a standard Vitamin B_1 preparation. The rat-growth test of Chick and Roscoe is based on the original definition of the international B_1 unit. The rat-growth unit is that quantity of Vitamin B_1 which produces in those rats which have ceased to grow from lack of Vitamin B_1, an increase in weight of about 12 gms. weekly. Since the value of this rat-growth unit fluctuated somewhat, the international unit was later defined differently. An adsorption by 3 kg. of Fuller's earth of an extract of 100 kg. of rice bran was established as standard preparation. 10 mg. of this adsorption contain one International unit. It is somewhat smaller than a rat-growth unit and about equivalent to 1.80 γ of the crystalline vitamin (in form of the free base), which is not used as a vitamin standard for the reason that its manufacture in pure form is too precise and costly. The color reaction adaptable to a colorimetric determination of Vitamin B_1 is based on the fact that the vitamin produces a red color with diazobenzolsulphoacid in a carbonized caustic soda solution of a fixed composition upon addition of formaldehyde (Kinnersley-Peters).

Requirement of Man. The requirement of B_1 in a healthy man differs from the other vitamins, as it presents no constant magnitude. It can only be approximately stated in figures. In a complex manner it is primarily dependent upon the quantity of nutriment taken, insofar that it is the greater, the more carbohydrates are supplied, and the less the more fats are consumed. In the elaboration of the organism B_1 is used up, so that its consumption runs parallel to the quantity of carbohydrates converted (Lecoq, Amantea) while the fats are saving the vitamin (Evans-Lepkovsky, Guerrant-Dutcher, et al). Correspondingly the incidence of an avitaminosis B_1 is accelerated by carbohydrates and impeded by fats. The B_1 requirement does not seem to depend upon the protein metabolism (Prunty-Roscoe). Because of the opposing effect of carbohydrates and fats and the B_1 consumption in the body, a consistent relation in figures between caloric supply and B_1 requirement does not exist in man. That 20 calories require one rat-growth unit B_1, as submitted by Jung is to be taken with reserve and only applicable to an ordinary mixed diet. The exact determination of the daily B_1 need in man is difficult since it is largely dependent upon the intensity of the metabolic processes (Cowgill-Palmierie). If the general metabolism is increased by the administration of thyroid or thyroxine, the B_1 requirement rises. It is possible, therefore, that symptoms of B_1 deficiency develop with thyroid administration with an otherwise sufficient B_1 supply, and conversely the clinical syndrome of hyperthyroidism may be favorably influenced by an abundant B_1 administration (Himwich, Goldfarb, Cowgill, Sure-Smith). The alcohol polyneuritis in a similar manner must be viewed as a sign of a B_1 insufficiency, the alcohol affecting a metabolic increase and thereby a greater consumption of Vitamin B_1 (Minot). There is also a direct numerical relation between the magnitude of body performance and B_1 requirement (Cowgill). A typical symptom of B_1 insufficiency is adrenal hypertrophy as seen under normal nutritional

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conditions after hard bodily exercise, which fails to occur if a working animal is supplied from 3 to 5 times the quantity of Vitamin B_1 normally required (von Beznak-Perjes). A rising external temperature increases Vitamin B_1 consumption (Kliger-Geiger-Mueller), which plays a role in tropical and infantile beriberi as well as in febrile diseases (Cowgill-Widenbauer). In infancy, during pregnancy and lactation, and also in the Spring (increased hormonal and metabolic activity) the need of Vitamin B_1 rises. Under these conditions phenomena of avitaminosis easily develop. A nursing rat, to raise healthy offspring, needs from 2 to 5 times more B_1 than is necessary for its own use (Sure-Evans-Burr). The Vitamin B_1 requirement increases, furthermore, with the body weight (Cowgill has submitted a formula permitting a calculation of the necessary Vitamin B_1 from the weight of the body). Finally it may be seemingly increased when the assimilation of the Vitamin B_1 supply is restricted by gastrointestinal affections.

Of great clinical import is the fact that the spread between the quantity of Vitamin B_1 necessary for the maintenance of health and that for optimal growth is particularly wide. A young rat, to grow, needs 3 to 5 times more Vitamin B_1 than is needed for it to maintain weight and normal well-being (Cowgill). Williams, moreover, has observed maximal growth only following a dose of Vitamin B_1 100 times the one preventing polyneuritis. Something similar applies to man. The cure of deficiency phenomena demands abnormally large Vitamin B_1 quantities which are frequently not applicable by way of diet. In such cases, especially when accompanied by gastrointestinal disturbances, the modern parenteral B_1 concentrates enter into their rights.

It follows therefore that a general rule for the Vitamin B_1 requirement of man can scarcely be made. The assumption that the daily minimum lies between 250 and 750 may approach the actual conditions. The Section of Hygiene of the League of Nations, figures it at 300 International Units, equalling 550 Burnet-Aykroyd Units. The optimum Vitamin B_1 supply, however, in man is doubtless much higher, perhaps between 1 and 2 mg. per diem.

Vitamin B_1 Behavior in the Organism. The Vitamin B_1 supplied with the food is absorbed in the small intestine (Scheunert-Schieblich) and stored in the organs. These Vitamin B_1 depots of the organs do not entirely disappear even after prolonged Vitamin B_1-free feeding. The vitamin is secreted into the gastric juice in which it is found abundantly (Komarov) except in pernicious anemia (Karczag). For activation Vitamin B_1 (Castle), just like the pernicious anemia factor, needs coupling with an endogenous ingredient of the gastric juice. The unused Vitamin B_1 is eliminated in the urine; it is only at times of great need of Vitamin B_1 that not a trace of it appears in the urine even after a large supply of B_1 (Baglioni).

Physiology. Vitamin B_1 does not increase oxidation, an effect formerly ascribed to it, but it exercises a pronounced influence upon the carbo-

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hydrate metabolism. Of particular importance and decisive for the spasm-preventing effect of the B_1 factor is its participation in the sugar metabolism of the central nervous system. Brain emulsion of Vitamin B_1 avitaminotic pigeons in the presence of lactic acid or glucose does take up far less oxygen than that of healthy animals, its respiration is, therefore, much weaker. Addition of crystallized Vitamin B_1 fully restores respiration (Grarilescu-Peters). For the process of sugar conversion Vitamin B_1 in indispensable. This fact allows a quantitative evaluation in the brain emulsion of beriberi pigeons (Katatolurim test of Passmore-Peters). Especially great seems to be the need of the vitamin in the cerebrum and in the basal ganglia. Also the respiratory quotient is reduced in the beriberi brain and is renormalized by addition of B_1. The extent of the respiratory decrease runs parallel to the symptoms of brain pathology. The point of attack of the Vitamin B_1 effect in the brain is not the lactic acid, since the beriberi brain still normally removes this acid (Meiklejohn), but its product of oxidation, the pyroracemic acid, which is normally catalyzed immediately. In beriberi, however, it accumulates at first only in the brain and later also in the blood, where it is easily shown (Thompson-Johnson). Somewhat different is the working mechanism of Vitamin B_1 in the heart muscle, in the sugar metabolism of which it is specifically engaged. Zwaardemaker could show that crystallized Vitamin B_1 stimulated isolated auricles to beat; it is therefore a genuine Automatin. The oxidizing ferment of lactic acid in the heart muscle, forming during the energy producing sugar catalysis, may only continue to oxidize in the presence of two auxiliary ferments, first the co-enzyme (of Banga-Szent Györgyi), second Vitamin B_1 (Birch, Mann). The sugar oxidation of the heart muscle in beriberi is not only impeded at the pyroracemic acid stage, but already at that of lactic acid. At an early period in avitaminosis B_1 a lactic acid stasis is established and a direct sequence of that is a sinus bradycardia (Birch-Harris). Later lactic acid is also increased in the blood and in other organs (Collazo-Bayo). The carbohydrate respiration is likewise dependent upon the presence of Vitamin B_1 (Thompson) in the kidney, but not in the other organs. In the liver Vitamin B_1 seems to be involved in the glycogen metabolism itself, but the manner of it is not clear (Sure, Abderhalden). The often found increase of Methylglyoxalidin in the blood and urine with avitaminosis B_1 (Vogt-Moeller, Geiger), claimed by Lehman to be non-specific, indicates the Vitamin B_1 is not only active in the catalysis of lactic acid, but also in its formation in the body. (Methylglyoxal is a precursor of lactic acid.)

The importance of the Vitamin B_1 substance for heart function:

Vitamin B_1 in its purest crystalline forms is accompanied by Vitamin B_4 and its carrier—adenin. Guha and Chakrovorty have shown that adenin (impure) acquires Vitamin B_1 effect by radiation. These facts point toward relations between Vitamin B_1 and the cardioactive Purin (Adenyl) derivatives, the properties of which are unknown.

Vitamin B_1 furthermore influences the Water economy of the body, though the mechanism of this process is not exactly known. Absence of this

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activity with Vitamin B_1 deficiency is followed by incidence of edemata, hypoproteinemia, serous effusions and water imbibitions of the heart muscle. The edemata are of extra-renal nature. Their genesis is not clear, since neither the capillary permeability nor the avidity for NaCl and water of the tissues is increased with the incidence of these edemata.

The often observed lipemia in beriberi is essentially effected by a disturbance of the normal close reciprocal relations of Vitamin B_1 and adrenal cortex. It hypertrophies during Vitamin B_1 deficiency and with hard muscular work, which raises the Vitamin B_1 consumption. In both cases by an increased supply of the vitamin the hypertrophy is impeded or reduced. Injections of cortin on the other hand may considerably improve the phenomena of Vitamin B_1 deficiency and retard their incidence (Schmitz, Lockwood-Hartman).

The varied gastrointestinal symptoms of lack of Vitamin B_1 indicate that the vitamin exercises a protective function in the gastrointestinal canal also. The extent of this intestinal activity cannot be definitely estimated and its study is rendered difficult by the fact that other factors of the Vitamin B group are engaged in the gastrointestinal tract. For the present it is established that Vitamin B_1 is indispensable for the maintenance of the normal tonus of the gastrointestinal musculature (Sure, Cowgill) as well as for the normal processes of absorption, especially that of fat (Evans-Lepkovsky).

Symptoms of Vitamin B_1 Deficiency. The clinical manifestations of Avitaminosis B_1, however varied they may appear, can be essentially reduced to two causes: The disturbances of the carbohydrate metabolism affecting the central and peripheral nervous system and the heart, and the damage to the water economy. The classic syndrome of polyneuritis accompanied by hemorrhage and degenerative changes in the peripheral nerve fibers, appearing most expressively in pigeons and chickens, but also existing in higher mammals (lion) and more rarely in rats (ataxia, opisthotonos, rotary spasms) has its histological correlation in hemorrhage, absence of the Nissl granules, chromatolysis, and degeneration of the medullary sheath. These lesions in contrast to those in man, where they are localized in the central nervous system, occupy the foreground and dominate the clinical picture. Furthermore signs of extra-renal disturbances of the water economy participate which may become dangerous to life by spreading to the heart muscle. There occur gastrointestinal symptoms, as atony, cessation of peristalsis, achylia, inflammation of the mucosa and in connection an early anorexia. The subnormal temperatures in beriberi result probably from the restriction of the carbohydrate metabolism.

It is of greatest practical importance that B_1 deficiency during growth, even if clinically latent may lead to a gene lesion which may only make its appearance in the second daughter generation. The offspring of rats, which were fed B_1 deficiently in their youth, present in the first generation 1%, and in the second generation 22%, of congenital obliteration of the pylorus (Mueller).

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B_1 Relations to Other Vitamins. The law that all vitamins form a functional unit, none of them unfolding its physiological effect independent of the others, is especially apparent in the close correlations existing between Vitamin B_1 and the rest of the vitamins. The relation of Vitamin A to Vitamin B_1 is antagonistic insofar as by generous A supply the symptoms of lack of Vitamin B_1 are increased and inversely a hypervitaminosis A is favorably influenced by B feeding (Yonechy, Chevallier). On the other hand Vitamin A as well as Vitamin B_1 oppose thyroxine and Vitamin D. A diet rich in Vitamin B_1 decreases the effect of an hypervitaminosis D (Jusatz). Moreover there is an antagonism between B_1 and B_2 within the Vitamin B group. Large doses of Vitamin B_1 accelerate an outbreak and aggravate the symptoms of pellagra (Kellogg-Eddy, Györgyi).

Vitamin B_1 Commercial Preparations. Solutions of pure crystalline Vitamin B_1 are not commercially obtainable so far in Europe. Concentrates of Vitamin B_1 from yeast or wheat germ are released by I. G. Farben Industry under the name of Betaxin (Amp. of 2 cc.—about 0.4 mg. of chlorhydrate of Vitamin B_1) and by the Glaxo Research Laboratory (London), (Name not pat.). E. Merck is the only firm making a pure crystalline Vitamin B_1 in Amp. of 1 cc., containing 5 mg. of Vitamin B_1 chlorhydrate. The employment of these preparations is principally indicated when it is desired to overcome acute signs of deficiency with heavy doses of Vitamin B_1 given parenterally. In all other cases, chiefly in non-specific conditions due to suboptimal Vitamin B_1 supply or for purposes of prophylaxis, the pure Vitamin B_1, not being available in sufficient quantity, we are limited to material made from yeast and given per os. Containing all the other vitamins of the Vitamin B group besides Vitamin B_1, they provide the necessary Vitamin B_1 and a coordinate supply of all other Vitamin B factors. Such are: (approximate content of Vitamin B_1 in 100 gm.):

Levurinose "Blaes" (about 5000)
Extract Cenovis (8000)
Ovamaltine (600)
Veguva (1000)
Bemax (Vitamin Ltd., London) (2500).

The yeast products Vitox, Marmite and Vegex are Vitamin B_1-poor. The required average daily dose in hypovitaminosis B_1 may be calculated from the Vitamin B_1 content in the particular preparation. For Levurinose it is 15 to 30 gm.

Hypovitaminosis B_1 as a Problem of Nutrition. Only a few years ago it was generally accepted that in tropical countries Vitamin B_1 was sufficiently provided and a lack of it as a cause of morbid conditions was out of the question. Von Tyszka in Germany and Alvarez and Cowgill in the United States could prove with a mass of statistics that under normal conditions the diets of the general population would guarantee a sufficient Vitamin B_1 supply. To conclude from these statistics that with us a danger

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of a lack of Vitamin B_1 is non-existent, would be a mistake. Even under physiological conditions (growth, gravidity, lactation, muscular action, and carbohydrate diet) and above all in morbid states (fever, gastrointestinal disease, hyperthyroidism) the Vitamin B_1 requirement rises to a multiple of the normal, so that a diet of an ordinary supply of Vitamin B_1 fails to suffice. This danger is especially imminent among white bread and sugar-eating people, who receive too little Vitamin B_1 (Mueller) in relation to their large carbohydrate consumption (Simpson). Hypovitaminosis B_1 plays, among the higher classes socially, a considerable and so far underestimated role (much greater than the lack of Vitamin A and Vitamin D) for the reason that Vitamin B_1 often fails to parallel the quantitative betterment of the nutrition. In our countries there is not only the danger of an occasional relative lack of Vitamin B_1, but the calculations of Schroeder and Wittmann have demonstrated that a series of the usual hospital diets contain so little of Vitamin B_1 that the minimum need is not even approximately covered. That pertains particularly to the ulcer, renal, diabetic, and ketogenic diets. More serious is the statement of Schroeder that the general house diet of a certain hospital in Munich, carefully examined at different seasons proved continuously quite inadequate as to Vitamin B_1 content. Hence it follows that avitaminosis B_1 constitutes, in our latitudes also, a hazard not to be underestimated, though it is not realized by the clinicians.

Indications for Vitamin B_1 Administration. Contrary to the well-known syndrome of Vitamin A, C and D deficiencies, the clinical signs of lack of required Vitamin B_1 have found but slight attention and have been studied but little. Its recognition will enable a physician to interpret many so far indefinite syndromes as consequences of Vitamin B_1 deficiency and thereby bring speedy relief with an abundant Vitamin B_1 supply.

1. Primary Non-tropical Avitaminosis B_1 in Man. Generally speaking the lack of Vitamin B_1 in our latitudes, giving rise to clinical manifestations, is secondary, i. e. due to an increased Vitamin B_1 need subsequent to other diseases or to an impeded Vitamin B_1 absorption from gastrointestinal affections. The primary form of Vitamin B_1 insufficiency is of rare occurrence in Europe and the United States. As an extreme expression it may sporadically appear in our countries—the edematous or dry beriberi (Brauchel, Staehelin). However, much more difficult to recognize, more important and widely disseminated, is the resultant status of a long continued Vitamin B_1-poor nutrition, described by Elsom. In adult patients fed for months on a diet very scant in all factors of the Vitamin B group, it was demonstrated by successively adding first Vitamin B_1—later B_2 and finally Vitamin B_1, B_2 plus yeast, what part each played in the symptom complex developed. The addition of Vitamin B_1, continued for twelve weeks, caused a number of symptoms to disappear, indicating thereby the signs of a straight Vitamin B_1 deficiency: general muscular weakness, pain and paresthesias of the arms and legs,

ecchymoses of the extremities, hypoproteinemia and edema, and loss of weight was connected with their effusion, furthermore, subnormal temperatures and lowered blood pressure. With the addition of Vitamin B_1 the temperature rose from 96.6 to 98.6, the systolic blood pressure from 95—100 to 130—135 mm. Hg., and albumin content of the plasma from 4.4 to 5.5%. Unimproved were the gastrointestinal disorders, the increased reflexes and the decreased sensibility and the glossitis. These phenomena do not arise from Vitamin B_1 deficiency or rather not from Vitamin B_1 deficiency alone. Appetite and body weight began to approach normal when all of the Vitamin B factors were present in the diet. It was observed that the addition of fat alone would improve the symptoms of Vitamin B_1 deficiency, but only for the period the fat was given, confirming reports that fat has Vitamin B_1-saving effect. Besides this rare, pure form of the primary Vitamin B_1 deficiency, sickness may appear as famine (hunger) edema concomitant with deficiency phenomena resulting from want of other vital nutritional factors, such as proteins. Here the signs arising from an upset of the water economy due to Vitamin B_1 deficiency are especially prominent. The famine edema like the edema of beriberi is accompanied by hypoproteinemia, often it is also combined with grave lesions of the central nervous system, which similize those of beriberi, and with funicular myelosis (disseminated sclerosis) (Schlesinger), again pointing to the fundamental Vitamin B_1 deficiency. Food rich in Vitamin B_1, but above all, injections of crystalline Vitamin B_1 effect a rapid disappearance of the famine edema. These related conditions in pediatrics are to be discussed later.

2. Secondary and Symptomatic Avitaminosis B_1. (a) *Neurology.* The clinical manifestations of a secondary or symptomatic Vitamin B_1 deficiency, very frequent with us and multiform, are easiest to recognize and interpret if symptoms arise resembling genuine beriberi, i. e. disturbances of the central nervous and peripheral nervous systems. Both occur. It has been shown that polyneuritis of seemingly different etiology develops upon the common ground of Vitamin B_1 deficiency and that they may be cured by an abundant supply of Vitamin B_1. In alcoholic polyneuritis the exciting factor is the alcohol (Minot) which raises the metabolic rate increasing the Vitamin B_1 requirement. Inferior nutrition and gastrointestinal disorders act frequently as causative agencies (Cowgill) (Shattuck). The evolution of polyneuritis of pregnancy is explained by the enormously increased need of Vitamin B_1 (Plass, Mengert). Administration of yeast or nourishment rich in Vitamin B_1, best with liver medication at the same time, cures the polyneuritis without exception, even if the alcohol consumption is continued (Minot-Strauss-Cobb, Strauss). Similar successes are obtained with yeast therapy in polyneuritis of pregnancy. The polyneuritis following malaria and other febrile diseases develop in an analagous manner, metabolism being increased and the Vitamin B_1 requirement raised. In Java, China, above all in Egypt and Brazil, beriberi appears very frequently following malaria (Cowgill). Its effect of raising the metabolic rate has been recognized by Du Bois. Diabetic polyneuritis is also a manifesta-

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tion of a Vitamin B_1 deficiency probably due to a synchronous disturbance of carbohydrate and Vitamin B_1 evaluation. It is also curable by yeast administration, or at least, it is favorably influenced by it (Wohl, Minot). Vorhaus reports curative successes with crystallized Vitamin B_1 in several cases of polyneuritis of undefined genesis.

The similarity of symptoms of infantile beriberi and chorea minor (choreatic movements, circulatory disorders, gastrointestinal symptoms) and then the fact that chorea almost invariably occurs during periods of increased need of vitamin, (following infectious diseases, during growth and pregnancy), seem to make it appear extremely reasonable that chorea is a disease due to a Vitamin B_1 deficiency. Indeed the administration of Levurinose (15 to 30 gm. daily) always effects a cure in infantile chorea minor and paralytica (Widenbauer). The funicular myelosis has to be regarded as a very important manifestation sequential to chronic Vitamin B_1 deficiency (Minot, Castle, Morewitz). It is often seen in beriberi and may be experimentally produced in dogs by Vitamin B_1-free feeding (Gildea-Castle-Kattwinkel). As a concomitant manifestation of pernicious anemia, pellagra, sprue, lathyrism and many forms of achylia, it is, however, not a partial symptom of these diseases, but secondarily enforced by coexisting nutritional disorders fundamental for a deficient Vitamin B_1 absorption (Rhoads), that accounts for the failure of the generally successful liver therapy, if the usual Vitamin B_1-free preparations are employed, while fresh liver rich in Vitamin B_1 often improves the cord symptoms also (Meulengracht). The funicular spinal lesion, the idiopathic form as well as the pernicious anemia, is essentially improved, indeed often cured, by administration of brewer's yeast or Levurinose (daily 20-30 gm.) or by injections of Vitamin B_1 liver preparations like Betaxin on the presumption that there are no irreparable destructions of the posterior column (Illing, Fouts). The curative success is especially impressive in cases where liver preparations had removed the anemia, but not the cord symptoms. Incontinence, ataxia, paresthesias and spastic symptoms disappear upon yeast feeding. According to Castle, Vitamin B_1 to affect the spinal symptoms, needs coupling with an endogenous principle just like the pernicious anemia factor. That agrees with the observation that duodenal juice of healthy individuals, containing the endogenous principle as well as the Vitamin B_1, has vanquished grave cord symptoms in pernicious anemia.

Starting from the idea that pure vitamins, beyond their function as accessory nutrients, might evolve real curative effects in diseases not due to vitamin deficiencies, and because of the fact that Vitamin B_1 is a specific neurotropic diet factor, investigations have been made of late to learn if applications of Vitamin B_1 might favorably influence neuralgic conditions, such as sciatica and trifacial neuralgia. In several severe cases of sciatica (acute and chronic), having proved refractory to all other treatment, parenteral application of Vitamin B_1 was used (2 cc.-10 mg. crystalline Vitamin B_1 chlorhydrate "Merck" every other day) (3-5 injections), or 1-2 ampules Betaxin (0.8-1.6 Vitamin B_1 chlorhydrate) daily, for 5-15 days, and a rapid, often striking, reduction of complaints and in addition the restitution of a normal walk occurred. Also two cases of trifacial neu-

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ralgia were markedly improved in a short time by Vitamin B_1 injections, while a coexisting facial paresis in one of the cases remained uninfluenced.

(b) *Internal Medicine.* It has been known since 1920 (Karr, Cowgill) that loss of appetite in an animal is the first sign of a beginning avitaminosis B_1. The loss of weight and the reduction of general metabolism appearing later in the course mean nothing else but the sequence of inanition due to the loss of the natural sensation of hunger. In man also a long continued anorexia, other causes not being established, may be induced by Vitamin B_1 deficiency (Kruse, McCollum). A recognition of this is of great importance, since on this basis a vicious circle may very easily evolve. Anorexia frequently leads to chronic lack of Vitamin B_1 despite sufficient supply, foreboding, in such instances grave symptoms of deficiency (especially in mental patients in closed institutions). Beriberi is widely known in the Orient in mental cases whose instinct of preservation is often reduced. In convalescents often a Vitamin B_1-poor hospital diet lasting for months is the cause of a continued anorexia, so that a lack of the vitamin must be considered. In several cases of obstinate loss of appetite (own observation with rheumatics) after all other remedies had failed, 1 or 2 injections of crystalline Vitamin B_1 (10 mg.) brought immediate improvement of appetite and general well-being. On the other hand the observation of Elsom that the administration of other vitamins are necessary to maintain a normal appetite is important.

Anorexia from lack of Vitamin B_1 is probably explained by the fact that the normal production of gastric juice, under a deficiency of Vitamin B_1, diminishes or ceases (Cowgill-Gilmann, Webster, Armour). In beriberi of infants achylia is a frequent symptom (Ohta). It pertains particularly to the juice constituents necessary for the normal function of the gastric mucosa, for in rats and dogs a Vitamin B_1-free diet leads to gastric ulceration (Dalldorf-Kellogg) (Sure-Thatcher). This also holds good for man. Investigations among Scandinavian country people whose nutrition is relatively vitamin-poor indicate with great probability that among the causes of gastric and duodenal ulcer formation the lack of Vitamin B_1 looms large (Schiedt). In view of these observations an attempt with parenteral Vitamin B_1 preparations in ulcer therapy holds out great prospects, especially since the Vitamin B_1 content of the usual ulcer diets are insufficient even for normal needs.

Avitaminosis B_1 in animal experiments is often accompanied by loss of peristalsis and of the normal tone of the gastrointestinal musculature. Gastrointestinal atony, usually combined with anorexia, may in man likewise be caused by a lack of Vitamin B_1. In such cases injections of crystalline Vitamin B_1 effect prompt improvement of the atonic state and of peristalsis, constipation vanishes and the appetite returns (Vorhaus). It has been variously asserted that inflammations of the intestinal tract are of Vitamin B_1-poor nutrition. Diarrheas with a colonic base, membranous and ulcerative colitis are favorably influenced by a diet rich in Vitamin B_1 (Larimore). However, in none of these cases had it been proven that the intestinal pathology was really based upon a Vitamin B_1 deficiency.

It must be reiterated that avitaminosis B_1 outside of the tropics almost

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never occurs in man in pure form, but usually combined with a deficiency of all Vitamin B factors. Thus the expressive intestinal symptoms, produced by the withdrawal of all B vitamins, do not respond to Vitamin B_1 additions, but disappear only when the whole Vitamin B group is given (Elsom). The vitamins possessing the curative effect are Vitamin B_2 and Vitamin B_7. Ulcerative colitis in particular is a symptom of a deficiency of Vitamin B_2. On the other hand successes have been obtained in colitis with large doses of Vitamin B_1 (Brown). This finding to be investigated further, indicates that regarding the prevention of inflammatory processes in the intestine there exist complicated reciprocal relations of function between the separate factors of the Vitamin B complex. Upon the evidence of animal work it is certain, however, that for the normal processes of absorption and utilization of food Vitamin B_1 is indispensable (Westenbrink, Griffith, Evans-Lepkovsky). This relates notably to the absorption of fat (Verzar). Intestinal affections with disturbances of fat absorption in man are therefore favorably influenced by abundant administration of Vitamins B_1 and B_2 (Thannhauser). The famine (hunger) edema, mentioned as the primary manifestation of Vitamin B_1 deficiency, may also appear secondarily in diabetes, ulcerative colitis and following operations upon abdominal organs and may be removed in these cases by generous doses of Vitamin B_1 (Brown). The functional deterioration of the intestinal epithelium ensuing from Vitamin B_1 deficiency, resulting in disturbances of absorption, may further bring about resorption of arthritis-producing toxins and diet residue (Fletcher, Wyatt et al). The frequent combination (Tiemann) of gastrointestinal affections with chronic articular rheumatism (held by American authors as essential) is probably evidenced by the surprising successes occasionally achieved by generous administration of Vitamin B_1 (Fletcher, Neuwarth, Pemberton). In animals Cerulli could also produce deforming arthritis. The British Medical Association officially recommends Vitamin B_1 concentrates in arthritis and fibrositis. The close relation of Vitamin B_1 to carbohydrate metabolism has stimulated the use of it in the therapy of diabetes mellitus. The hypoglycemic and glycosuria-reducing effect of peroral yeast administration has been known a long time and in animal experimentation, at least, assured beyond a doubt (Beckel, et al). Twenty years ago von Euler and Svanberg established the antidiabetic effect of yeast extracts, which has also been observed in man. It has been suggested that daily doses of dry yeast (10 to 30 gm.) in cases of diabetes of medium grade may entirely or partially replace insulin (Vogt, Hoepfner-Klotz, Melcer, Mansberg, Winter-Smith). Von Drigalski alone failed with yeast with his diabetics. The reason may be found in the length of time he used the yeast (11 days), while Melcer, Gringoire, et al., insist on giving it for six or eight weeks before success may be expected. The effect lasts much longer than that of insulin. One might explain this with the necessity for refilling the depleted depots. However, further investigation is necessary. Whether the insulin-like substance of the yeast (von Euler) is identical with Vitamin B_1, has not been determined with certainty so far. In pigeon beriberi, a rise of blood sugar and blood lactic acid is almost constantly found, and is removed by

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Vitamin B_1 (and allegedly by insulin). On the other hand as has been mentioned, the point of attack of Vitamin B_1 in sugar economy is entirely different from that of insulin. This does not contradict the possibility that Vitamin B_1 and insulin have a similar effect, since we know that the radiation products of ergosterin (Vitamin D and A. D. 10) may entirely replace the parathyroid hormone, however different their working mechanism may be. Clinical trials with crystalline Vitamin B_1 have not shown any positive results so far. Purified Vitamin B_1 preparations in the hands of Sainton, Mills and Labbé have proven to be strongly effective in diabetes. While Stepp failed to influence the blood sugar in health and diabetes, Williams and co-workers have reported frank successes with large doses of pure Vitamin B_1 in diabetes. It is evident that dosage plays a considerable role. Further investigations in this direction are urgently desired, because of the possibility that we may possess in Vitamin B_1 for the first time, a true and physiologically vital peroral antidiabeticum in an isolated and chemically homogeneous form. Since thyroxin increases the need for Vitamin B_1, as mentioned, the danger of symptoms arising from Vitamin B_1 deficiency in hyperthyroidism is real. Care is therefore necessary in morbus Basedow to procure an adequate supply of Vitamin B_1 (besides Vitamin A).

Administration of extracts of yeast affect symptoms of Basedow favorably (Abelin). Conversely with a deficiency of Vitamin B_1 the production of thyroxin is restricted. Usually with avitaminosis B_1 atrophy of the thyroid is found and also the clinical symptoms of hypothyroidism (Verzar, Pighini, Kühn). Because of this fact a chronic hypovitaminosis B_1 has been made responsible for endemic goitre besides the iodine deficiency. It has been shown in regions of Switzerland, where goitre is rampant, that the nutrition of the people is markedly deficient in Vitamin B_1. In cows kept in barns during the winter and given a vitamin-poor diet, colloid goitres appeared which were reduced as satisfactorily with feed rich in Vitamin B_1 as with iodine (Fischer). In view of the close relationship between fat metabolism, iodine and thyroid (Chidester) the restorative action of Vitamin B_1 is possibly due to the fact that Vitamin B_1 may normalize the fat absorption and the lipoid economy.

(c) *Pediatrics.* Less frequently in the adult than in the nursing infant and the small child we meet with disease conditions subordinate to deficiencies of supply or of assimilation of Vitamin B_1. In infancy the Vitamin B_1 requirement is far larger than it is later, and the principal nourishment, mother's milk, itself containing little of Vitamin B_1, grows poorer still if mother's diet is short in Vitamin B_1. It is of interest that the symptoms of Vitamin B_1 deficiency appear in the nursling due to inadequate Vitamin B_1 in the mother's diet despite the mother's health being perfect clinically (the opposite in diabetes). In contrast to the sporadic occurrence of non-tropical beriberi in the adult the infantile beriberi is not at all rare in our latitudes. The recognition of its symptoms (pallor, irritability, loss of weight, gastrointestinal and cardiovascular disturbances, liver swelling, edemata, oculomotor and recurrent pareses and meningitis), however, is not sufficiently established (Rice, Hoobler). The good results following

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a generous supply of Vitamin B_1 in infantile beriberi are reported especially by American authors (Bloxsom, Waring, Haas). In the United States, an abortive form of beriberi is widely spread in nursing children at an age of 3 to 12 months. The symptoms are: pallor, loss of weight, motor unrest, neck stiffness and muscular spasms of the extremities and secondary anemia (also adduced to Vitamin B_1 deficiency as reported by Stiner in Switzerland). Such a hypovitaminosis B_1 is quickly cured with yeast (one-half teaspoon daily) or with a concentrate of wheat germ, which is more palatable and miscible with the food. If more notice were taken in our country (Germany) of the phenomena of Vitamin B_1 deficiency, sickness would certainly be recognized. In weak anemic and indisposed children beyond the nursing age a daily dose of prepared yeast 5-10 gm. for a short time (Mueller, Hess, Hoobler, et al) brings well-being and thriving growth. Between beriberi of infants and spasmophilia are fluent connections. Beriberi symptoms (cardiac enlargements, nerve degenerations, etc.) are likewise noted in spasmophilia, in the etiology of which a lack of Vitamin B_1 doubtless plays an active role (Reyher). The curative results with yeast in the treatment of spasmophilia are thus explained (Macciotta). Flour (Ohta) and milk sickness (Widenbauer) may also go together with manifestations of Vitamin B_1 deficiency, as indicated by flour raising the Vitamin B_1 need and the shortage of the vitamin in the milk. There are great possibilities for Vitamin B_1 therapy in this field.

The symptoms relating to a disturbed water economy arise in isolated form in nursing infants, and that in relation to one or the other tendency of diarrhea or of edema. The intestinal autointoxication (exsiccosis) is comparable either to the dry beriberi or to the famine (hunger) edema corresponding to the moist beriberi. Both diseases despite opposing symptoms are related (Stolte); they have in common the tendency to acidosis, scanty diuresis and their response to salt (NaCl) and Vitamin B_1. In the nurslings, the symptoms of exsiccosis, like all manifestations of Vitamin B_1 deficiency, are aggravated by high external temperatures. There is found an increased methylglyoxal elimination in the urine, indicating the etiological role of Vitamin B_1 deficiency (Geiger-Rosenberg). A condition closely resembling exsiccosis may be produced in a dog with Vitamin B_1-free feeding (Stucky, Rose). Following the experience of Cowgill, it is recommended not to inject large quantities of saline, as in the past, (the diuresis forcing elimination of Vitamin B_1, thereby increasing the need of the vitamin), but to stress the supply of Vitamin B_1 besides an abundance of liquids. Reyher could remove the exsiccosis with doses of dry yeast and the diarrhea desisted with remarkable rapidity. What was said of the famine edema of the adult holds good equally for the infantile edema (for example, in diabetes because of the restriction of the diet).

Among the causes of infant mortality avitaminosis B_1 plays its part. On the South Sea island of Nauru, during 1927-1928, 45% of all infants died during the first year of life. Shortly before, the pregnant natives had been forbidden to drink a brew of coconut milk, a toddy rich in Vitamin B_1. The deaths were therefore the sequence of an avitaminosis B_1, caused by a Vitamin B_1 deficiency in the nourishment of the mothers. After a gen-

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erous supply of Vitamin B_1 had been instituted by the authorities, the infant mortality dropped from 45 to 9% within a year (Bray).

One of the earliest known phenomenon of Vitamin B_1 deficiency in a young animal is inhibition of growth. The slow growth of American school children of the poorer classes and their reduced weight was traced without dissent to an insufficient supply of Vitamin B_1 (Morgan-Barry, Harris). Indeed by adding a Vitamin B_1 concentrate of grain to their diet, the growth of healthy normally nourished American children could be raised 3-4 times the expected value during the period of maintenance of such addition (Sommerfeldt). A disease of childhood the Swift Fehr vegetative neurosis, acrodynia or pink disease, the etiology of which is not quite clear, presents an avitaminosis B_1 developing upon the base of a peculiar disposition and complicated by infectious processes. By giving yeast or Vitamin B_1 concentrates of grain germ it is favorably influenced, indeed at times clinically cured (Nesbit, McClendon, Maldon-Massot). The disease appears in widely varying forms, besides signs of pure Vitamin B_1 deficiency (anorexia, paresthesias, gastrointestinal disturbance) symptoms are seen that similize pellagra or lepra (physic changes, exanthemata, trophic ulcerations and mutilations) which make it probable that there exists at the same time besides a Vitamin B_1 deficiency one of B_2 as well. This agrees with the observation of Györgyi who treated acrodynia with fresh liver.

(d) *Gynecology.* The marked rise of Vitamin B_1 requirement during the pregnant state is the cause of the development of light forms of Vitamin B_1 deficiency at this time. This may be the rule in tropical countries. Practically all the gravid natives in southern India are sick with beriberi (Balfour-Tolpade). Among the special forms of avitaminosis B_1 to be considered in the pregnant woman is the polyneuritis of gravidity. It is improved by yeast and diets rich in Vitamin B_1; it may be cured as Plass reports by injections of crystalline Vitamin B_1. It is recommended to proceed prophylactically and at the incidence of vomiting, which is the exciting factor of polyneuritis, to prevent it by administration of yeast (Plass-Mengert) or Vitamin B_1. The hyperemesis gravidarum may be not only the cause of vitamin deficiency, but also the sequence of a deficiency of Vitamin B_1, as is easily conceivable. Strauss and McDonald were able to cure several cases of vomiting of pregnancy by large doses of yeast. It has furthermore, been proven that the tendency to abort in India (Wills et al) but also in America (Maurer-Tsai) is a consequence of Vitamin B_1 deficiency. It is to be desired that in Europe likewise the necessity of an abundant supply of this vitamin for the prophylaxis of abortion may be regarded more seriously. The milk is increased in nursing mothers by a diet rich in Vitamin B_1 (Tarr-McNeile).

(e) *In Other Fields of Medicine.* In rats dental caries is produced by the withdrawal of Vitamin B_1. Food rich in Vitamin B_1 prevents acid reaction upon enamel (Kellogg-Eddy). Upon regeneration of bone and formation of callus, Vitamin B_1 has a favorable effect, the nature of which is still unknown (Lauber). An essential anti-infectious activity is not possessed

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by Vitamin B_1 (Lauber). The well-known curative effect of yeast in furunculosis is probably not contingent upon its Vitamin B_1 content.

ADDENDUM

When this section upon Vitamin B_1 was completed, there appeared the work of Vorhaus, Williams, and Watermann (Journal of the American Medical Association, 105, 1580, 1935) in which all of the experiences of therapy with crystalline Vitamine B_1 were brought up to date. Further indications for the clinical use of Vitamin B_1 have since been developed in the neurological field. Treatment of post diphtheritic paralysis with injections of Betaxin (daily 2 cc.) was successful within three weeks. In amotrophic lateral sclerosis with prolonged treatment with Vitamin B_1 (15 injections of Betaxin, 2 cc. 3 day intervals) the paresis, speech and deglutition disturbances and the muscular weakness were improved. In multiple sclerosis the spastic stiffness of the legs were diminished (Betaxin 2 cc. a day, 12 days). Neumann Muench. med. Wschft., II, 1959, 1935. The therapy of Funicular Myelosis of Neumann and Thaddea (Vitamin B_1 administration for a long time) has been confirmed. In Herpes zoster (Kühnau two cases) injections of Vitamin B_1 (3-5 times each 1 cc. Vitamin B_1 Merck) had pronounced analgesic effect.

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VITAMIN B_1 CONTENT OF FOODSTUFF

in γ per 100 gm. fresh weight
(1 γ equals 0.001 mg.)

Beef raw	90*	Potatoes raw	70*
Mutton raw	110	Potatoes cooked	55
Veal cooked	90	Radishes	110
Beef liver cooked	270	Rhubarb raw	0
Mutton kidney raw	340	Yellow beets raw	70
Roast mutton	90	Spinach raw	125
Chicken fried	70	Yellow beets cooked	trace
Pork roast	580	Watercress	110
Ham cooked	400	Apples	70*
Pork brain raw	110	Banana	90
Pork kidney raw	610	Dates	55*
Codfish raw	70	Figs, dried	180
White fish	55*	Grapes without skin	trace
Halibut fried	110	Grapefruit	70
Sardines canned	55*	Oranges	70*
Shrimp cooked	55*	Pears	55*
		Plums	70
Cow's milk	40	Prunes dried	160
Cheese Gorgonzola	55	Raisins	135
Cheese Cheddar	0	Mandarines	70
Cheese Cheshire	55*	Tomatoes	70
Egg yolk cooked	250	Almonds	140*
Egg white cooked	trace	Chestnuts	160
		Hazel nuts	360
Beans dried	220*	Walnuts	270
Red beets cooked	125	Coffee berry ground	250*
Savoy cabbage raw	110-145	Cocoa powdered	0
Brussels sprouts raw	110	Moor beets raw	110
Celery raw	trace	Whole wheat	415-610
Cauliflower raw	200	Wheat germ	1060-3375
Cauliflower cooked	55	Wheat bran	235*
Cucumber	55*	Oatmeal	585
Lentils raw	380	Rice bran	1010-1370
Head lettuce	160	Rye germs	1350
Mushrooms raw	90	Barley germs	2500
Onions raw	70*	Corn germs	830*
Preserved pods	220*	Brewers yeast dry	1100-4150

* Value uncertain, error more than 50%.

The values of this table are calculated on the basis of the equation of 1 International unit = 1.8 γ crystalline Vitamin B_1 base.

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BIBLIOGRAPHY FOR VITAMIN B

Abelin, Klin. Wschr., 2205, 1931.
Alvarez & Mitarb, American Journal of Digestive Diseases and Nutrition, 3, 102, 1936.
Baker, Lancet I, 605, 1936.
Barletta, Rass. ital. d'ottalm 1, 210, 1932.
Bennholdt-Thomsen, Kinderärztl. Praxis 545 and mundl. Mitt., 1936.
Bergel, D. m. Wschr., 1643, 1936.
Bessau, Med. Klin. 513, 1936.
Bessau, Med. Welt, 525, 1937.
Bloxsom, American Journal of Diseases of Children, 37, 1161, 1929.
Böhm, Psych.-neurol. Wschr., 418, 1936.
Boshamer, M. m. Wschr., 2045, 1935.
Brain, Trans. ophthalm. Soc. Un. Kingd., 54, 221, 1934.
Brauchle and Staehelin, Med. Welt 340, 341, 826, 1933.
Bray, Trans. Roy. Soc. Trop. Med., 9, 22, 1928.
Bray, Proc. Roy. Soc. Trop. Sect., 27, 486, 1934.
Brown, zit. nach Williams-Eddy, Yearbook Carnegie Inst., 33, 300, 1934.
Bremer, Neurologentagung, Frankfurt a. M., 22.8.36.
Campanacci, Ferretti, Giorn. Clin. Med., 16, 1923, 1935.
Campbell, Warner: Lancet I, 61, 1930.
Carmichael, Stern, Brain 54, 189, 1931.
Cerulli, Lo Sperimentale 89, 248, 1935.
Clément, Presse Méd., 1420, 1932.
Cowgill, The Vitamin B Requirement of Man., Yale Univ. Press, 1935.
Cowgill, Gilman, Ann. Int. Med., 8, 53, 58, 1934.
Dalldorf, Kellogg, Journal Exp. Med., 56, 391, 1931.
Dennett, Journal of the American Medical Association 92, 769, 1929.
Douthwaite, British Medical Journal, 535 (Nr. 3949), 1936.
v. Drigalski, Arch. f. Verdauungskrkh., 57, 1, 1935.
Dupouy, Courtois, Encephale 25, 301, 1930.
Elsom, Journal Clin. Invest. 10, 14, 1935.
Ely, Journal Nerv. Ment. Dis., 56, 115, 1922.
Etzel, Fol. clin. et biol. (São Paulo), 7, 261, 1935.
Evans, Lepkovsky, Journal of Biological Chemistry, 96, 179, 1932.
Fellinger, Wien. klin. Wschr. 1542, 1936.
Fetscher, Fortschr. Ther., 633, 1936.
Fischer, Schweiz, med. Wschr., 749, 1933.
Fletcher, Journal Lab. Clin. Med., 15, 1140, 1930.
Fletcher, Journal of the American Medical Association 101, 1264, 1933.
Flouts, Gustavson, Zerfas, American Journal of Obstetrics, 28, 902, 1934.
Gaehtgens, M. m. Wschr., Nr. 18, 1936.
Garamvölgyi, Különlenyomat a Népegészegügy, 1936.
Geiger, Rosenberg, Klin. Wschr., 1258, 1933.
Géronne, Verh. Ges. inn. Med. 96, 1936.
Gildea, Kattwinkel, Castle, New England Journal of Medicine, 202, 523, 1930.
Glanzmann, Z. Vitaminf. 3, 105, 1934.
Grebel, Therapeut. Ber. (I.G.) 13, 316, 1936.
Gruenfelder & Mitarb., Klin. Wschr., 983, 1933.
Grünig, Mitt. Lebensmittelunters, 22, 52, 1931.
Gyorgyi, Biochemical Journal 29, 741, 1935.
Haas, Arch. Pediatr. 46, 467, 1929.
Harris, Ann. Int. Med., 4, 149 (Ulkus), 1930.
Harris, British Medical Journal, II, 231 (Wachstum), 1933.
Heiman, Wien. klin. Wschr., 1271, 1936.
Heiman, Med. Kl. 1501, 1936.
Hesse, M. m. Wschr., 356, 1936.
Hofer v. Lobenstein, M. m. Wschr., 510, 1936.
Hoobler, Journal of the American Medical Association, 96, 675, 1931.
Howes, Vivier, American Journal of Pathology 12, 689, 1936.
Illing, Ergebn. inn. Med. 48, 340, 1935.

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Jörgensen, Nord. hyg. Tidskr., 14, 363, 1933.
Johannes, Kindt, Arch. Psych., 104, 611, 1936.
Jolliffe, Colbert, Journal of the American Medical Association, 107, 642, 1936.
Jolliffe and Joffe, American Journal of Medical Science, 191, 515, 1936.
Kagawa, Mitt. med. Ges. Tokio, 45, 193, 1931.
Keefer, New York State Med., 32, 1405, 1932.
Kellogg, Eddy, Dental Cosmos, 74, 334, 1932.
Kirsch, Sirca, zit. nach Muller, Nutrition (Paris), 5, 425, 1935.
Koch, Mündl. Mitteilung
Kühnau, J., D. m. Wschr., 352, 1937.
Kühnau, J., Schroeder, Wolff, D. m. Wschr., im Erscheinen, 1937.
Kühnau, W., M. m. Wschr., 1772, 1933.
Labbé, Nepveux, Gringoire, Bull. Acad. méd., 109, 689, 1933.
Labbé, Nepveux, Gringoire, Soc. Biol. 113, 152, 1933.
Lajos, Biochem. Z. 280, 284, 1936.
Lajos, Gerendás, Z. exp. Med. 98, 739, 1936.
Larimore, Journal of the American Medical Association 90, 841, 1928.
Larson, Jones, Pritchard, American Journal of Diseases of Children, 48, H. 6, 1934.
Lasch, M. m. Wschr., 1390, 1936.
Lauber, Med. Welt, 415, 1937.
Lauber, Vgl. Bruns' Beitr., 63, 158, 1933.
Leak, Lancet I, 867, 1936.
Löhr, Med. Welt, 553, 1936.
Löhr, Arch. exp. Path. 180, 344, 1936.
Lowry, Pearse, zit. nach Harris-Leong, Lancet I, 886, 1936.
Macciotta, Clin. Pediatr. 10, H. 11, 1930.
McClendon, Arch. Pediatr., 50, 666, 1933.
Magyar, Z. exp. Med. 99, 272, 1936.
Marks, Med. Journ. & Rec. 1062, 1932.
Maurer, Tsai, Illinois Medical Journal 30, 61, 1932.
Minot, Ann. int. Med. 3, 216, 1929.
Minot, Strauss, Cobb, New England Journ. Med., 208, 1244, 1933.
Minski, Journ. of Neur., 16, 219, 1936.
Monauni, Z. Klin. Med., 131, 553, 1936.
Morgan, Barry, American Journal of Diseases of Children, 39, 935, 1930.
Nagl, Z. klin. Med., 131, 781, 1937.
Nesbit, Arch. Pediatr. 49, Nr. 3, 1932.
Neumann, M. m. Wschr., 1959, 1935.
Neuwirth, Schweiz. med. Wschr., Nr. 24, 1934.
Nonne, D. m. Wschr., 166, 1907.
Ohta, Jb. Kinderheilk., 1, 128, 1930.
Pemberton, Chronic Arthritis, Philadelphia, MacMillan, 1934.
Perkins, Journal of Nervous and Mental Diseases, 83, 505, 1936.
Plass, Mengert, Journal of the American Medical Association, 101, 2020, 1933.
Primangeli, Policlinico, sez. prat., 1250, 1934.
Reyher, Arch. Kinderheilk., 76, 215, 1925.
Reyher, Arch. Kinderheilk., 77, 114, 162.
Reyher, Arch. Kinderheilk., 55, 84, 1928.
Ribadeau-Dumas, Mathieu, Presse Méd., Nr. 10, 1931.
Rhoads, Yale Journ. Biol. & Med., 6, 75, 1933.
Rice, Arch. Pediatr., 50, 358, 1933.
Rowlands, Browning, Lancet I, 180, 1928.
Ruschke, D. m. Wschr., 181, 1936.
Russell, Edinburgh Med. Journ. N. s. 43, 315, 1936.
Sainton, Progrès méd., 60, 2260, 1933.
Sauer, Jb. Kinderheilk., 80, 148, 1936.
Schauf, M. m. Wschr., 1504, 1936.
Schiödt, Acta med. scand., 84, 456, 1934.
Schönbrunner, D. m. Wschr., 257, 1937.
Schülein, Die Bierhefe als Heil-, Nahr- und Futtermittel, Dresden, 1935.
Schwochow, M. med. Wschr., 98, 1937.
Sciclounoff, Broccard, Schweiz. med. Wschr., 985, 1936.
Shastid, American Journal Ophthalm. 12, 903, 1929.
Soga, Acta Soc. ophth. jap., 39, 66, 1935.

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Sparks, Collins, American Journal of Digestive Diseases and Nutrition, 2, 618, 1935.
Stahler, M. m. Wschr., 327, 1937.
Stepp, M. m. Wschr., 1307, 1935.
Stepp, Schroeder, M. m. Wschr., 763, 1936.
Stiner, Schweiz. med. Wschr., 1129, 1934.
Stolte, Med. Kl. 999, 1933.
Strauss, American Journal of Medical Science, 189, 378, 1935.
Strauss, MacDonald, Journal of the American Medical Association, 100, 1230, 1933.
Stucky, Rose, American Journal Phys., 1, 89, 1929.
Sturm, Med. Kl., 1326, 1935.
Summerfeldt, American Journal of Diseases of Children, 43, 284, 1932.
Sure, Buchanan, Proc. Soc. Exp. Biol. 33, 77, 1935.
Sure, Thatcher, Arch. Path., 16, 809, 1933.
Tarr, McNeile, American Journal of Obstetrics, 29, 811, 1935.
Thaddea, Med. Kl., 1589, 1935.
Thannhauser, Schweiz. med. Wschr., 269, 1935.
Theobald, Lancet I., 834, 1936.
Thomas, American Journal of Disease and Nutrition 2, 557, 1935.
Tisdall, Journal of the American Medical Association, 105, 1583, 1935.
Tislowitz, Klin. Wschr., 226, 1937.
Villaret et al, Bull. soc. méd. Hôp. Paris, 52, 1155, 1936.
Vining, Med. Journ. & Rec., 128, 351, 395, 453, 1928.
Vorhaus, Williams, Waterman, Journal of the American Medical Association, 105, 1580 (Polyneuritis, Atonie), 1935.
Vorhaus, Williams, Waterman, American Journal of Digestive Diseases and Nutrition, 2, 541 (Diabetes), 1935.
Waring, American Journal of Diseases of Children, 38, 52, 1929.
Webster, Armour, Proc. Soc. Exp. Biol. 31, 463, 1934.
Wechsler, Med. Journ. & Rec., 81, 440, 1930.
Weech, Internat. Clin., Ser. 2, 46, 223, 1936.
Weil-Hallé, Layain, Bull. soc. méd. Hôp. Paris, 51, 145, 1927.
Widenbauer, Klin. Wschr., 608 (Chorea), 1935.
Widenbauer, Med. Welt H. 49, (Polyneuritis), 1936.
Williams, Waterman, Keresztesy, Science, 535, 1935.
Wills et al, Indian Journ. Med. Res., 18, 263, 663, 1930.
Wohl, Journal of the American Medical Association, 87, 901, (Diabet. Neuritis), 1926.
Wohl, Journal of the American Medical Assocaton, 106, 265 (Hypothyreose), 1936.
Wyatt, Chron. Arthritis and Fibrositis, Wm. Wood, 1933.
Wyllie, Stern, Arch. Dis. Childh. 6, 137, 1931.
Yoshio, Bruns' Beitr., 146, 621, 1929.
Yudkin, Arch. of Ophthalm. 14, 112, 1935.

VITAMIN B_2 COMPLEX

History and Definition. In the early days of vitamin research Vitamin B was considered uniform; only beriberi-preventing and growth-stimulating properties were ascribed to it. American vitamin investigators (Seidell, Smith-Hendrick) in 1926 showed that the growth factor of the so-called Vitamin B was in reality the result of the coactivity of two chemically different and water-soluble diet factors. The one, heat and alkali resistant, alcohol-insoluble, proved clearly distinct from the other, identical with the antineuritic Vitamin B_1. About the same time Goldberger showed that the heat-stable yeast factor was not restricted to stimulation of growth. By feeding a diet of only the B_1 fraction of the B group he could produce in rats a disease closely resembling human pellagra, usually associated with a macrocytic anemia. Since then the anti-

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neuritic Vitamin B_1 has been differentiated from Vitamin B_2, pellagra-preventing or (incorrectly, since other vitamins also have growth effects) as growth vitamins. A blood-regenerating action was ascribed to this vitamin also. Soon, however, it became evident that it was possible to produce pellagra in rats without inhibition of growth (Sure-Smith), or the latter without the concomitant pellagra (Sherman-Sandels), or finally pellagra without anemia (Guha), so that since 1931 the conception of a uniform Vitamin B_2 could not be maintained. On the other hand close relationships of the then hypothetical fractional factors of the Vitamin B_2 complex and their almost common coexistence, could not be denied. For this reason the fractional factors have been continuously thrown together of late. Since the growth factor at one time and the pellagra-preventive at another time were designated as Vitamin B_2, it was more difficult to clarify the situation. Our knowledge of the Vitamin B_2 problem may be precisely put as follows.

Vitamin B_2 consists of at least three (probably five) chemically and physiologically distinguishable components, which, however, to accomplish optimally their physiological function, must be administered together to man, so that there exists between them a biological and perhaps also a chemical correlation. From the labors of Chick-Copping-Edgar and Györgyi (1935) it is evident that each factor unit exercises its specific effect, though to a lesser extent, when given alone, but that its full activity is realized only when the other factors are embodied at the same time, so that one might think of the reciprocal activation as a catalysis. The underlying processes are hazy; only one thing is certain—that Vitamin B_2 complex represents a functional unit. Györgyi's proposal (at the present the best solution) is to designate the growth-stimulating component of the complex in a narrower sense as Vitamin B_2, and the pellagra-preventive as Vitamin B_6, while the anemia-preventive has no identifying letter so far. From the functional uniformity of the Vitamin B_2 complex and from the usually simultaneous occurrence of its components in nature, it follows that symptoms of deficiency, as a result of a lack of supply of one factor unit alone, does not happen in man and that manifestations of insufficient supply of the Vitamin B_2 complex may not with certainty be attributed to single components of the complex. The discussion of the clinical symptoms of B_2-complex avitaminosis and the resulting indications for a therapeutic application of Vitamin B_2 complex will be included in the description of the components.

Introduction. 1. *The growth-factor (Vitamin B_2 in a narrower sense —Lactoflavin).* The production in pure form and the reconnoitering of the chemical nature of the growth-factor units is one of the greatest successes that the biologically oriented chemical research may boast of lately. Though at the end of 1932 little more was known than the mere existence of the vitamin, its isolation, the recognition of its constitution, and its synthesis were successfully established in the following two years. The fruitful investigations of Vitamin B_2, in which German students decisively participated, began with the observation that all growth-effecting prepara-

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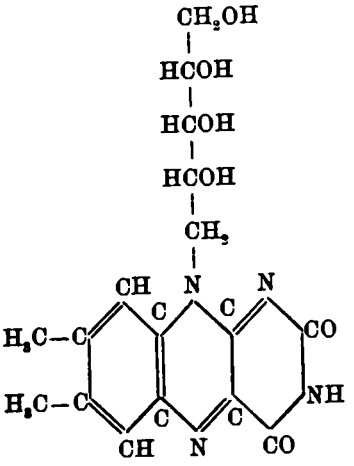
tions obtained from organs, egg white or milk, showed a yellow color and a yellow-green fluorescence and the dyeing intensity ran parallel to the magnitude of the incitation of growth. Because this observation pointed to possible connections of growth effect and dyeing character, several groups of workers affirmed that the yellow-green fluorescing, water-soluble, dyestuff was widely present in nature.

They contained nitrogen, it was found, and were designated as Lyochromes (Ellinger-Koschara) or Flavins (Kühn-Györgyi-Wagner-Jauregg). The most important of this group of dyes proved to be lactoflavin, which was obtained from whey, yeast, egg white and liver (therefore also called ovo- and hepatoflavin) and identified with the vitamin of growth B_2.

Chemistry. Lactoflavin has the formula $C_{17}H_{20}N_4O_6$; it forms needle-like yellow crystals, has a melting point of 280 degrees centigrade, is easily soluble in water (slightly in alcohol), is insoluble in chloroform and is in alkaline solution optically active ((a) $^{20}_{D}$ = — 114° in n/20 NaOH). Its spectrum shows in visible light one band, in the ultraviolet three bands (445, 372, 269, 225 μμ), its chemical constitution is a 6, 7 Dimethyl—9 (l-d-ribityl) isoalloxazin of a formula as follows:



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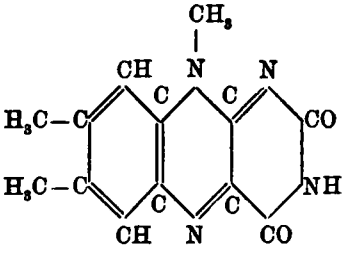

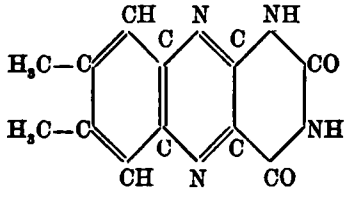

Besides the lactoflavin, other flavins, such as the 7-Monomethyl-ribityl-isoalloxazin (Euler-Malmberg), and the 6, 7-Dimethyl-arabityl-isoalloxazin (Györgyi), also possess vitamin activity though in a lesser degree. There are several substances of Vitamin B_2 character. The synthesis of lactoflavin was accomplished almost simultaneously by Kühn and Karrer in 1935.

By means of strong reducing agents Lactoflavin is changed to a colorless leucoderivative which in the air is reoxidized by itself to the vitamin, thus forming a redox system upon which its specific biological effect depends. Radiation with visible and ultraviolet light destroys the vitamin by splitting up the hydrocarbon chain. In alkaline solution lumiflavin is formed, which, contrary to lactoflavin, is soluble in chloroform (Formula II Kühn). In neutral and acid solution the colorless leucochrome containing the ring system of Alloxazin (Formula III Karrer) appears. Both substances have

lost their vitamin activity. The lumiflavin fluoresces yellow-green, the lumichrome blue. Such blue fluorescing substances are widely distributed in the animal and vegetable worlds (especially in the retina, corpus luteum and in yeast). The photochemical catabolism of Vitamin B_2 also plays a role in the organism. Vitamin B_2 is taken in with the nutriment not only as free lactoflavin but also (as in spinach) in a form combined with albumen as a phosphoric acid ester of lactoflavin (Theorell). This flavin-albumen combination may be formed by a partial synthesis in the animal from free flavin. The real Vitamin B_2 is not the free lactoflavin, but the lactoflavin phosphoric acid mentioned, which is formed in the intestine by esterification of the lactoflavin contained in the food. If this esterification in young rats is stopped by poisoning them with iodoacetic acid, there occurs cessation of growth which may not be reestablished by additions of lactoflavin, but may be by that of lactoflavin phosphoric acid.

Determination. Detection of the Vitamin B_2 content of organs may be done by biological methods as follows. Young rats having stopped growing from four weeks of Vitamin B_2-free feeding, receive additions of the substance to be examined daily in equal quantities. A unit comprises that dose, which by daily administration for 30 days, effects an increase of weight of 40 gm. Besides this curative method there is a prophylactic one that may be employed for the rat-growth test. Usually a Vitamin B_2-free diet is given which must include Vitamin B_1 concentrates containing at the same time Vitamin B_4 and yeast, yielding Vitamin B_6. One rat unit corresponds to 8-10γ of crystalline lactoflavin. The conversion of a rat unit to proportions of weight of lactoflavin offers difficulties, as one rat unit is already contained in 0.1 gm. of dry yeast (Roscoe). This fact may be explained in that the lactoflavin of natural products like yeast, is associated with substances which increase the growth effect in the organism three to five times. Since lactoflavin has been obtained in pure form, chemical methods are being employed increasingly for the determination of the Vitamin B_2 content. They are, however, to be used with certain precaution, because they also detect biologically inert flavins and flavin derivatives. The chemical determination proceeds as follows. The solution to be examined is rendered alkaline, radiated, and after acidification is extracted with chloroform, and then the dyeing intensity of the extract is ascertained by means of a scale photometer (Kühn). The yellow-green fluorescence may also be directly estimated photometrically. A separation of the free flavin from that bound to egg white is possible by dialysis.

Occurrence. The great biological importance of Vitamin B_2 is evidenced by the fact that the lowest forms of life, bacteria and yeast, possess the ability to synthesize flavin (butyric acid bacteria contain, for example, 13.6 mg. % in the dry residue). Vitamin B_2 occurs in every cell of plants and animals. Unsprouted seeds are generally poor in lactoflavin, the pea is an exception. Within a few days after budding a manifold increase of flavin content ensues. (Euler-Dahl). Particularly potent sources of Vitamin B_2 are yeast, egg white, liver, kidney, heart muscle of mammals, and liver extracts like Campolon and Lilly 343 (not Hepracton). In the other

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mammalian organs only slight quantities are found. The following table gives a survey of Vitamin B_2 (lactoflavin) contained in various foodstuffs. It is evident from this table that Vitamin B_1 and B_2 do not occur together, as is frequently accepted. Egg white, rich in Vitamin B_2, contains no Vitamin B_1, while wheat, potatoes, carrots, tomatoes, and onions are very good sources of Vitamin B_1 and have only traces of Vitamin B_2. The pellagra-preventive Vitamin B_6 has likewise a different field of distribution from that of Vitamin B_2.

VITAMIN B_2 CONTENT OF FOODSTUFFS

Vitamin Content per 100 gm. of Fresh Substance

	I. Biologically determined Rat Units	Lactoflavin	II. Colorimetrically determined Flavin
Beef liver	500	4000	1500–1700
Beef kidney	—	—	800–1600
Beef heart	130	1040	—
Beef muscle	35	280	—
Veal	50	400	—
Chicken	30–35	240–280	—
Salmon, herring, cod	Trace	—	—
Cod liver	Trace	—	—
Egg yolk	50	400	550
Egg white	35	280	450
Milk	10	80	100
Potatoes	5–10	40–80	10
Cabbage	15	120	50
Spinach	20	160	80
Carrots	—	—	20
Peas	—	—	90
Tomatoes	5–10	40–80	50
Wheat	—	—	20
Corn	—	—	100
Barley, sprouting	—	—	60
Bananas, peeled	—	—	8
Apricots, dried	—	—	57
Light beer	—	—	30
White wine	—	—	10
Lemon juice	—	—	3
Honey	—	—	105
Malt extract Loeflunds	—	—	210
Cenovis yeast extract	—	—	4300
Dry yeast	—	—	1800–2100
Vitox	—	—	3300

N. B. Vitamin B_2 occurs in foodstuffs principally in high molecular combinations as "yellow ferment" (in spinach 80-90%, in egg white, yolk and peas 90-95%, in sprouting grain 60-70% of the entire albumin-bound flavin [von Euler & co-workers]). Only milk contains, almost exclusively, free flavin.

Requirement of Man. The absolute necessity of the lactoflavin for nor-

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mal growth has so far only been determined for the rat (Györgyi) and the chick (Elvehjem-Koehn). For the pigeon the Vitamin-B_2 complex is not vital. Furthermore it is uncertain whether the lactoflavin fulfills in man the functions of a growth-vitamin, or if it is not needed as a base for the yellow ferment. In man a genuine Avitaminosis B_2 is not known. Therefore, the daily human requirement cannot be stated with accuracy. We do not know how large a proportion of the Vitamin-B_2 complex effect may be attributed to lactoflavin. It cannot be considerable, since fish, which is a specifically valuable food in the treatment of human pellagra—a Vitamin B_2 complex avitaminosis—contains practically no Vitamin B_2. The organism needs the lactoflavin on the other hand for the construction of the yellow ferment, to regulate the cell metabolism. If we, therefore, estimate the human need of Vitamin-B_2 complex with Jung to be 150 rat units we still cannot draw conclusions as to the lactoflavin requirement for man. The conversion of the 150 rat units into lactoflavin might furnish suggestions for the magnitude of the requirement, but for reasons mentioned previously it meets with difficulties. Figures result which lie between 0.3 and 1.5 mg. of lactoflavin a day according to the kind of food and its content of substances activating lactoflavin. One may not go very far wrong by estimating the daily human minimum need of Vitamin B_2 to be 1 mg. The Vitamin B_2 optimum lies, however (as with Vitamin B_1) far above the minimum (Sherman, Sherman-Ellis)—about 2 to 4 mg. During lactation the need of Vitamin B_2 is increased (Bomskov). The calculations of Schroeder and Wittmann show that the Vitamin B_2 content of human food and of special diets is generally sufficient and will meet even increased demands. For man the danger of a Vitamin B_2 avitaminosis is therefore slight.

Behavior of Vitamin B_2 in the Organism. The lactoflavin taken up with the food and that released in case of a colloidal compound is absorbed in the small intestine, and while still in the mucosa is esterized with phosphoric acid (Rudy). Assimilated in the animal cell this ester is moored to a colloidal carrier substance of protein nature ready in the organism, and thus, as yellow ferment, stored in the organs (Theorell et al). The flavin of the organs is present almost exclusively (80-90%) as a high molecular compound (Euler-Adler). Solely in one place in the body, the pigment epithelium of the retina of mammals and fishes, Vitamin B_2 occurs in very considerable quantities in a free and dialysable form. The retinas of many fishes belong to the richest known tissues in Vitamin B_2 (content of growth-effective flavin of fresh cod retina is 50 mg. %). Since the retinas of albinotic animals contain abundant flavin, it is probable that Vitamin B_2 participates in the organ of vision (Euler).

The obligated combination of Vitamin B_2 and albumen in other organs explains why their content of Vitamin B_2 depends in proportion but lightly upon the supply of albumen. Since the flavin part of the yellow ferment comprises only 45% of the entire ferment molecule, the normal liver alone must contain in its dry residue 1% of the yellow ferment. If this value may be but little increased by a tenfold supply of Vitamin B_2, it is apparent that the storing capacity of the liver tissue is limited by the quantity of the available colloidal carrier (Kühn-Kalt-Schmidt-Wagner-Jauregg). It is

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affirmed on the other hand that Vitamin B_2 may be stored in the organism up to a certain degree (von Drigalski). Conversely the content of Vitamin B_2 diminishes but little even on a Vitamin B_2-free diet continued for a long time, death in the avitaminotic B_2 animals supervening at a time when their organs (liver chiefly) still hold considerable quantities of Vitamin B_2 (Kühn and co-workers, Vivanco). Feeding avitaminotic B_2 animals with additional lactoflavin incites immediate growth, before the depleted vitamin depots of the organs are refilled. Within the organism Vitamin B_2 is probably subject to a partial catabolism setting in at the carbohydrate side chain and leading to flavin carbon acids.

Vitamin B_2 after thus splitting off its albumen portion is eliminated in free form by the urine and the feces (Vivanco). The export by the feces is about double that of the urine. The normal human urine contains about 1.5 mg. of flavin in a liter. The urinary flavin is indeed not a pure Vitamin B_2, but to a great extent consists of a catabolic product of the vitamin, the aquoflavin (Koschara). The elimination of flavin, however, stops in Vitamin B_2-free fed animals with cessation of their growth, while it continues even then in the feces. Vitamin B_2 passes also into the milk and the spinal fluid (von Drigalski).

Mode of Action and Physiological Importance. The growth effect of Vitamin B_2 seems to depend essentially upon the fact that it is a base of the yellow ferment (Warburg-Christian) and indispensable for the activation of the energizing processes of oxidation in the cell. It has been designated as the "methylene blue of the cell" in view of the frequently employed faculty of this dyestuff in experiments to act as an oxidizing catalyzer. Like methylene blue lactoflavin may be reduced in biological systems to a leucobase and reoxidized by the oxygen of the air. From this property arises the power of transferring hydrogen, which the free flavin possesses only in a very restricted measure. However, esterified with phosphoric acid and albumen bound as yellow ferment (flavin enzyme), aided by the hydrogen-transferring ferment, it can oxidize a series of combustible products of metabolism (malic acid, citric acid, ethyl alcohol, hexophosphoric acid, and under certain conditions grape sugar) by transporting the hydrogen to suitable acceptors. Furthermore it may transfer the oxygen of the air directly to these substances, an action of which the free flavin is never capable. The yellow ferment is therefore, a genuine respiratory ferment, but insensitive to cyanic acid. The fact that the yellow ferment acts as a go-between in sugar metabolism is perhaps explained by the observation that lactoflavin injections lower the blood sugar of diabetics (Stepp).

However, the free lactoflavin, not egg-white bound, nor the phosphorester, plays an important role in the process of vision. Under the influence of light the flavin of the retina is changed to a "primary, activated photobody" of unknown structure and this reaction seems to incite the excitability of the optic nerve. The primary photo-body, however, is very sensitive, and decomposes from oxygen deficiency forming deuteroleucoflavin. The retinal oxygen impedes decomposition reforming the original flavin out of the photo-body (Theorell). Also in twilight vision the flavin

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of the eye performs a special function, changing the short wave light to long wave light by means of its fluorescence (Euler).

Phenomena of Deficiency. During animal experiments (rats and chickens) the avitaminosis B_2 appears in the cessation of growth, excepting the non-specific dermatitis in Vitamin B_2 and Vitamin B_6-free fed rats, which is occasionally cured only with lactoflavin (Chick-Copping-Edgar). Lately Györgyi has shown in rats fed only with Vitamins B_1 and B_6 of all the B factors, there develops a peculiar skin affection, differing from the B_6 and H avitaminoses (formation of yellowish-white scales dispersed over the entire body and later loss of hair), which is cured by additions of B_2.

BIBLIOGRAPHY OF VITAMIN B_2 COMPLEX

Dann, Journal of Nutrition, 11, 451, 1936.
Fanconi, Abh. Kinderh., 21, 1, 1928.
Györgyi, Klin. Wschr., 1241, 1933.
Heiman, Wien. klin. Wschr., 1271, 1936.
Kisch, Wien. m. Wschr., 194, 1937.
Lucksch, Z. klin. Med., 32, 130, 1936.
Lucksch and Flinker, zit. n. Flinker, Erg. inn. Med., 49, 522, 1935.
Stepp, M. m. Wschr., 1307, 1935.
Verzár, Laszt, Pflügers Arch., 236, 693, 1935.
Verzár, Laszt, Pflügers Arch., 237, 476, 483, 1936
Verzár, Laszt, Pflügers Arch., Z. Vitaminf., 5, 265, 1936.
Wagner—Jauregg, Wien. klin. Wschr., Nr. 9, 1936.
Widenbauer, M. m. Wschr., 1071, 1935.
Zehnder, Klin. Wschr., 553, 1937.

VITAMIN B_6

Introduction. *The pellagra-preventive (Vitamin B_6, P-P factor.)* When rats are fed a diet containing, of the Vitamin B group, only the antineuritic Vitamin B_1 there develops a clinical syndrome consisting of cessation of growth and a symmetrical localized dermatitis of the fore and hind paws, ears, nose and the angles of the mouth with reddening, scaling and swelling, which shows a certain similarity to human pellagra, and is called by its discoverer—Goldberger—rat pellagra. A more accurate analysis of this symptom complex by Chick-Copping-Edgar and Györgyi showed that for its cure and prevention administration of two vitamins was necessary, the growth-promoting Vitamin B_1 and the dermatitis-preventing B_6. For reasons not well known these vitamins exert their efficacy only when supplied simultaneously. However, by feeding a Vitamin B_6-free diet and adding a generous supply of Vitamin B_2 a symptom complex has been successfully produced in which the skin phenomena are outstanding, so that the symptoms of the Vitamin B_6 avitaminosis may be studied. Its similarity with human pellagra seems to justify the conclusion that the Vitamin B_6 is indispensable for man, also.

Properties. Vitamin B_6 has not been developed in pure form; its chemical nature is unknown. Like Vitamin B_2 it is probably a dye-stuff

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(Györgyi). It is water-soluble, very heat and alkali stable and dialyzes through cellophane. By radiation with visible and ultraviolet light it is destroyed (Györgyi, Hogan-Richardson).

Determination. The determination of the Vitamin B_6 content in nutrient material is done as follows:

For 6 to 8 weeks young rats receive a diet containing of the B vitamins, only Vitamin B_1 with additions of the material to be analyzed, with the appearance of the skin changes usually accompanied by inhibition of growth. One rat unit of lactoflavin is added each day. That quantity of the daily fed test material which cures the dermatitis and, as usually happens, at the same time re-establishes growth, is defined as a rat unit (Györgyi).

Occurrence. The following table gives in rat units the content of Vitamin B_6 in some foods. It is evident that Vitamin B_2 and Vitamin B_6 contents do not run parallel. Though beef liver is the richest food, both in Vitamin B_2 and Vitamin B_6, egg white has much Vitamin B_2 but no Vitamin B_6, while fish of every kind is a very good source for Vitamin B_6, but practically free of Vitamin B_2. That is a matter of importance also for human nutrition, since fish is one of the best curative means to treat human pellagra. B_2 occurs in yeast, egg-yolk, lettuce, spinach (Chick-Copping) and rice bran (Lepkovski-Jukes). Cornstarch, wheat germs, and corn and linseed oils cure rat pellagra. However, the identity of the factor contained in these materials, ether and alcohol-soluble, with Vitamin B_6, is not assured (Hogan, Richardson).

Vitamin B_6 Content of Food in Rat Units (Györgyi) per 100 gm. of fresh substance

Beef liver	330	Egg white	0
Beef heart	130	Milk	10
Veal	130	Salmon, Cod, Herring	200
Beef muscle	100	Cod liver	50
Chicken	100	Wheat germ oil	500

Requirement of Man. The Vitamin B_6 requirement of man is not known. It is assumed to be commensurate with Vitamin B_2 and to amount to 150 rat units.

Behavior in the Organism. Only this much is known—that it cannot be demonstrated in the blood, but that it is eliminated in the urine and milk (Holmer). The crystalline lens is Vitamin B_6 free.

Physiological Importance. The P-P factor enters into the sulphur metabolism in a manner still unknown (Sullivan-Dawson). In human pellagra the sulphur of the fingernails is reduced (Payne-Perlzweig). The disease is improved or even cured by injection of thiosulphate (Sabry). In rat pellagra the glutathione of the liver and blood is diminished. Feeding cysteine and glutathione alone, without additions of the Vitamin B_2 complex, effects growth and restores the coat of hair (Itter, Orent and McCollum). Whether these underlying processes concern a specific disturbance

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of the sulphur metabolism under a lack of Vitamin B_6 (Perhaps because of interference with the function of the adrenal, by which the sulphur economy is principally influenced, cf. pellagra adrenal changes) or an insufficient assimilation of cysteine, has not been determined. Considering their propriety there exist dim relations between the pellagra-preventive factor and iron economy. A disease wholly similizing pellagra may in rats be produced by iron deficiency alone (Bliss-Thomason). The cure of human pellagra may be materially accelerated by large doses of iron (Biggam-Ghalionngui). It may be argued that Vitamin B_6 aids constructing metabolic catalyzers containing sulphur and iron and that Vitamin B_6, as well as sulphur and iron are necessary to prevent pellagra, but on this subject very little is known. Whether the P-P factor, as has been often surmised, plays a similar role in the proteid metabolism as Vitamin B_1 does in the carbohydrate metabolism, is uncertain so far. Probably Vitamin H and not Vitamin B_6 is the factor which enters into the protein metabolism as a regulator.

Phenomena of Vitamin B_6 Deficiency. The symptom complex of rat pellagra, avitaminosis, described above occurs sometimes in a more nonspecific dermatitis with loss of hair about the head and the eyes in spectacle form. The similarity of human and rat pellagra is still more marked by the fact that gastrointestinal disturbances (diarrheas, intestinal hemorrhages, colitis and stomatitis and glossitis) and affections of the central nervous system (vacuolization of the anterior horn cells) are observed. Yet these symptoms may not be those of a true lack of Vitamin B_6, but equally due to a deficiency of other divisional factors of the Vitamin B_2 complex. In the Vitamin B_6-free fed chicks pellagra symptoms develop similizing those of the rat (Kline, et al). It is of importance to note that another etiologically entirely different disease, the egg-white dermatitis (probably a form of avitaminosis H) produces clinical symptoms in the chick just like pellagra (Lease-Parsons, Norris-Ringrose, Gorter). This has led to great confusion in the Vitamin literature, the more since Vitamin H deficiency and toxic action of egg white play a role in human pellagra as well. In the avitaminosis of the Vitamin B_2 complex in the dog, the skin signs recede, while gastrointestinal symptoms and the lesions of the central nervous system dominate the clinical syndrome (Zimmermann-Bureck). There occur degenerations of the medullary sheaths in the posterior columns and occasionally also in the anterior and posterior roots. This avitaminosis B_2 of the dog proceeding with purely central nervous symptoms, where apparently the lack of Vitamin B_6 stands out prominently, differs clearly from the so-called dog pellagra also called black tongue.

> In this (dog sickness of Stuttgart), a disease of dogs in Europe and in America which may appear spontaneously or be experimentally produced, affections of the gastrointestinal tract—inflammations, ulcerations, and pigmentations of tongue, mouth and oesophagus—are prominent, above all besides diarrheas and anemia; central nervous symptoms may also occur, but they are not marked. Though the seasonal frequency and geographical distribution and anatomical substratum of human pellagra and black tongue are exactly alike

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(Wheeler), the latter cannot be considered as a full analogon of human pellagra, because its main symptom is the hyperchromatic anemia, which in pellagra of man is seen only occasionally. That points toward an insufficient supply of the anemia factor as being of decided importance for the origin of black tongue. To cure it a divisional factor of the Vitamin B_2 complex, unknown so far, is required, the lack of which is probably involved in the intestinal symptoms (Rhoads-Miller). Black tongue is a matter, therefore, of a complex avitaminosis arising from a lack of the anemia factor, of Vitamin B_6 and likely carotin (Underhill-Mendel), besides lack of another partial factor of the Vitamin B_2 complex in the feed.

While this article was in the press Birch, Györgyi and Harris suggested that the Vitamin (P-P factor) was different from the Vitamin B_6, but probably identical with the black-tongue-preventing factor. That would make the previous assumption that Vitamin B_6 was of importance for man and that the rat pellagra was an analogon for the human untenable. Further investigations must clarify the situation. The assumption of Birch and co-workers rests upon the observation that the distribution in the foodstuffs of Vitamin B_6 and P-P factor varies, thus the P-P-free, pellagra-producing corn contains an abundance of B_6. We, therefore, supplement our former statements with another table of qualitative data showing the occurrence of the P-P factors especially significant for man.

The P-P Factor Content of Various Foods.

High	Moderate
Dry yeast	Milk
Hog liver	Cod Fish
Liver Extract (Lilly 343)	
Wheat Germs	
Salmon	
Fresh Beef	
Chicken	
Low	**None**
Caseine	Oatmeal
Butter	Cornmeal
Whole Wheat Grains	Rice
	Peas
	Tomato Juice
	Pork

BIBLIOGRAPHY FOR VITAMIN B_6

Ballner, Österr. Sanitätswesen, Nr. 17—20, 1910.
Barondes, American Journal of Digestive Diseases and Nutrition, 3, 330, 1936.
Birch, Györgyi, Harris, Biochemical Journal 29, 2930, 1935.

Posted for noncommercial historical preservation and educational use only by seleneriverpress.com

hick, Lancet, II, 341, 1933.
orter, Z. Vitaminf., 5, 1, 1936.
ucksch, Med. Klin., 159, 1937.
ucksch, Z. klin. Med., 32, 130, 1936.
etri, Acta path. scand., 13, 350, 1936.
ebrell, Public Health Reports, 49, 754, 1934.
pies, Arch. int. Med., 52, 945, 1933.
pies, Journal of the American Medical Association, 104, 1377, 1935.
pies et al, Journal of the American Med. Association, 100, 144, 1933.
ydenstricker et al, American Journal of Medical Science, 1, 192, 1936.
mith, Ruffin, American Journal of Medical Science, 189, 512, 1934.
ukes, Journal Biological Chemistry, 117, 11, 1937.
outs, Lepkovsky, Helmer, Jukes, Proceedings of the Society of Experimental Biology, 35, 1937.

MISCELLANEOUS GROUPS OF VITAMIN B COMPLEX

Introduction. *The anemia factor ("Extrinsic Factor", Castle, Haemogen Reimann).* After Guha and Mapson had proven for the first time that the concommitant hyperchromatic anemia of the experimental rat pellagra was caused by the lack of a specific vitamin in the diet, Castle and Strauss ascertained in 1932 that also in human pathology the anti-anemic vitamin played a large role in so far as all kinds of hyperchromatic anemia occurring in man rested upon the loss of function of the anemia factor and that its working mechanism differed from that of all other vitamins. The discovery of Castle, decisive for the entire research of anemia, that not the anemia factor as such, but only after coupling with the hormone-like, endogenous factor, secreted from the gastric wall, unfolded its activity in the organism, and that it was stored in the liver, resulted in two possibilities for the development of hyperchromatic anemias:

1. The lack of the endogenous factor with sufficient supply of the anemia factor,
2. Insufficient offering of the anemia factor with production maintained of the endogenous principle of the gastric juice.

The first modus leads to the development of genuine pernicious anemia—hyperchromatic. The second of greatest interest in this discussion, (usually combined with the lack of all other factors of the Vitamin B_2 complex), is followed by the development of megalocytic, yeast-curable anemias, which appear under various conditions either alone or more frequently with the other symptoms of deficiency of the Vitamin B_2 complex. To enter into the physiology of the anti-pernicious anemia principle resulting from coupling of the gastric juice and anemia factors, and the coordinate deficiency disease, the pernicious anemia, would transgress the limits of this discussion. Proceeding we are occupied only with the anemia factor as such, and the manifestations resulting from the lack of it in the food (under normal production of gastric juice).

From the fact that only such materials as are rich in Vitamin B_2 acquire pernicious anemia efficacy by incubation with gastric juice, Castle and Strauss have concluded that the anemia factor and Vitamin B_2 are identical. Since the complex character of this vitamin has been ascertained, the question of identity has been repeatedly investigated and it has been proven that the anemia factor occurring in various foods and the growth and pella-

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gra-active part of the Vitamin B_2 complex are of like origin (egg white, Wills-Naish; yeast, Diehl-Kühnau; liver, Block-Farqhar). However, the combined occurrence of the anemia factors and the other Vitamin B_2 components and the very frequent combination of hyperchromatic anemias and other signs of lack of Vitamin B_2 complex prove that the anemia factor is closely related to the other factors of the Vitamin B_2 complex.

Chemistry. The chemical character of the anemia factor is not known. It is ascertained that it is soluble in water, 80% alcohol and acetone, and that it is very heat-stable even with alkaline reaction (Reimann).

Determination. The determination of the anemia factor is impossible directly, but only with the aid of Castle's original experiment, by conversion into the anti-pernicious anemia principle. The testing proceeds best with a man ill of pernicious anemia by ascertaining that quantity which given parenterally evokes after 3 to 9 days a reticulocytic crisis of certain proportion, to be obtained from the erythrocytic count at the start of the investigation after the formula of Riddle. Attempts made so far to evaluate the anti-pernicious anemia principle in animal experiments have met with little success, because the experimental megalocytic anemias of the pigeon, chicken and rat used for the purpose are not complete analoga of the human pernicious anemia. Lately the healthy guinea pig which reacts upon administration of anti-pernicious anemia material with a reticulocytosis has been recommended as a test object (Jacobson). All these tests suffer from the fact that the reticulocytic crisis does not represent a specific reaction of the anti-pernicious anemia principle. Other test reactions proposed for this reason (for example, methemoglobin test of Duesberg) have, however, not been confirmed. Assured quantitative data of content in foodstuffs and for the need of man of anemia factor cannot, therefore, be given at the present time.

Occurrence. The anemia factor is found chiefly in yeast, muscle and liver, in the latter in much greater amount than the finished anti-pernicious anemia material (Reimann). The therapeutically employed liver extracts contain it, also, though apparently not so copiously as whole liver. It is found furthermore in chicken eggs (especially in the egg white), malt extracts, barley, wheat germs, wheat grit and rice bran (Singer, Rhoads-Miller, Ungley, Castle). If the content of the anemia factor is put at 100, that of liver is 100-200, of muscle 5 and of eggs 2.5 (Reimann-Fritsch, Bomskov).

Statements about the occurrence of the anemia factor in other organs (kidney, spleen) are unreliable. The anemia factor contrary to the anti-pernicious anemia factor is absent in yeast, musculature and chicken eggs. The successes occasionally observed from yeast treatment in pernicious anemia (Goodall, Ungley) may perhaps be based upon the condition of the gastric juice still containing some endogenous factor in these cases.

Behavior in the Organism. The anemia factor taken in with the food is coupled in the human stomach and duodenum with the gastric juice

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principle as the anti-anemia factor and as such stored in the liver. Since liver and muscle contain abundant free anemia factor, it may be assumed that it is also absorbed without having been tied to the endogenous gastric juice principle. Besides there exists the possibility (Reimann) that it serves in the liver as a stored inactive form of the anti-pernicious anemia element, regenerated from it by auto-liver ferments and respectively, if need be, reconverted to it (analogy: glucose-glycogen economy in the liver). At any rate the coupling may also happen parenterally (Singer). In the form of anti-pernicious anemia principle the anemia factor is eliminated in the urine (Leiner); in the cow secreted in the milk (Rominger), and in the human supplied with abundant anti-pernicious anemia element (Mach) it enters by way of the placenta into the fetal organism, where it is stored in the liver (Berglund). In the hog as in man, the binding of the anemia factor occurs in the gastrointestinal tract. Therefore, if the hog is fed on a diet containing no anemia factor, a symptom-complex may be established which likens human sprue or pernicious anemia to a great extent. Indeed it may come to a disappearance of the endogenous principle in the gastric juice (Miller-Rhoads). The dog, however, does not produce any endogenous factor at all (Singer, Richter-Ivey-Meyer) and converts the anemia factor directly to hematopoiesis. In dogs there is, therefore no analogon to pernicious anemia, and the anemia of "Black tongue" is a true avitaminosis of the anemia factor (not influenced, for example, by parenteral injections of liver extract). In the guinea pig on the other hand the withdrawal of the anemia factor results in loss of weight and rapid death, while the anemia recedes in the background (Miller-Rhoads).

Phenomena of Lack of Anemia Factor. The only function that may be ascribed to the anemia factor with certainty is its influence upon blood formation. It is the mother substance of the "ripening element" formed by the action of the gastric juice principle which transmutes the embryonal to the definite type of hematopoiesis. According to the theory generally accepted today the sequences resulting from the lack of this maturing element in the organism, or its precursor in the food, consist in a reversion of the erythropoiesis to the embryonal modus, in an effusion of short-lived megalocytes of inferior value biologically, in a compensatory increase of the erythropoietic apparatus and its activity (substitution of the yellow for the red bone marrow, overproduction of short-lived cells), and finally in an intensified demand upon the blood destroying mechanisms. It comes furthermore to a bone marrow barrage, manifest by a diminution of the blood reticulocytes in spite of increased bone marrow activity, though normally the reticulocyte count runs parallel to the activity of the bone marrow. If the anemia factor or (as in pernicious anemia) the finished anti-pernicious anemia element is administered, the bone marrow barrage is removed and a discharge of reticulocytes proceeds, which, however, lasts only a short time, since the simultaneously increased bone marrow activity, and with it the production of reticulocytes, is reduced to a physiological measure. Hand in hand with this process the quality of erythrocytic production is normalized and the increased blood catabolism, gone astray, is again led into normal channels.

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Very little is known of the effect of the anemia factor or anti-pernicious anemia element upon the leucocytes. It is known only that the lack of the anemia factor in the nutriment impedes granulopoiesis and may be to such an extent that a clinical syndrome is developed of the type of agranulocytosis.

BIBLIOGRAPHY FOR VITAMIN B COMPLEX (ANEMIA FACTOR)

Castle, Science 82, 159, 1935.
Dakin-Ungley-West, Journal of Biological Chemistry, 115, 771, 1935.
Dedichen, Acta med. scand., 90, 195, 1936.
Dedichen, ebd. Suppl. 78, 250, 1936.
Powers-van Doren, Journal of Clinical Investigation, 14, 649, 1935.
Reimann et al, Z. klin. Med., 129, 659, 1936.
Roth, Klin. W., 1431, 1936.
Singer-Wechsler, Klin. W., 668, 1936.

More divisional factors of the Vitamin B_2 complex (Sprue and Cataract-preventing Factor). With advancing recognition of the nature of the diseases arising from insufficient intake of Vitamin B_2 complex it becomes more and more obvious that in the production of the physiological activity of this complex, there are still participating, besides the three vitamins described, two others, of which our knowledge is almost nil. One of them is a factor needed for normal intestinal function. The lack of it leads to inflammations of the mucosae of the mouth and intestine, and to diarrheas and fatty stools, seeming to be essentially concerned in the incidence of the clinical syndrome of sprue. The remarkably frequent coincidence of sprue and hyperchromatic anemia, and the curative action of liver and liver extract in sprue have been the reasons why the anemia and sprue-preventing factors have been considered identical up to very lately. That that is not the case recent investigations have shown, since in the usual commercial process of enrichment of anti-pernicious anemia principle of liver extracts, the sprue-preventing vitamin is partially lost (Rhoads-Miller). It occurs in yeast. Whether it has other functions to perform in the body, or what its chemical properties are, is not known. Of the fifth divisional factor of the Vitamin B_2 complex, the cataract-preventive, probably also of import to man, little more than its existence is known. Deficient supply of Vitamin B_2 complex in rats causes, in a varying high percentage corresponding to the composition of the main diet, a cloudiness of the lens and inflammations of the cornea (Day-Langston-O'Brien, Sen-Das-Guha, Guida-Yudkin, von Drigalski). These eye symptoms are not relieved with Vitamin A. That there is involved here a lack of a specific diet factor Bourne and Pyke have been able to show. The richer the food is in carbohydrates the greater the need of Vitamin B_1 as well as the cataract-preventing factor. Cataract may be produced in experimental animals solely by feeding large quantities of lactose or galactose without reducing the supply of vitamins (Mitchell). The disturbance of the lens metabolism causing cataract formation con-

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sists in loss of reduction power of the lens substance (Ray-Györgyi-Harris). This disappearance of reducing power may be prevented by additional feeding of egg white and liver, but not by additions of Vitamin B_2 and B_6; these foodstuffs contain, therefore, the anti-cataract factor. Since the power of reduction of the lens is dependent upon its content of ascorbic acid, there ensues interesting relationships between the Vitamin B_2 complex and Vitamin C.

BIBLIOGRAPHY FOR VITAMIN B COMPLEX (SPRUE AND CATARACT-PREVENTING FACTOR)

Bourne, Pyke, Biochemical Journal, 29, 1865, 1935.
Day et al, Journal of Nutrition, 7, 97, 1934.
Day et al, Journal of Nutrition, 12, 387, 395, 1936.
Napier, Lancet, II, 679, 1936.
Tschesche, Wolf, Z. physiol. Chem., I, 244, 1936.
Subbarow, Jacobson, Journal of Biological Chemistry, CII, 114, 1936.
Wills, Clutterbuck, Evans, Lancet, I, 311, 1937.

CLINICAL DISCUSSION

1. Symptoms of deficient supply of the Vitamin B_2 complex in Man.

The close mutual relations and the common occurrence of the components of the Vitamin B_2 complex render it impossible to arrange the symptoms of the single factors of the Vitamin B_2 complex in man separately, which forces a general discussion of all of them. On the other hand the components of the Vitamin B_2 complex are not contained in all foodstuffs in the same quantitative relationship. An equalized lack of all divisional factors cannot be expected therefore from a Vitamin B_2 complex poor nutrition. It is found that in relation to the feeding, one of them may be lacking to a greater extent than the others. In addition the need of the single factors varies according to individual conditions. It follows that the symptoms of the Vitamin B_2 complex deficiency may combine in a most varying manner and intensity and appear in the form of several different clinical syndromes, which, however, are joined together by flowing transitions. To understand the incidence of these clinical pictures and to adjudge the scope of indications of the therapy of the Vitamin B_2 complex, it is necessary to recognize the specific symptoms of the Vitamin B_2 complex deficiency diseases, many of which individually appear as signs of a Vitamin B_2 complex hypovitaminosis.

(a) The gastrointestinal symptoms arising in the course of the various forms of B_2 complex avitaminosis merit special interest for the reason that they may not only be the sequence but also the cause of a lack of Vitamin-B_2 complex. It is known that pellagra and megalocytic anemias develop with disease of the gastrointestinal tract, particularly when they are associated with continued diarrhea. This applies also to rat sprue (Rominger), which may be cured without being specially supplied with vitamin only relieving the diarrhea by feeding toasted bread. Even with a sufficient supply of vitamin the diarrhea in these cases inhibits the

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absorption of Vitamin B_2 complex and is thus the cause of the development of the avitaminosis. Because of the fact that the lack of Vitamin B_2 in itself may early incite gastrointestinal disorders, there may arise under certain circumstances a vicious cycle endangering life. In a single case it is often impossible to decide whether a gastrointestinal affection is cause or consequence of simultaneous Vitamin B_2 complex avitaminosis. For this purpose vitamin therapy (giving parenterally liver extract in high dosage) is combined with symptomatic treatment of the gastrointestinal disturbance. A manifestation of chronic Vitamin B_2 deficiency is the more or less complete loss of hydrochloric acid in the stomach, which was observed, for example, in almost 100% of all cases of pellagra (King), but was also observed as a sign of a suboptimal intake of Vitamin B_2 by country folk of northern Sweden (Schiödt, Odin). Experimentally achylia may be produced in swine by feeding rations short of Vitamin B_2 complex (Miller-Rhoads). In rats multiple hemorrhages of the intestine are characteristic symptoms. Likewise in the genesis of human intestinal bleeding and ulceration, deficit of B_2 complex takes an active part (Schiödt). In pellagra bloody stools are frequently observed. The Vitamin B_2 complex is indispensable for the normal function of the mucosa of the colon. Failing supply or failing absorption of the Vitamin B_2 complex are the chief causes of the incidence of chronic ulcerative colitis roentgenologically demonstrated which very frequently develops secondarily because of a resorptive disorder (Mackie). The exceedingly frequent combination of ulcerative colitis with other typical symptoms of lack of Vitamin B_2 complex (stomatitis, glossitis, pellagrous skin changes, anemia and cessation of growth in children) points to the etiological importance of the deficiency of the Vitamin B_2 complex for the incidence of colon pathology. By intramuscular or intavenous injections of liver extracts, which simultaneously remove the other deficiency symptoms, the colonic lesion is favorably and with astonishing rapidity influenced. Because of failure of resorption, liver and yeast given perorally are frequently unsuccessful. Colitis ulcerosa, however, is only a specific phenomenon of the intestinal affection resulting from a deficiency of the Vitamin B_2 complex which may manifest itself in profuse and continued diarrheas and disturbances of fat resorption. The stools in such cases are fermenting strongly, vesicular, yellow and mostly fatty (steatorrhea). These fatty diarrheas are classical symptoms of a Vitamin B_2 deficiency and, as such, constituents of the clinical syndromes of sprue, celiaca, and goat milk-anemia. They are often seen in pellagra (Neusser, Morawitz-Mancke, Nauck). In dogs and swine fatty diarrheas may be produced experimentally by withdrawal of the Vitamin B_2 complex (Miller-Rhoads). Probably many of the fatty diarrheas, diagnosed as purely pancreatogenic result in reality from a deficiency of Vitamin B_2 complex and must be treated accordingly.

(b) Among the diseases in the genesis of which the lack of the Vitamin B_2 complex is active, there appear almost regularly changes of the tongue and of the mucosa of the mouth. An early symptom of Vitamin B_2 complex avitaminosis in man, is the hypertrophic inflammation of the anterior one-third of the tongue (strawberry tongue) which frequently pro-

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ceeds, as the disease progresses, to a diffuse glossitis with aphthous, at times gangrenous, ulcerations finally ending up in a smooth atrophy. Such tongue changes as well as individual lesions appear (Ness-Thayson) as in company of ulcerative colitis (Mackie), sprue, pellagra and pernicious anemia. (The question however in the latter case as to how much is due to lack of Vitamin B_2 complex has not quite been answered.) In exactly the same form as in man on a Vitamin B_2 complex-free diet (Findlay, Hutter-Middleton-Steenbock, Rhoads-Miller) they may be obtained experimentally in dogs and rats. These investigators have given to the dog disease, which must be considered an analogon of human pellagra, sprue and pernicious anemia, the name "Black tongue". Glossitis in man following a long continued diet inadequate in all of the B vitamins subsides rapidly when B_2 complex preparations of yeast or liver are given (Elsom, Miller-Rhoads). Almost always with the glossitis simultaneous inflammations of the mucosa of the mouth appear. They are localized stomatitides with aphthae, pigmentations and salivation, spreading diffusely and leading to necroses and ulcerations. The glossitis frequently seen with colitis, sprue, and pellagra may likewise experimentally be produced with nutriment free of the Vitamin B_2 complex. In its gravest form it makes its appearance in dogs as the so-called "acute black tongue". It exhibits a pronounced, by the synchronous loss of neutrophils, yet more marked similarity with the mouth changes of human agranulocytosis (Miller-Rhoads). Grave stomatitides in man, though they may not occur combined with other symptoms of a lack of Vitamin B_2 complex, for example, scarlet fever, are favorably influenced with peroral doses of yeast or with local applications of yeast solution (Widenbauer).

(c) To fix the skin changes characteristic of a Vitamin B_2 complex avitaminosis is not a simple matter since pellagra is a complex deficiency disease and since with the other Vitamin B_2 complex deficiences the skin is involved only occasionally. However, it is safe to state that the pellagra erythema (appearing also in colitis ulcerosa), a strictly symmetrical localized dermatitis, developing in its course pigmentations, atrophies and follicular hyperkeratoses, is a true symptom of a Vitamin B_2 complex deficiency. In the absence of other skin changes, loss of hair and nail defects point to a latent lack of Vitamin B_2 complex, which is easily relieved by a respectively reversed diet. The symmetric disposition of the dermatitis is also a characteristic sign of rat pellagra, an experimental Vitamin B_2 complex disease.

(d) What applies to the skin changes is similar to that of the nervous symptoms of the Vitamin B_2 complex avitaminosis, which stand out in the foreground of the clinical picture in the dog, but arise in man only under certain conditions. Phenomena of irritation, spasms and increased reflexes characterizing the second stage of pellagra in the central nervous system, may develop independently of other pellagra symptoms and are not then recognized as manifestations of an insufficient Vitamin B_2 supply, especially when they are not marked. The increased reflexes arising from deficient provision of the B vitamins disappear promptly upon additions

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of Vitamin B_2 complex (Elsom). Muscular weakness, general hyperirritability, sleeplessness and depression are signs of a latent lack of Vitamin B_2 (Rud) or of an incipient pellagra (Spies) and react well upon administration of yeast. Another peculiar group of symptoms of chronic Vitamin B_2 deficiency consist in vasomotor-trophic changes of hands and feet (acrocyanosis). They are not only seen in pellagra but also in other diseases, in the genesis of which a lack of the Vitamin B_2 complex is active (for example acrodynia and lepra). The fact that a chronic acrocyanosis with trophic changes develops sometimes in sequence of gastrointestinal disorders (Stokvis, Palma, Heymans, Cheinisse) point likewise to the fundamental deficit of the Vitamin B_2 complex. Equally the necrotic ulcers of the mucosa of the mouth in pellagra and black tongue are of a trophic nature (Lillie).

(e) Megalocytic hyperchromatic anemias or anemias presenting transitions to hyperchromatic anemias are observed in all human diseases resulting from deficient Vitamin B_2 complex supply (in sprue, celiaca, goat-milk-anemia, ulcerative colitis, pregnancy complications in the tropics and frequently in pellagra). At the same time there is seen a more or less complete transformation of the yellow bone marrow to the red—the active marrow. The hyperchromatic deficiency anemias react promptly upon yeast and liver administration in sufficient dosage. Anemias of the pernicious type may be experimentally produced by withdrawal of the Vitamin B_2 complex or of the anemia factor in dogs, swine and rats. Vitamin B_2 complex deficiency anemias (like pernicious anemia) usually run along with high rate of diminution of neutrophilic leucocytes at times, which indicates that the Vitamin B_2 complex is also of importance for the granulopoiesis. Such a leucopenia with relative lymphocytosis is frequently observed in pellagra (Wasserman deems it a characteristic pellagra symptom) and more often still in sprue. In extreme cases it may come to aleukia-like syndromes.

2. The diseases of Vitamin B_2 Complex Deficiency in Man

(a) Pellagra. We have positive assurance today that pellagra is not a true Vitamin B_2 complex avitaminosis, but a complex deficiency disease, in the genesis of which there are besides the lack of the Vitamin B_2 complex also perhaps the lack of participating Vitamin H and of vital amino acids. Since Vitamin H is required for the normal evaluation of egg white, and because of its lack in the diet certain kinds of nutrient albumen act as toxins (dermatitis-producing), the old corn theory, for important reasons lately revived by Chick, according to which, among corn-eating folks pellagra is due to a toxic effect of spoiled corn or its proteins respectively, might well fit in with the conception of a Vitamin H deficiency. Though in Italy, the classical pellagra country, the disease has almost entirely disappeared, it is still responsible in the southern states of the United States and in Roumania for thousands of lives lost yearly (1933 in the U. S., 4000; in Roumania 2800 deaths). Pellagra is widely spread in Jugoslavia and in southern Russia, and it is of interest that its sporadic appearance is not at all rare in Germany, Austria, Switzerland, Scan-

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dinavia and England. Staehelin and F. Meyer justly stress that light and atypical cases of pellagra are overlooked and not recognized. This applies particularly to cases in which the skin lesions are continuously or intermittently absent (pellagra sine pellagra). The determination of other symptoms of lack of Vitamin B_2 complex leads here to a proper diagnosis. The recognition, especially of the widely spread latent pellagra (Rud), evidenced in sleeplessness, conditions of irritability, adynamia, loss of weight and hair and nail defects, may frequently be arrived at only by giving successfully a diet rich in Vitamin B_2 complex. In accord with our knowledge today two forms of pellagra must be distinguished. First, the primary resulting immediately from qualitatively insufficient nutrition, presenting a true deficiency disease, and then the secondary, in which the supply of vitamins of the B_2 complex is satisfactory, but the absorption of them is stopped by gastrointestinal disease. As a complication pellagra is seen in colitis, cancer of the intestinal tract, intestinal tuberculosis, ileus, dysentery, biliary diseases, ulcers of the digestive tract and following gastrointestinal operations (Turner, Urbach, Meyer, Thannhauser, Chotzen, Simpson, Morawitz-Mancke). These distinctions carry therapeutic importance, because the primary form is readily improved by supplying nutriment rich in the Vitamin B_2 complex, while a successful treatment of secondary pellagra is only possible by parenterally administered preparations containing the Vitamin B_2 complex.

> When Flinker declined recently to divide pellagra into a primary and secondary form, he disregarded the fact that gastrointestinal phenomena may well be cause and sequence of a Vitamin B_2 deficiency.

It is remarkable, and for therapeutical purposes significant, that the cases observed in Mid-Europe are almost always of secondary nature. Pellagra of alcoholics occurring in Germany, Switzerland and in the United States are secondary, because of the digestive disorders associated with anorexia resulting from alcoholism (Aykroid, Zimmermann-Cohen-Gildea). A specific form of secondary pellagra proceeding with bone atrophies and disturbances of the endocrine and adrenal function is the "symptom-complex of Freiburg" (Thannhauser, Froboese-Thoma). It is still uncertain whether other adrenal changes seen in pellagra are also sequences of the lack of Vitamin B_2.

The strongest support of the vitamin deficiency theory generally recognized today is the fact that the administration of the Vitamin B_2 complex in proper dosage given for a sufficient length of time, brings recovery from whatsover form of pellagra. Since pure preparations of Vitamin B_2 complex, and especially the P-P factor are not available on the market, a generous dietary supply of the B_2 complex is necessary for the purpose, and *that* in the form of liver, fish, milk, eggs, yeast, peas, tomatoes and cabbage. If the need of the Vitamin B_2 complex is urgent, yeast extracts rich in the Vitamin B_2 complex (Vitex, Marmite, Vigex) per os, or liver extracts (Campolon, Lilly 343, not Hepracton!) parenterally, may be given in addition. The application of liver extract, successfully employed by

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Spies and Flinker, is specifically indicated in the presence of serious gastrointestinal symptoms. In latent or incipient pellagra it suffices to give besides fish and eggs, 3 times a day 1 teaspoonful of brewer's yeast, in lighter cases with moderate skin and mouth symptoms one or two tablespoonfuls of dry yeast or liver extract or extract of wheat germs, best in iced milk, according to the severity of the case up to four times daily (Spies, Ruffin-Smith, Ramsdell-Magness) are prescribed. In case the gastrointestinal disorders are considerable or if the disease has progressed much, intravenous or intramuscular injections of liver extract (Campolon) are made 5 times daily. Occasionally even in secondary pellagra one succeeds without injections. Thus Simpson cured pellagra following gastric resection with peroral doses of marmite and a Vitamin B_2 complex preparation of egg yolk. With pellagra of alcoholics the Vitamin B_2 complex therapy is also successfully pursued in the manner described above (Zimmermann-Cohen-Gildea, Spies-de Wolf, Meyer).

It is emphasized by the contestants of the vitamin deficiency theory that yeast per os is often ineffective (Flinker). That is explained, however, by the fact that the gastrointestinal disturbances associated frequently with pellagra impede the absorption of the yeast vitamins. Therefore, a parenteral therapy of the Vitamin B_2 complex is necessary in such cases. Also the fact of lactoflavin injections not influencing pellagra does not militate against the vitamin deficiency theory, because it is not Vitamin B_2, as known, but Vitamin B_6 that represents the real pellagra preventive.

The best pellagra prophylaxis applied in the U. S. and in Italy from governmental initiative, consists in propaganda urging nourishment rich in the Vitamin B_2 complex, as named above. The use of this prophylaxis so successful in these respective countries would reduce the incidence of pellagra likewise in mid and northern Europe, but most decidedly in the closed institutions and asylums (Mterna).

(b) Sprue. Flowing transitions join pellagra and sprue. The latter differs from the former in the gastrointestinal manifestations with steatorrhea of a severe order, the hyperchromatic anemia dominating the clinical syndrome, while the skin and nervous symptoms recede in the background. Stomatitis and glossitis are usually more marked than in pellagra. Though sprue is chiefly a tropical disease, it does occur, not infrequently, in our latitudes and especially in Scandinavia (Hess-Thaysen, Engel, Thorfinn, Duenner-Hirschfeld-Geraldy). Just why the lack of the vitamin B_2 complex is expressed once as pellagra and then as sprue cannot be answered precisely as yet. Besides the constitutional element, the fact that the inferior valence of the nutriment inciting pellagra and sprue does not extend over the same divisional factors of the Vitamin B_2 complex seems to be decisive. In addition sprue also is not a single deficiency disease, but a mixed one of the Vitamin B_2 complex and an avitaminosis C (Slot). It is still more difficult in sprue than in pellagra to decide whether the gastrointestinal phenomena heading the clinical syndrome are of primary or secondary nature. Though the real sprue symptoms, steatorrhea and anemia, usually develop in association with pre-existing gastrointes-

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tinal disease, the Vitamin B_2 complex therapy brings about regularly in both human and also rat sprue recovery of the intestinal lesion (Rhoads-Miller). Therefore, an eternal vicious circle must be expected in sprue also.

Sprue not only shows relationships to pellagra but to pernicious anemia, and is often conceived of as a connecting link between the two diseases. In many cases of tropical sprue the factor of Castle is lacking in the gastric juice and then the otherwise successful yeast treatment fails. On the other hand, with us, in cases of pernicious anemia there are seen occasionally sprue-like fatty diarrheas. The clinical picture of "black-tongue" producible by Vitamin B_2-complex-poor feeding in dogs, unites in itself the symptoms of sprue, pernicious anemia and pellagra, while the rat sprue (Rominger) is more analogous to the goat-milk anemia. Manifestations of bone atrophy, frequent in sprue, and osteoporosis with decreased blood calcium and symptoms of tetany, are possibly due to disturbances of calcium absorption. In the "Freiburger symptom complex", a species of pellagra, the bones are calcium deficient and susceptible to spontaneous fractures. Supply of Vitamin B_2 complex reverses calcium metabolism by normalizing gastrointestinal function. In the presence of signs of decalcification in the bone, it would be well to prescribe not only calcium and viosterol, but also provide nutrition rich in the Vitamin B_2 complex.

The character of sprue as an avitaminosis reflects the unfailing success of the treatment with the Vitamin B_2 complex. Besides prescribing a mixed diet it suffices to give in light and moderate cases Vitamin B_2 complex concentrates in the form of Vitox or Marmite (Castle-Rhoads). In severe fatty diarrheas peroral yeast often fails. In such event intramuscular or intravenous injections of liver extract (Campolon, hepatrat pro infusione) are made several times daily with success even in the gravest of cases.

(c) Celiac Disease. *(Heubner-Herter intestinal Infantilism, Idiopathic Steatorrhea)* is in our latitudes a sickness of children, a species of sprue, arising secondary to a specific disease of the large intestine. As early as 1925 Reyher perceived it to be an avitaminosis. It exhibits the same symptoms as sprue and is merely differentiated by cessation of growth, and inclination to multiple overdistensions of the gut forming numerous fluid levels. Occasionally such conditions appear in adults (Wendt, Lister, Bennet, et al). Hess-Thaysen, however, maintain that celiaca and sprue are the same disease. Celiac disease is likewise improved by the use of preparations of yeast containing the Vitamin B_2 complex (Vitox, Marmite, 10-15 gm. per day or Levurinose, 1 teaspoon 3 times a day), or liver (Fancony, Rhomer, Vaughan-Hunter, Widenbauer). Györgyi recommends giving Vitamin B_2 complex in the form of a soup of 120-200 gm. ground or cooked beef heart (or besides 50-150 gm. heart muscle digested with papain for one-half hour at 50 degrees.)

(d) Goat-Milk-Anemia holds, as conceived of today, a unique position in that it unites the symptoms of an isolated deficiency of the anemia factor, as well as of a deficiency of iron. The high B_2 and B_6 content of goat-milk argues against an avitaminosis Vitamin B_2 complex being concerned

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in goat milk anemia. However, by feeding goat milk to young rats a clinical syndrome may be produced corresponding to sprue (Rominger) which points to a kinship of goat milk anemia to other forms of a Vitamin B_2 complex avitaminosis. Indeed goat milk anemia in the child is improved by food containing all of the components of the Vitamin B_2 complex, for example, liver; (50 gm. of raw calf's liver and 1 ampule of Compolon daily Györgyi), yeast (Cenovis extract 20-30 gm. a day), beet root extract (Aron), and wheat grits and cow's milk; that holds good also in rats (Rominger). Complete recovery, however, results only when substances containing Vitamin B_2 complex (or anemia factors) are combined with preparations of iron (Györgyi, Haase, Wolff-van Eekelen, Parsons-Hickman). The great success of the liver treatment depends partially perhaps upon the heavy iron content of the liver preparation.

(e) Tropical B_2 Complex Avitaminosis. In China, Indochina and Western Africa, apparently also in Europe (London abortive case of Goodwin) occurs a Vitamin B_2 complex deficiency disease, sharply distinguished from pellagra, yet seemingly related with symptoms as follows: very painful oozing crust forming eczemas of the angles of the mouth and of the scrotum, nervous disorders (ataxia, paraesthesias, increased reflexes and disturbances of sensation) and retrobulbar optic neuritis with atrophy of the nerve (progressive diminution of vision) (Landor-Pallister). This symptom arises in natives living on a one-sided, limited diet, especially in prisons and schools. By giving 15 gm. Marmite daily or 100 gm. brewer's yeast or 250 gm. cooked liver, recovery is obtained unless the disease has progressed too far. The character of the nervous symptoms infers a participation of a Vitamin B_1 deficit. Hyperchromatic anemias and diarrheas are absent.

3. Other Spheres of Therapeutic Application of Vitamin B_2 Complex

(a) Lepra. As regards some symptoms there exists a certain similarity between pellagra and lepra. Numerous investigations have shown that the development of lepra is favored by insufficient supply of the Vitamin B_2 complex. The skin and intestinal symptoms of experimental rat lepra are increased by lack of the B vitamins (especially Vitamin B_2 complex) and their incubation period is shortened (Lamb, Badger-Sebrell). The food of lepra patients is almost constantly of inferior value in Vitamin B_2 complex (Basu). Yeast improves symptoms of lepra in many cases. In British Sudan the natives are the more resistant to lepra because of the milk they consume (Atkey); milk is well-known to be rich in the Vitamin B_2 complex, and one of the best pellagra remedies.

(b) Acrodynia (Swift-Feer Vegetative Neurosis). In this disease of childhood etiologically not quite clarified symptoms of lack of Vitamin B_1 combine with those of a Vitamin B_2 deficit. Györgyi, like Uffenheimer, points out the similarity of acrodynia and pellagra and attributes the success of liver treatment in acrodynia to the content of Vitamin B_2 complex

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of the liver. The curative effect of yeast in acrodynia is governed by its abundance of Vitamin B_2 complex with Vitamin B_1.

(c) Agranulocytosis. Miller and Rhoads made the important discovery that "acute black-tongue", producible in dogs by a certain deficient diet (deficient in the Vitamin B_2 complex) likened in all particulars the human agranulocytosis (ulcerative stomatitis inclined to gangrene, extreme granulopenia and typical changes of the bone marrow). A Vitamin B_2-complex-free feeding leads also to an agranulocytosis in rats, which disappears when yeast is supplied (Day-Langston Shukers). It is possible that a lack of Vitamin B_2 complex (and specifically of the anemia factor) participates in the origin of agranulocytosis and aleukia (panmyelophthisis). A granulopenia (leucopenia with relative lymphocytosis) is present in all diseases, in the genesis of which an insufficient supply or a defective assimilation of the anemia factor is engaged, thus in sprue and in the various megalocytic anemias, pernicious anemia especially, and in pellagra very frequently (Anding-Sinain, Chotzen, Mollow, Nauch, et al). In this connection it is remarkable that sprue, pernicious anemia and both riocephalus and the goat-milk anemias may pass on to aleukia (Buettner, Schultz). The leucopenia so often found by Wendt in chronic gastroenteritis likely depends therefore upon a disturbance of absorption of the anemia factor normally needed for leucopoiesis. That corresponds with the fact that agranulocytosis and aleukia develop occasionally as sequellae of chronic gastrointestinal affections, for example, following typhoid (Schultz, Blackie) or in alcoholism (Naegeli) (as has been stated, alcohol is a frequent cause of a secondary Vitamin B_2 complex avitaminosis). Supply of the anemia factor or the pernicious anemia stuff in sprue, pernicious anemia and pellagra relieves the anemia as well as the leucopenia. The action of the anemia factor improving granulopoiesis explains perhaps the effective results of liver therapy in agranulocytosis (von Bonsdorf, Fora-Sheaf-Trimmer, et al) and aleukia (Matthes et al). The treatment has to be conducted with very large doses of extract (several times daily, quantities equal to 100 gm. liver) while the toxic recurrent aleukia occurring subacutely (hypoleukia) readily reacts to small doses of Campolon. The relationships, revealed by these observations, between agranulocytosis or aleukia and the Vitamin B_2 complex avitaminosis urgently need further work and enlightenment.

(d) Keratitis and Optic Neuritis. The keratitis and cataract-preventing factor of the Vitamin B_2 complex seems to be of importance to man also. Thus in celiac disease due to lack of Vitamin B_2 complex opacities of the lens frequently occur (Bennet-Hunter-Vaughan). In the Philippines in pregnant and nursing women, lesions of the cornea have been observed, which disappeared upon supply of the Vitamin B group (not of Vitamin A) (Ayuyae). However, it is difficult to decide if such keratitides do not partially depend upon a lack of Vitamin B_1 (neuritis of the first trigeminal branch). On the other hand the retrobulbar optic neuritis is a symptom frequently associated with pellagra (Stepp-Voit, Cronin, Levine). As mentioned it is also a symptom of the tropical Vitamin B_2 complex avita-

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minosis. It may be cured even if it occurs alone by supplying B vitamins (Shatid). The importance of the Vitamin B_2 complex for the prevention and cure of diseases of the eye does not seem to be sufficiently recognized.

(e) Heavy Metal Intoxications. Jacoby and Eisner affirm that an otherwise fatal uran intoxication in rabbits ends in recovery if the animals are fed generously with the Vitamin B_2 complex. This finding gives rise to the thought that the Vitamin B_2 complex may perhaps be drawn upon successfully for the treatment of human heavy metal poisoning (lead).

OTHER VITAMINS OF THE B GROUP

For the maintenance of normal health of man there are besides the vitamins B_1 and B_2 complex still other vitamins of the Vitamin B group needed. On a long continued otherwise normal diet, in which all of the B vitamins are lacking there develop in man, besides the manifestations of a deficiency of Vitamin B_1 and of the Vitamin B_2 complex, disease symptoms which do not disappear upon supply of Vitamin B_1 and Vitamin B_2 complex but only when all B vitamins are added in the form of yeast. They are, chiefly gastrointestinal symptoms (feeling of fullness, constipation, roentgenologically visible gastric atony and failing peristalsis) and further reduced sensibility and prolonged clotting time (Elsom). Which vitamins are necessary for the prevention and relief of these symptoms is not known as yet. Vitamin B_4, the lack of which in animals produces ataxia, disturbances of coordination and a spastic gait, is said to be of importance for man as well. Its absence in the nutriment, according to the opinion of some authors, is co-responsible for the development of beriberi, and might effect the disturbances of sensation, but that has not been confirmed. The gastrointestinal symptoms depend perhaps upon a lack of Vitamin B_7, which is required for the normal function of the intestinal mucosa and musculature. It appears that these little known vitamins of the B group, still supplement Vitamin B_1. In cases of Vitamin B_1 deficiency not responding upon administration of highly purified Vitamin B_1 preparations in a manner expected, it is recommended therefore to prescribe yeast (brewer's or dry) which contains all the vitamins of the Vitamin B group.

BIBLIOGRAPHY FOR VITAMIN B GROUP

Adie, Brain 55, 97, 1932.
Alt, Journal Clin. Invest., 14, 649, 1935.
Atkey, International Journal of Leprosy, 2, 193, 1934.
Aykroyd, Nutritional Abstract Reviews, 3, 337, 1933.
Aykroyd, Alexa, Nitzulescu, Arch. Roum. path. exp., 8, 407, 1935.
Aykroyd, Krishnan, Indian. Journal of Medical Research, 24, 411, 1936.
Ayuyao, Journal of Philippine Island Medical Association, 13, 158, 1933.
Badger, Sebrell, Public Health Reports, 50, 855, 1935.
Barré et al, Rev. neurol., 542, 590, 1934.
Bazu, Z. Vitaminf., 3, 194, 1934.
Bennett, Hunter, Vaughan, Quarterly Journal of Medicine., N. S. 1, 600, 1932.
Blankenhorn, Spies, Journal of the American Medical Association, 107, 641, 1936.
v. Bonsdorff, Kl. W., 1079, 1934.
Boshamer, M. m. W., 2045, 1935.

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Bradley, Seych. Ann. med. Rep., 1928.
Brouwer, Nederl. Tijdschr. Geneesk., 43, 1933.
Cardona, Riv. di patol., 48, 188, 1936.
Chick, Lancet, II, 341, 1933.
Corr, Annals of Internal Medicine, 9, 1182, 1936.
Cronin, Journal Nervous and Mental Diseases, 35, 78, 1933.
Davidson, British Medical Journal, I, 100, 1933.
Davidson, Nutritional Abstract, Reviews, 3, 901, 1934.
Day, Langston, Shukers, Journal of Nutrition, 9, 637, 1935.
Elsom, Journal of Clinical Investigation, 14, 40, 1935.
Fanconi, Intest. Infantilismus, Berlin, 1928.
Findlay, Journal of Pathology and Bacteriology, 1, 31, 353, 1928.
Flinker, Erg. inn. Med., 49, 522, 1935.
Froboese, Thoma, Z. klin. Med., 124, 478, 1933.
Fullerton, Innes, Lancet, II, 790, 1936.
Goodall, Slater, Edinburgh med. Journ., N. S. 43, 368, 1936.
Goodwin, British Medical Journal, II, 113, 1934.
Gowlland, British Medical Journal, II, 277, 1935.
Györgyi, Kl. W., 1241, 1933.
Haase, Mschr. Kind., 60, 241, 1934.
Hansen, V. Staa, Die einheim. Sprue, Leipzig, 1936.
Hassin, Thomason, Journal of Nervous Diseases, 80, 430, 1934.
Haug, Mschr. Psych., 85, 126, 1933.
Hess-Thaysen, Non-tropical Sprue, Kobenhavn, 1932.
Hutter, Middleton, Steenbock, Journal of the American Medical Association, 101, 1305, 1933.
Jacoby, Eisner, Biochem. Z., 268, 322, 1934.
King, Journal of the American Medical Association, 101, 576, 1933.
Lamb, Journal of Biological Chemistry, 109, LI, 1935.
Landor, Pallister, Transactions Royal Society of Tropical Medicine, 29, 121, 1935.
Levine, Arch. Ophthalm., 12, 902, 1934.
Lichtenstein, Nederl. Tijdschr. Geneesk., Nr. 2, 1936.
Lille, Bulletin National Institute of Health, 13, 162, 1933.
Lucksch, M. Kl., 159, 1937.
Ludwig, Schweiz. m. W., 473, 1936.
Mackie, Journal of the American Medical Association, 104, 175, 1935.
Mac Leod, British Medical Journal, I, 352, 1930.
McLester, Journal of the American Medical Association, 95, 719, 1930.
Materna, M., Kl., I, 708, 1935.
Matthes, Dt. Arch. klin. Med., 68, 180, 1937.
Meyer, Kl. W., 1811, 1933.
Miller, Rhoads, Proceedings of the Society of Experimental Biology, 30, 540 (Fettdiarrhoen), 1933.
Miller, Rhoads, Journal of Clinical Investigation, 14, 153 (Achylie), 1935.
Miller, Rhoads, Journal of Experimental Medicine, 61, 173, (Glossitis, Agranulozytose), 1935.
Miller, Rhoads, American Journal of Medical Science, 191, 453, (Sprue), 1936.
Moore, Ann. trop. Med., 28, 295, 1934.
Nicholls, Ind. Med. Gaz., 61, 241, 1934.
Odin, Acta med. Scand. Suppl., 10, 59, 1935.
Parsons, Hickman, Archives of Diseases of Childhood, 8, 95, 1933.
Petri, Wanscher, Hosp. tid., 79, 1003, 1936.
Plum, Thomsen, Ugeskr. Laeger, 1062, 1936.
Ramsdell, Magness, American Journal of Medical Science, 185, 568, 1933.
Rhoads, Miller, Journal of Experimental Medicine, 58, 585 (Glossitis), 1933.
Rhoads, Miller, Journal of the American Medical Association 103, 387, (Sprue), 1934.
Rice, Archives of Pediatrics, 53, 626, 1936.
Rietschel, Ernährung, 1, 127, 1936.
Rohmer, Bull. Soc. Pédiatr., 28, 128, 1930.
Rohrer, Helv. Med. Acta, Nr. 5, 1936.
Romberg, Schaltenbrand, D. m. W. (im Druck), 1937.
Rominger et al, Z. exp. Med., 89, 786, 1933.
Rominger et al, Kl. W., 149, 1935.
Ross, Trans. Roy. Soc. Med. Hyg., 30, 1936.

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Rud, Hosp. tid., 513, 1934.
Ruffin, Smith, American Journal of Medical Science, 187, 512, 1934.
Sauer, Jb. Kind., 80, 148, 1936.
Schiödt, Acta med. Scand., 84, 453, 1934.
Schultz, Kongr. inn. Med., 179, 1935.
Schütte, Lohmann, Sprenger, zit. Pharma-Medico, 5, 175, 1937.
Scott, Annals of Tropical Medicine, 12, 109, 1918.
Simpson, Quarterly Journal of Medicine, N. S., 4, 191, 1935.
Spies, Journal of the American Medical Association, 104, 1377, 1934.
Spies, Journal of the American Medical Association, 105, 1028, 1935.
Spies, de Wolf, American Journal of Medical Science, 186, 521, 1933.
Strachan, Practitioner, 59, 477, 1897.
Thannhauser, M. m. W., 291, 1933.
Tschesche, Wolf, Z. physiol. Chem., I, 244, 1936.
Uffenheimer, Mschr. Kind., 51, 123, 1932.
Waltner, Mschr. Kind., 30, 52, 1925.
Weller, American Journal of Digestive Diseases and Nutrition, 3, 324, 1936.
Widenbauer, M. m. W., 1071, 1935.
Wills, Lancet I, 1283, 1933.
Wills, Bilimoria, Indian Journal of Medical Research, 20, 391, 1932.
Wolff, van Eekelen, Acta brev. Neerl., 5, 64, 1935.
Wyllie, Stern, Archives of Diseases of Childhood, 6, 137, 1931.
Zimmermann, Cohen, Gildea, Archives of Neurology, 31, 290, 1934.

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CHAPTER THREE

VITAMIN C

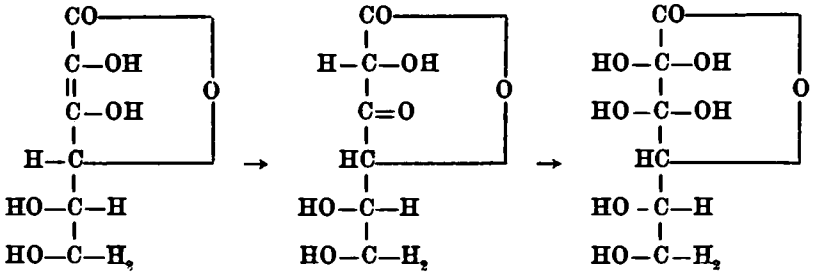
Brief historical Introduction. The Vitamin C deficiency disease, scurvy or Scharbock, has been known for some centuries as a nutritional disorder. This early recognition has resulted from experiments made in grand style, and unintentionally, by the sea-faring folk in times long past. During protracted voyages there appeared among the crew after a certain time and with great regularity, the much-feared symptoms of scurvy, which promptly subsided when there were chances on landing to get fresh vegetables and fruit. In this connection it is astonishing to note the unerring folk instinct for picking out the very vegetable product as specifically curative, which by the most modern methods of investigation have proven to yield a high vitamin content. Thus one of the earliest reports (Cartier, 1534) dealing with the management of scurvy praised the medicinal property of fresh extract of pine leaves. As a matter of fact, during the years before the synthesis of Vitamin C was accomplished, besides other sources, pine leaves have been used in the preparation of Vitamin C on a large scale. In spite of the very old knowledge of the origin of scurvy, there was still a great deal of contention about its etiology up to a few decades ago. The view that scurvy was due to a nutritional disturbance was opposed chiefly by the theory of infection, founded particularly upon the remarkable appearance of the disease in the course of grave epidemics. This observation has been positively settled and interpreted, as will be demonstrated in the following.

From the recognition of scurvy as a disease resulting from a fault in the nutrition to the isolation or synthesis of the lacking vitamin was a long road. Only at the beginning of the century could Holst and Froehlich submit the experimental proof in guinea pigs that scurvy could be produced by withdrawal of green fodder from the ordinary food. With a limited diet of pearl barley and white bread guinea pigs succumbed to a clinical syndrome similizing human scurvy. Not all animal species, however, depend upon the provision of Vitamin C. Aside from the guinea pig it is indispensable for man and the ape.

Most all animals of our zone remain well if Vitamin C is withdrawn from their nutriment, because they are able to form the specific substance themselves in the liver. The Hungarian investigator—von Szent-Györgyi —in 1928 finally succeeded in isolating Vitamin C from the beef adrenal. Recognizing the newly discovered substance as highly important for the oxidation-reduction metabolism of the plant cell, he named it at first

hexuronic acid. Later when the identity of the acid with Vitamin C was established, the new body was called ascorbic acid. Under this term it is generally known at present. Following the discovery of its constitution by several German and English Chemists, Reichenstein finally by way of the plant sugar l-arabinose succeeded in synthesizing both the d- and l-ascorbic acid, identical with Vitamin C. To manufacture ascorbic acid today the chemical industry generally employs the synthetic method.

Chemistry. Ascorbic acid is a nominally constructed hexuronic acid derivative, a 3-ketoguloacid anhydride. The pure crystalline L-ascorbic acid (empirical formula—$C_6H_8O_6$) presents a fine white powder very easily soluble in water. The substance melts at 192° and in aqueous solution has a specific version [a] $\frac{20}{D}$ + 24°, in methanol + 50°.



L. Ascorbic Acid Ketoform — Reversible Oxidized Form

In its chemical reaction it is distinguished by its strikingly strong power of reduction. The oxidized Vitamin C, still possessing full vitamin activity, may easily be reduced to its original form by the tissues and may act catalytically by processes of oxidation. By this faculty ascorbic acid is very likely charged with an important function in the vital processes of the cell. In neutral and alkaline solution ascorbic acid is quickly destroyed by the oxygen of the air. In acid solution the rate of oxidation of the acid is considerably less.

Very remarkable and still unexplained is the fact that ascorbic acid within the tissue of the plant, for example, lemon, is much more stable than the isolated Vitamin C. Possibly this phenomenon is to be ascribed to the action of protectins. The dextrogyral form and different other chemically-related substances possess, if any, far less scurvy effect (Dalmer). It is evident, therefore, that the vitamin effect of L-ascorbic acid is lost with even slight changes in the molecule. The l-rhamno-ascorbic acid carrying, instead of group $HOCH_2$ at the end, the grouping of

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HOCH-CH_3, solely possesses approximately the same antiscorbutic effect as the l-ascorbic acid (Rheichstein).

Determination. The most positive method of detection of ascorbic acid is still the biological test carried out with guinea pigs. If these animals are fed a certain diet free of Vitamin C, there occurs a drop in weight usually on the 15th day, leading later to death. That daily dose is designated as the smallest Vitamin C protecting dose, which, preventing weight loss in such animals, inhibits development of scurvy in so far as the treated animals, at the death of the controls (fed with Vitamin C), are practically scurvy-free. In applying this method 0.5 mg. of ascorbic acid have the efficacy of 1.5 cc. of fresh lemon juice.

To ascertain the Vitamin C content of the various plants and fruit, the titration method, worked out by Tillman and co-workers, is usually employed by using a blue-dye-stuff, the 2-6 dichlorophenolindophenol, the dye being reduced to its leuco form. The titration test with a properly diluted solution depends likewise upon the reduction power of ascorbic acid. The chemical detection of it in animal tissues and fluids is made difficult by the fact that other reducing substances, especially sulphhydryl compounds may dissipate the titration.

Occurrence. Among the plant products having a high Vitamin C content are particularly: oranges, lemons, onions, tomatoes, hips and green paprika pods. Besides Vitamin C is abundantly found in green spruce and pine leaves. In a general way it may be said that ascorbic acid occurs in living plant tissue, i. e. in those with normal metabolism. If the metabolism of the plant has been reduced or has ceased, as in seeds, the active substance vanishes. On reawakening of cell life with the germinating seeds, it reappears in the green sprouts in rather generous quantities. Its occurrence is, however, not restricted to the world of plants. In the human and animal organism it is found in liver, spleen, kidney, and in surprisingly high concentrations in some organs with internal secretions: the adrenals (Szent-Györgyi), the hypophysis, the interstitial tissue of the testes and the corpus luteum (Giroud and co-workers). It is contained besides in especially large quantity in the vitreous, the aqueous humor and the lens (Mueller, Buschke and von Euler).

Requirement of Man. Exhaustive tests with guinea pigs have demonstrated that a daily dose of 0.25-0.5 mg. of ascorbic acid suffices to inhibit the loss of weight of the Vitamin C-free fed animals and prevents their death (Moll). However, it is only after a dose of 1.0-1.5 mg. of ascorbic acid that the pigs fail to show any histologically demonstrable changes whatsoever, for example, in the teeth.

As daily Vitamin C requirements the following quota used to be figured as average.

Minimum for nurslings: 2.5 mg. crystalline ascorbic acid.
Minimum for adults: 10-20 mg. crystalline ascorbic acid.

By more recent investigations these values have been proven to be too low. For healthy men the daily need of Vitamin C is about 50 mg. It has to be considered, however, that the human need of vitamin C depends

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upon diverse factors and is subject to great fluctuations. Further discussion will be continued under clinical applications of ascorbic acid. For the problem of Vitamin C requirement in man, it is of great import that (judging by animal tests) there exists in scurvy close reciprocations between the course of the disease and the vitamin supply. Even small amounts of Vitamin C suffice in clinically demonstrable symptoms of scurvy, though there are assuredly pathological changes existing in the sense of scurvy.

Comparing the daily quota of other vitamins needed it is a conspicuous fact that a very much greater dose of Vitamin C is necessary. Vitamin C is further distinguished from other vitamins in that a hypervitaminosis has not been reported, at least, so far.

Elimination. With an ordinary diet only very small amounts (about 10 mg. daily) of Vitamin C are excreted in the urine. On a daily supply of ascorbic acid, say 300 mg., an increasing elimination by the urine is noted day by day, reaching its height on about the 4th day after loading with the vitamin. Evidently the healthy organism becomes repleted with it and excretes the excess with the urine (Schroeder, Harris and Ray, Johnson and Zilva).

Commercial Preparations. Pure crystalline Vitamin C in tablets and in ampules of 0.025, 0.05 and 0.1 gm. are on the market. Well-known commercial preparations are: Cebione (Merck), Redoxon (Hoffmann LaRoche) and Cantan (I. G. Farben Industry). Application peroral or parenteral.

Value of Vitamin C in the Organism. In view of the high reversible power of reduction of ascorbic acid, abundantly present in the green parts of plants, attention was directed at once to a principle value of Vitamin C in the fundamental vital processes in the plant, such as respiration and fermentation. Today the function of Vitamin C in cell life is not clarified. There is evidence, however, that the vitamin fulfills a general function in the animal economy. The clinical syndrome of avitaminosis C is signified by the decline of a series of cell functions. Characteristic of scurvy are the hemorrhages resulting from inability to produce the necessary intercellular cement-substance. The well-known changes in the osseous system, due to avitaminosis C depend mainly upon the complete disorganization of the cartilage cells leading to osteoporotic pictures. Typical of scurvy are separations of the epiphysis and hemorrhages in the medullary space and around the fractures.

Pathogenically, scurvy does not present a uniform disease process, however. This is indicated by the fact that withdrawal of all water-soluble vitamins may produce scurvy in rats (Kollath).

According to experiments as well as to observations in man it appears as though beriberi and scurvy have a common base of morbidity. Slot believes that sprue which occurs in the tropics is to be regarded as a specific avitaminosis C actuated by strong light. The anemia of sprue is considered as a sign of a lack of Vitamin B_2.

Vitamin C Pharmacology. Up to the isolation of ascorbic acid our

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knowledge of the Vitamin C effect was very limited, scarcely reaching beyond the well-known clinically and pathologically demonstrable manifestations of the avitaminosis C scurvy. Only when a well-defined chemical substance of the pure isolated Vitamin C was submitted could an accurate analysis be carried out. For the time being the question must be left open as to what extent the general actions of ascorbic acid combine with its antiscurvy effect. In the same way the pharmacological properties of Vitamin C do not allow an inference to the pathogenesis of scurvy.

An exact pharmacological analysis was of special interest for the reason that the other isolated vitamins had shown that their modus operandi could not be made clear in any way by the manifestations of deficiency in the respective avitaminoses. As Bürgi, working with chlorophyll, similarly could show that the vitamins, separated from their compounds, having new and unexpected physiological properties, are justified to be listed among medicaments, and indeed the most efficient known to us. This has been briefly stated before.

In determining the toxicity it has been shown that ascorbic acid in quite considerable doses either perorally or parenterally are borne without any ill effects. Following intravenous injection of relatively large quantities of ascorbic acid the blood pressure was temporarily lowered. That Vitamin C evidently plays an important role in the plant and animal economy is demonstrated by the fact that by means of ascorbic acid various ferments are activated. Thus Vitamin C is, for example, the activator of proteolytic ferments as Papain (Maschmann and Helmert), Kathepsin (von Euler, Karrer and Zehender), Arginase (Eldbacher and Leuthardt). Intravenous injections of ascorbic acid increase the activity of catalase in the blood (Jusatz). For the explanation of clinical observations respecting the process of clotting important information is submitted by Kühnau—that by the l-ascorbic acid in vitro at a pH greater than 7.4, the clotting is accelerated and that this effect of the acid is increased by traces of iron. Kühnau connects this clot-promoting activity of the acid with activation of the thrombin. The clotting effect of Vitamin C has, however, nothing to do with its vitamin character; it rather depends upon the power of reduction of the acid which is common to all, even those isomers and homologons of ascorbic acid which are ineffective antiscorbutics (Kühnau). Interesting and very likely of physiological import is the ability of ascorbic acid to raise the activity of the economy's own substances as adrenalin, cholin and thyroxin. Specifically important is the activation of adrenalin by ascorbic acid as shown by the blood pressure as well as in the rabbit uterus (Kreitmair). In vitro the acid is capable of greatly impeding the oxidation of adrenalin in the air, readily recognized by the reddish tinge (Schroeder). It is this observation perhaps which explains the increased adrenalin effect by Vitamin C. According to investigations so far, Vitamin C seems to play a role at least in the physiology of the adrenals. Pointing that way is the hypertrophy of the adrenals in scurvy and the finding of von Euler that adrenalin injections reduce the Vitamin C content of the adrenals. Favorable reactions of

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Vitamin C seen in disturbances of the pigment metabolism point also to close relationships between adrenalin and Vitamin C, which will be referred to later. In a similar manner, as with adrenalin, Vitamin C may also prevent the formation of the melanoid pigment (von Szent-Györgyi). In addition it has been discovered recently that the activity of the cortical hormone of the adrenal in Addison's Disease is increased by the administration of Vitamin C. Vitamin C, in the role of activator, does not extend by far to all of the economy's own substances or hormones. In certain cases the efficacy of ascorbic acid is bound up with normal metabolism, for example, insulin. Of not less practical import is the discovery that ascorbic acid has the power to increase the effect of essential remedies and to reduce their toxicity (von Euler). In some instances of Germanin, for example, this observation has disclosed new possibilities for treatment with this agent and has been made use of already in practice and clinics. Besides, a marked detoxication of the diphtheria toxin by ascorbic acid has been noticed (Harde and Philippe).

Because of apparent relations of Vitamin C to the blood, the effect of ascorbic acid upon blood regeneration has been thoroughly investigated. Actually it has been shown that in the blood picture of "sponin anemic" cats, the acid was capable of exerting a blood-regenerating effect, and by peroral as well as by parenteral administration a rise of the erythrocyte count and hemoglobin index was noted (Kreitmair). Ascorbic acid apparently does not possess direct general metabolic activities. The gas exchange as well as the protein, fat and mineral metabolism remain uninfluenced by peroral or intravenous use of ascorbic acid (Kreitmair, Stepp). As to working mechanism so far there is little enlightenment in the observation that the blood sugar sinks markedly following intravenous injections of fairly large doses of ascorbic acid (Stepp, Schroeder and Altenburger).

Reciprocations. Isolation and synthesis of the best known vitamins have afforded new perceptions of the reciprocations of the vitamins. The necessity of a vitamin equilibrium for optimal operation of the vital functions in the animal economy has been known a long time. Hypervitaminoses, resulting from limited feeding with large quantities of vitamins, are regarded as disturbances of correlation of vitamins. By simultaneous supply of water- and fat-soluble vitamins, an hypervitaminosis cannot be produced, though they may be given in very large quantities. The fact that the carotin and Vitamin C of plants are found together in high concentration seems to indicate relative connections between Vitamin A and Vitamin C (von Euler). Indeed in the light of recent experimentations there seems to exist an antagonism between Vitamin A and Vitamin C, because a simultaneous feeding of proper doses of ascorbic acid with an excess of Vitamin A does not allow development of an hypervitaminosis A (Wendt and Schroeder).

Clinical Applications of Vitamin C. *Scurvy.* It is self-evident that the clinical application of Vitamin C is useful in the first place, when a pronounced lack of Vitamin C exists, as in scurvy and in the so-called

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Moeller-Barlow disease. Though in our latitudes fully developed avitaminoses C are not so frequently seen as in times past, a glance over the literature concerned will prove that with us also, scurvy is not at all a rare disease. During recent years reports of epidemics of scurvy have been frequently published in European countries as well as outside of Europe. Least often scurvy is seen in Germany itself. Ever since greater attention has been brought to bear upon scorbutic and prescorbutic conditions these diseases have been observed more frequently. For the purpose of taking timely therapeutic measures in a given case, especially following persistent dietetic treatments—gastric ulcer, typhoid, celiac disease and in sequence of long continued infections—it is necessary to watch for symptoms of scurvy. All diseases due to scurvy are cured by ascorbic acid in a short time, even in cases, when for some reason nutriment rich in vitamin C may not be indicated for the time being. Indeed a striking improvement or cure of scurvy, even in grave cases, may be achieved by intravenous application of ascorbic acid. Daily doses of 50 to 100 gm. are used intravenously (Schultzer, Bauke). In many cases the intravenous application is superior to the peroral because under certain conditions Vitamin C perorally given is imperfectly absorbed in the gastro-intestinal tract, or not at all (Stepp). Indeed there have been cases of scurvy reported which behaved refractorily under peroral Vitamin C treatment, but reacted promptly upon intravenous injections.

That ascorbic acid is well tolerated is of specific advantage in the treatment of infantile scurvy, Moeller-Barlow disease, because it is commonly known that fruit juice in large quantities in nurslings and smaller children may give rise to disturbances of the gastrointestinal apparatus. On account of great solubility and agreeable taste of the remedy the treatment with ascorbic acid in children does not meet with difficulties (Brugsch).

In a given case ascorbic acid may be given intramuscularly, as there is no occasion of any local reaction to be feared, since the sodium chloride salt of it has to be employed for parenteral use. Just how excellent the results from ascorbic acid are in Moeller-Barlow disease has been proven by reports of cures having been obtained in the course of two or three weeks in children with extensive hemorrhages in the skin and zones of destruction roentgenologically demonstrable at the bone-cartilage junctions.

The dose for children is 30 to 50 mg. daily per os. Here also additions are never of disadvantage, since the remedy is excellently tolerated and there is no danger of an hypervitaminosis C.

Hypovitaminosis C. The clinico-diagnostic preponderance does not lie in the well-known classical syndrome of scurvy, but more often in the prescorbutic forms, the hypovitaminoses. Disease conditions of undefined character are designated hypovitaminoses due to an impoverishment of the economy of one or more vitamins without giving evidence of typical symptoms of avitaminoses. With Vitamin C it was strikingly shown that there existed a gradual dependence of the gravity of the scorbutic disease to the quantity of Vitamin C supplied. The difference is very great between

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the vitamin quota, merely restricting the appearance of scorbutic manifestations and those necessary to prevent pathologically demonstrable scorbutic changes, of teeth or bone, for example. In reference to man these experimental results presage that there exists a great span between the lowermost limit of the minimum requirement, determined by purely clinical means, and an optimal supply to the organism.

During the past years many investigators have paid special attention to the prescorbutic hypovitaminotic symptom complex. Today a series of disease conditions are ascribed to a relative Vitamin C deficiency. Among them, for instance, are tendency to bleeding gums, spring fatigue, susceptibility to gastrointestinal and respiratory infections, obstinate pyurias, certain capillary hemorrhages, and dental caries (Morawitz, Reyher).

In the prodromal state of scurvy Morawitz has observed particularly complaints of exhaustion, anorexia, dyspnea, heart trouble and rheumatic pains in the legs. Essential features of a relative lack of Vitamin C in children are designated: retarded progress of weight and longitudinal growth; pallor; reduced appetite; tendency to infections (also called dysergy) and the occurrence of muco-bloody stools.

According to Göthlin, who believes by using a special method of testing the capillary tonus that he can objectively apprehend very early conditions of hypovitaminosis C, there exists frequently in Swedish children, at least, a malnutrition with reference to Vitamin C.

A deep insight into the metabolism of Vitamin C and an understanding of the development of an hypovitaminosis C could be gained only when the pure substance was at hand and investigations could be carried out on a larger scale. Elimination tests gave proof that in many disease conditions the Vitamin C consumption of the human economy was increased as compared with the normal. This was demonstrated in febrile infections, as, for instance, pneumonia, gastroenteritis, typhoid, tuberculosis and conspicuously in cancer and diabetes (Schroeder). Without compulsion and without referring to a theory of infection these observations explain the frequent appearance of scorbutic conditions in the course of epidemics. It has been known for a long time that the growing organism consumes much larger quantities of vitamins than the adult, the same holding true during the period of pregnancy. In addition Stepp has pointed out that a disturbance of absorption of the vitamins may be responsible for many hypovitaminotic conditions, for instance, in gastroenteritis, where less vitamin is resorbed because of accelerated passage through the small intestine. Noteworthy besides is the fact that Vitamin C is quickly destroyed by certain intestinal bacteria, for example, the coli group and paratyphoid B. With a pathological colonization of the stomach and upper jejunum by such bacteria this might lead to a considerable loss of vitamin C (Stepp and Schroeder).

Hemorrhages. The indications for treatment are obvious. In all conditions mentioned one would seek to get an increased supply of vitamin by a suitable diet and only take recourse to the isolated vitamins in case of com-

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plete anorexia. The range of indication for ascorbic acid has been extraordinarily extended, since it has been recognized that like all other vitamins ascorbic acid is an active remedy possessing new and entirely unexpected curative properties other than the specific antiscorbutic effect. (Pfannenstiel, Stepp). Investigation of the clinical possibilities of isolated Vitamin C is greatly facilitated by the fact that it has no toxic effects, peroral or parenteral doses of ½ gram or more being well tolerated. It is commonly known that hemorrhages are outstanding symptoms of Vitamin C deficiency. It seems reasonable, therefore, to try ascorbic acid in diseases associated with hemorrhage. As a matter of fact the acid proved to be an excellent hemostatic in many cases (Boeger and Schroeder). It is principally indicated in hemorrhagic diatheses. In cases of Schoenlein-Henochs purpura and of essential thrombopenia, the most serious hemorrhages of this sort have been successfully arrested by intravenous injections of Vitamin C in large quantities.

The often-time striking improvement of hemorrhagic diatheses appearing as a consequence of infectious diseases and the increased consumption of vitamin C during various infections lead to the question as to whether an hypovitaminosis may not be coresponsible for the capillary toxicosis in the sense of Schoenlein and Henochs disease. Not commensurably successful are the treatments of the hemorrhages in Werlhof's disease with isolated Vitamin C. Perhaps it is particularly through these varying therapeutic experiences in this malady, pathogenically still undefined, that a better insight of the essence of it may be obtained.

Hemophilia, so difficult of treatment, may be influenced with eminent success by the pure Vitamin C. The good results, first reported by Boeger and Schroeder, from the use of ascorbic acid in this dreaded blood disease, have been confirmed by others many times. Just how the ascorbic acid is linked in detail with the blood chemistry of hemophilia is not entirely clarified. It is true indeed that a peroral or better a parenteral treatment with the pure Vitamin C succeeds in reducing bleeding and clotting time from 6 to 10 hours to a few minutes, and to markedly improve the general condition of the patient. However, a continued or only interrupted by short intervals, treatment is necessary. In addition recent clinical observations indicate that ascorbic acid acts favorably upon pulmonary (Alexander) gastrointestinal-, renal-, and the dreaded post-icteric and post-typhoid hemorrhages. Most excellent is the effect upon the juvenile genital hemorrhages (Vogt, Junghans). To achieve success with these bleedings it is necessary, however, to supply Vitamin C parenterally in doses of 200-500 mg. daily.

The working mechanism of ascorbic acid as to hemorrhages is not entirely cleared up. It appears that Vitamin C has a vascular effect in the sense of rendering the capillary walls impermeable. This is indicated by the observation in Warlhof's disease, for instance, that the bleeding ceases at a time when the blood platelets have not yet increased (Boergerand, Schroeder). In all cases of thrombopenia an increased formation of blood platelets prevails following parenteral vitamin treatment. Ac-

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cording to the general behavior of the blood platelets ascorbic acid evidently has a favorable influence upon the bone marrow in the sense of an increased thrombocytopoiesis. As a matter of course the observation of Kühnau also has to be referred to for the explanation of the Vitamin C effect upon hemorrhages,—that the clotting is accelerated by ascorbic acid because of an activation of the thrombin.

The question is still undecided whether the hemostyptic effect of Vitamin C is linked with the observed increase of the albuminous portion of the blood plasma. According to Boeger and Schroeder the albumen content of the plasma is materially increased following administration of ascorbic acid.

Through the manifold working possibilities of ascorbic acid its beneficial action upon hemorrhages, entirely unlike genetically, appears rational. In hemophilia, for instance, it is the clot-producing faculty of the acid which must be regarded mainly as the curative factor. In the other diatheses it is either the effect upon thrombocytopoiesis and capillary permeability, perhaps also the changed blood chemistry, or it is the sum of all activities of ascorbic acid to which the hemostyptic power is due.

From our knowledge to date about the working mechanism of Vitamin C, it is evident that its specific field of application is for treatment of capillary hemorrhages, as they occur in the most varying disease conditions. In the hemorrhages from larger vessels ascorbic acid at best is useful only in a supporting sense.

Vitamin C and the Red Blood Picture. As mentioned above pharmacological investigation of the acid had demonstrated a marked action upon the red blood picture of "saponin anemic" cats. In man a direct effect upon hemoglobin and erythrocytes has not been made evident (Boeger and Martin).

Administration of Vitamin C alone fails to successfully establish an improvement either of the secondary or of the hemolytic anemias. An increase of the reticulocytes in the blood following intravenous injection of Vitamin C does speak, however, for certain relations between the vitamin and the hemopoietic system (Seyderhelm and Grabe). It seems to be a fact that ascorbic acid promotes liver activity in the treatment of Biermer's anemia with Campolon. Good results from Vitamin C and iron combined in secondary and achlorhydric anemias commend the use of Vitamin C in these diseases, at least, as a supporting measure (Boeger and Martin).

Upon the white blood picture, Vitamin C has no effect worthy of note.

Vitamin C and Pigment Metabolism. There is some contention about the relationship of ascorbic acid and the pigment metabolism. Pathological pigmentation as a symptom of various avitaminoses is well known. Indeed the existence of pigment vitamins has been taken for granted. Processes approaching avitaminoses lead probably to formation and precipitation of skin pigments (Morawitz). It does not mean, naturally, that Vitamin C is the sole pigment vitamin. Some experimental and clinical observations, however, make it appear that ascorbic acid has a bearing

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upon pigment formation. The demonstration of melanin formation in vitro being inhibited by ascorbic acid (Szent-Györgyi) was supported by other investigations, showing that in the so-called Dopareaction the darkening of the pigment-forming skin cells in histological sections by a solution of dioxyphenylalanin was prevented by the presence of ascorbic acid (Schroeder). In addition it is a conspicuous fact that ascorbic acid occurs in high concentration in the organs which are of importance to the pigment metabolism, namely, the adrenals and the hypophysis. Recently Vitamin C has been demonstrated in pretty generous amounts in the epidermis of the skin (Giroud and co-workers). Other than such single determinations, so far an accurate knowledge of the interrelation of ascorbic acid and pigment has not resulted. Practical experiences, however, with Vitamin C treatment of certain pathological pigmentations are giving promise of success. In Addison's disease a clearing up of the skin may be obtained by an energetic peroral or parenteral therapy with Vitamin C. In some cases after the disease itself has been successfully treated with cortin, the hyperpigmentation reacted favorably only after Vitamin C had been supplied. Furthermore ascorbic acid is of good effect especially when used parenterally, in chloasma-like melanoses and pathological pigmentations, often appearing with chronic diseases of the gastrointestinal tract, for example, gastroenteritis and achlorhydric anemias, and disease symptoms also designated at Addisonism. Successes with Vitamin C in other hyperpigmentations such as chloasma uterinum do not correspond. Treatment of the disturbances of the pigmentary metabolism with ascorbic acid proceeds quite analogously to that of the hemorrhages. Here again it is recommended to institute an energetic parenteral therapy if the supply of nutriment rich in Vitamin C or ascorbic acid, perorally given, fails of results.

Vitamin C and the Gastrointestinal Tract. Previously it was mentioned on occasion of the hypovitaminoses that a relative depletion of vitamin might appear in certain diseases of the gastrointestinal tract despite an adequate supply of vitamins, thus, for instance, through faulty absorption of vitamins in gastroenteritis. Besides it is to be considered, as certain investigations have shown, that in sequence of an achylia in the stomach a reduction of the Vitamin C depot may obtain in spite of a nutrition rich in the vitamin (Schnell, Ragnar). On the other hand, Verzar has pointed out that some vitamins especially favor resorption of nutriment in the gastrointestinal tract by inciting the motility of the intestinal villi. Thus a resorption-acceleration effect, of glucose for example, has been demonstrated for Vitamin B complex (Verzar) and Vitamin C (Schroeder). That Vitamin C is of consequence to the intestinal tract is elucidated by evidence that in many mammals the wall of the small intestine is one of the depots of ascorbic acid. As to storage of the acid it does not make any difference if the vitamin is supplied orally or parenterally. In the guinea pig fed a Vitamin C-free diet it is worthy of note that the wall of the small intestine as a Vitamin C depot is filled first after the supply of ascorbic acid has begun (Zilva, Hopkins, Jacobson). This close

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relation of locality between vitamin and gut wall seems to have a meaning for the biological events. There exists in fact a signal tendency to infections of the gastrointestinal tract with Vitamin C deficiency. In animals it has been shown experimentally that mechanical insults of the duodenal mucous membrane heal rapidly and completely under a diet rich in vitamins, while peptic ulcer arises with lack of Vitamin C. Indeed according to other investigations gastric and duodenal ulcers developed in a high percentage of cases when the nutrition was made up by a diet poor in Vitamin C (Smith and McConkey).

In accord with these studies it appears as if Vitamin C is of special importance in the prevention of ulcer formation in the gastrointestinal tract. Finally, it must be mentioned that the intestinal bacteria vary greatly in their reaction toward Vitamin C. While some species do not seem to have any visible influence upon ascorbic acid, others, for example, some coli strains and b. paratyphosus B, under the same conditions, are able to rapidly destroy the pure Vitamin C. The possibilities of absorption of Vitamin C, when the stomach and upper intestine have been pathologically colonized with such germs, are evident. For prevention and treatment of scorbutic and prescorbutic symptoms due to disturbances of resorption of varying nature, the opportunity of a parenteral administration of Vitamin C is specifically welcome. On the basis of clinical observations, many years ago Stepp recommended a generous supply of Vitamin C in gastric and duodenal ulcer. In addition recent experiences indicate that in these intestinal lesions the tendency to bleeding is reduced by Vitamin C at the same time.

In combatting anorexia it is important to remember that according to Bickel the secretion of the digestive glands in avitaminoses is torpid only because food poor in vitamins fails to strongly incite secretion.

Vitamin C and Dental and Osseous System. The sequels of a Vitamin C deficiency appear to be noticed first in the teeth and at so early a time that other manifestations of the disease are not demonstrable histologically (von Euler, Vilton and Hoejer and Westin, Walkoff). It amounts to a degeneration of the odontoblasts. The process goes on to a reduction of protoplasm with proliferation of connective tissue. Proceeding it results in an infolding of the inner side of the dental cone and also in a deposit of hard tissue against the predentine zone. By continuation of the process the pulp is finally changed to an acanalized indurated tissue. It is worthy of note that all these degenerative changes are enabled to regenerate following administration of Vitamin C. Studies of tissue sections have shown that the ascorbic acid is localized in the immediate proximity of the enamel and the dentine-forming cell stratum. The importance of the vitamin for the teeth is also emphasized in the well-known changes of the gums, appearing with lack of Vitamin C. Beginning with a swelling of the interdental papillae and a bluish discoloration of the gum margins it leads easily to bleeding and to very sensitive ulcerative changes between the teeth. The development of caries by faulty formation of enamel is likewise initiated by a Vitamin C deficiency. From what has

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been said it is very evident that the diseases of teeth and gums are the field of indication for Vitamin C. To improve tooth formation in children it is important not only to look to an adequate supply of Vitamin D, but also to bear in mind the great importance of Vitamin C for dental development and maintenance. Experiences of prominent dentists indicate another field for application of ascorbic acid in gingivitis, paradentosis and alveolar pyorrhea, so difficult to treat. In this connection it is of interest to note that a recipe has been found in the herb-book of Matthiolus of 1563 and another of Tabernae-montanus-auhinus of 1731, in which the hip berry, now known as containing much Vitamin C, was recommended in the treatment of bleeding teeth and in the form of tooth powder for strengthening and firming the gums.

Roused by the bony changes in scurvy pure Vitamin C has also been given in cases of a tendency to fractures and to accelerate healing of fractures.

Vitamin C Metabolism in Pregnancy, Lactation and Growing Age. In view of the impossibility of discussing all problems comprising the Vitamin C metabolism during pregnacy, lactation and the age of growth, only the newly gained knowledge supplied by the isolation and the possibility of quantitative determination of Vitamin C may be used. For a long time a diet especially rich in Vitamin C has been recommended for the expectant mother because of the increased need in the organism for Vitamin C during pregnancy. Nevertheless, the manifestations of hypo- or avitaminoses are frequent in pregnant women and more portent of danger, as they may mean harm to the child's economy. Well known is the rising appearance of caries during pregnancy. To a great extent that must be due to a relative lack of Vitamin C in the food. Indeed based upon animal tests it has been accepted that under these circumstances a Vitamin C deficiency in the food might be the cause of feminine sterility and of a tendency to abortions and miscarriages.

Already the embryonic adrenal is able to provide Vitamin C and it is also known that the placenta possesses an ascorbic acid storage function (Neuweiler). Perhaps this elucidates the observation that in gravid animals on a Vitamin C-free diet the development of scurvy is retarded, but later their collapse is obtained very much quicker. Weight reduction and scorbutic blood changes occur twice as severe in gravid as in normal animals.

Of interest is the evidence showing that nurslings on a Vitamin C-free diet during the early months of life are able to form the vitamin themselves (Beszonoff). In fact, scurvy in infants up to 3-4 months of age is as good as unknown. Only after the age of one year the organism of the child loses this faculty. In man a congenital scurvy has not been described to be certain.

The proper composition of mother's milk is of the highest import to the infant's nutrition. The occurrence of deficiency diseases in nursing children shows that even mother's milk may be inadequate as to its vitamin content. Normal human milk has 4-7% of ascorbic acid which is much

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more than the cow's milk tests. However, in women who receive very little Vitamin C in their food; the ascorbic acid content of their milk may drop to less than 1 mg. %. By a Vitamin C-rich nutrition and peroral or parenteral ascorbic acid medication it is easily possible to enrich the milk. Therefore, the Vitamin C content of human milk depends upon the kind of nourishment (Neuweiler).

As Guggisberg has justly emphasized, the provision of an incontestable cow's milk is one of the most urgent demands of modern hygiene. Just how essential a sufficient Vitamin C content is in cow's milk may be proven by the fact that scurvy is found practically only in artificially nourished children. It is unknown in nursing infants. According to recent investigations cow's milk contains 0.07 to 1.1 mg. % of Vitamin C which is only a fraction of that of mother's (Neuweiler). At the same time the Vitamin C content of cow's milk is subject to great fluctuations depending upon the kind of food; therefore, the summer milk contains more vitamins than that of spring and winter.

Furthermore, the Vitamin C content of cow's milk is also dependent upon the manner in which it is handled, a reheating of an already pasteurized milk is especially harmful. Investigations of this problem have shown that in pasteurizing, the kind of metal the milk comes in contact with plays a role. When the milk is heated for 30 minutes to 60° C in an aluminum vessel only 20-40% of the Vitamin C content is lost, but in a copper vessel the loss is 80-100%. When the milk is heated at 120° C for an hour practically all of the vitamin has disappeared from it (Report of the Medical Research Council).

Contributing to the destructibility of Vitamin C by heating is always the free access to air. In the autoclave the Vitamin C-containing substances may be heated to higher temperatures without suffering an appreciable loss. Recent experiences indicate, however, that the primary Vitamin C content of milk is the most valuable. The changes the vitamin substances are subject to by the usual methods of handling are of subordinate importance.

Doubtless the ideal vitamin content of cow's milk because of varying favorable housing and feeding conditions of the cows is not always obtained. Therefore, it surely signifies progress in dietetics that a quantitative vitamin determination may be entered upon and that the vitamin content of the milk may be regulated by increasing the supply of vitamin, and, if need be, adding the isolated form.

Generally speaking Vitamin C is not growth promoting. Nevertheless like all vitamins it plays a large role in disturbances of growth in the child. With a deficient provision of Vitamin C in the child's organism comes an inhibition of growth without scorbutic symptoms being in evidence. This may perhaps be an expression of a metabolic dysfunction. With a generous supply of Vitamin C in such children an increased start and a promotion of longitudinal growth is achieved.

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VITAMIN C CONTENT IN SOME FOODS

in milligrams per 100 grams of substance

Substance	*Raw*	*Cooked*
Milk, butter		
cheese		
cow's	0.5-1	
Flour Products		
Potatoes	10	5-10
Vegetables		
Spinach	8	2
Cauliflower	50	8
Green Kale	75	16
Brussels sprouts	50	50
Asparagus	25	0
Cabbage	40	2
Cabbage, red	50	8
Kohl Rabi	100	16
Beets, Red	8	0
Beets, Teltow	22	0
Rutabaga		10
Black Roots	5	5
Horse Radish	100	
Legumes		
Green Beans	10	1-4
Yellow beans	16	6
Green peas		8
Vegetable Fruit		
Tomatoes	15	10
Melons	8	
Endive	10	
Watercress	16-50	
Celery	6	
Black Radish	10	
Radish	25	

Substance	*Raw*	*Cooked*
Onion	5	
Green Leek	50	
Parsley	100	
Fruit		
Oranges	50-100	
Mandarines	25	
Lemons	50-100	
Grape fruit	50-100	
Strawberries	50	
Currants, Black	100	
Currants, Red	16	
Raspberries	25	
Gooseberries	28	
Apples	2-5	
Pears	1-3	
Quinces	15	
Cherries, yellow	5	
Cherries, black	15	
Blueberries	10	
Blackberries	22	
Cranberries	15	
Grapes	5	
Apricots	12	
Peaches	8	
Plums, dried	8	
Cucumbers	8	
Salads		
Field lettuce	20	
Head lettuce		
Green leaves	8	
Yellow leaves	8	
Bananas	8	
Pineapple	8	
Hip-rose berries	100	
Figs	5	
Dates	3	

Ever and again pediatrists have called attention to the dysergy of the child's organism under Vitamin C deficiency. It is manifest in lowered immunity and resistance to infectious diseases several months before symptoms of scurvy appear. In these conditions an energetic treatment with ascorbic acid has its proper place. It is indeed surprising to note the variously reported differences in duration of recovery from frequent infections in children, for example, pyuria, before and after Vitamin C therapy (Conti, Reyher).

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VITAMIN C_2

The old conjecture that there existed, besides the one known, a second Vitamin C seems to find confirmation in the results of recent investigations of von Euler. It was demonstrated that guinea pigs, fed Vitamin C-free diets, could be more thoroughly protected against infections with pneumococci by lemon or orange juice, than by pure ascorbic acid. Therefore, von Euler assumes that in lemon or orange juice still another Vitamin C exists to which the preventive effect toward bacteria mainly must be ascribed. This has been named Vitamin C_2 and recently Vitamin J.

BIBLIOGRAPHY FOR VITAMIN C

Altenburger, Klin. Wschr., II, 1129-1131, 1936.
Auler, Frankfurter wissensch., Woche, 1935.
Bauke, M. m. W., Nr. 32, S. 1240, 1934.
Bezsonoff, Compt. rend. Soc. Biol., Nr., 27, 1414, 116, 1934.
Bickel, Z. f. Volksernähr, H. 12, 1935.
Bircher, "Der Wendepunkt", Nr. 10 and 11, Oktober 1936.
Böger and Martin, M. m. W., Nr. 12, 1935.
Böger and Schroeder, M. m. W., Nr. 34, 1934.
Böger and Schroeder, Klin. Wschr., Nr. 23, 842, 1934.
Brugsch, D. m. W., Nr. 32, S. 1202, 1934.
Conti, Arch. f. Kinderh., Bd., 76, S. 106, 1925.
Dallmer, D. m. W. Nr. 32, S. 1200, 1934.
Diehl, unveröffentlichte Versuche
Edlbacher and Leuthardt, Klin. Wschr., 47, 1483, 1933.
Einhauser, Zschr. f. exper. Med., Heft 4, 1936.
v. Euler, Ark. Kem. Mineral. Geol. Ser. B., 11, Nr. 19, 6 Seiten, 1933.
v. Euler, Chem. Zol. 1, Nr. 7, 1934.
v. Euler, Karrer and Zehender, Helv. Chim. Acta 17, 157, 1934.
Finkle, Proc. of the Soc. F. Experiment. Biol. and Med., 32, 1163-1164, 1935.
Gander and Niederberger, M. m. W., Nr. 34, 1386, 1936.
Giroud et al., Bulletin de la Société Franc. de Derm. et Syph., Nr. 3, Mars 1935.
Göthlin, Klin. W., 1469, 1932.
Harde and Philippe, E. R. hebd. Seances Acad. Sci., 199, 738, 1934.
Harris and Ray, Lancet, 12, 71, 228, Jan. 1935.
Höjer and Westin, Dental Cosmos, Bd. 67, S. 1, 1925.
Hochwald, Ztrbl. f. inn. Med., Nr. 38, S. 769, 1935.
Hopkins, Chemistry and Industry Nr. 42, 53, 874, 1934.
Jacobsen, Hospitalstidende, Nr. 5, 131, 1935.
Jeney and Törö, Virch. Arch., Bd. 1, Heft, 298.
Jezler and Niederberger, Klin. Wschr., I, S. 710, 1936.
Johnson and Zilva, Biochem. J., Nr. 4, 28, 1934.
Junghans, Klin. W ., Nr. 25, 1935.
Jusatz, Klin. W., S. 727, 20, 1934.
Kahler and LaCroix, Klin. W., Nr. 52, S. 1851, 1935.
Kollath, Klin. W., II, 1841, 1932.
Kreitmair, Arch. f. exp. Pathol. & Pharm., H. 2/3, 176, 1934.
Kühnau, Schles. Ges. f. vaterl. Kultur., II, 15, 1934.
Kühnau, Verhdlg. d. Ges. f. Stoffwechselkrankh., Wiesbaden 1934.
Lauersen and Sauerbruch, Klin. W. Nr. 32, S. 1137/1138, 1935.
Löhr, Ztrbl. f. inn. Med., Nr. 15, S. 358, 1935.
Mahlo, Dtsch. m. W., Nr. 3, 1936.
Martini and Bonsignore, Biochem., Z., 170-177, 273, 1934.
Maschmann and Helmert, Z. f. physiol. Chem., H. 3/4, 127, 223, 1934.
Morawitz, Handb. d. inn. Med., IV, I, Klin. W., Nr. 9, 324, 1934.
Müller and Buschke, Schweiz. m. W. Nr. 12, 277, 34.
Neuweiler, Z. f. Vitaminforschg. 4, Nr. 1, 39, 1935.

Posted for noncommercial historical preservation and educational use only by seleneriverpress.com

Pfannenstiel, Frankfurter wissensch., Woche 1935.
Reichstein, Helv. Chim. Acta 17, Nr. 2, 311, 1934.
Reyher, Arch. f. Kinderh. Bd., 76, S. 215 and 291, 1925.
Schafer, Klin. W. I, 406-407, 1936.
Schnell, Ragnar, Hygiea (Stockholm) 95, 728-733, 1933.
Schroeder, Klin. W. Nr. 14, S. 484-487, 1935.
Schroeder, Med. Klin., Nr. 21, 1934.
Schroeder, Klin. W., Nr. 15, 553 (Zit. von Stepp), 1934.
Schroeder, Verhandlg. d. Ges. f. Stoffwechselkrankh., Wiesbaden, 1934.
Schroeder and Dormann, Endokrinologie, April 1936.
Schultzer, Lancet, 225, 589, 1933.
Seyderhelm and Grebe, Monographie, J. A. Barth, Leipzieg, 1934.
Slot, Diss. Amsterdam, 1931.
Smith and McConkey, Arch. int. Med., 51, 413-426, 1933.
Stepp, Verhandlg. d. Ges. F. Stoffwechselkrankh., 1934.
Stepp, Frankfurter wissensch., Woche, 1935.
Stepp and Schroeder, Klin. W. Nr. 5, 147, 1935.
Stepp and Schroeder, Z. f. exp. Med., Bd. 98, H. 5, 1936.
Stepp, Schroeder and Altenburger, Klin. W., Nr. 26, S. 933, 1935.
Szent-Györgyi, D. m. W. 15, 556, 1934.
Szent-Györgyi, Nature, 129, 576, 690, 1932.
Szent-Györgyi, D. m. W., 852, 1932.
Szent-Györgyi, British Medical Journal, 22, 558, September 1934.
Tillmans et al, Z. Unters. Lebensm. 1, 21, 241, 267, 276, 63, 1932.
Tillmans et al., Biochem. Z. 250, 312, 1932.
Zerzár, Pflügers Arch. S. 675, 206, S.
Vogt, M. m. W., Nr. 7, 263, 1935.
Vogt, M. m. W., Nr. 21, 791, 1934.
Wacholder, Klin. W., I, S. 593, 1936.
Walkoff, Die Vitamine in ihrer Bedeutung fur die Entwicklung, Struktur usw. Herm. Meusser, S. 100, 1929.
Walkoff, Z. f. Vitaminforschg. 1, 176, 1932.
Wendt and Schroeder, Z. f. Vitaminforschg. Bd. 4, H. 3, 1935.
Widenbauer, Klin. W. I, S. 815, 1936.
Wilton, Acta Pathologica Skandinav. Bd. 8, S. 258, 1931.
Zilva, Biochemical Journal, Nr. 1, 100, 29, 1935.

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CHAPTER FOUR

VITAMIN D

Brief Historical Introduction. The symptomatology of the English disease or rachitis was fully described by the English physician Glisson in 1650 after its occurrence had been observed some 30 years previously in Dorset- and Somerset shires. We may assume, however, that the disease has accompanied mankind since time immemorial; indeed in prehistoric animals bone changes have been found supposed to be rachitic. Much thought has been given to the question of origin without arriving at a uniform conception. The theory of infection acting as a cause was opposed by the assumption that rachitis be regarded as a deficiency disease, or that it resulted through environment. The environment theory pointed to the peculiar geographic distribution of the disease, and to the fact that it occurred especially in children being brought up in dark habitations. Only in recent decades positive proof was successfully established that rachitis, like other deficiency diseases, could result from absence in the nourishment of a so-called accessory food-factor, Vitamin D. It is, therefore, a matter of indifference in the end whether the lack of vitamin is due to absence of the real vitamin in the food or whether the want of radiant-energy effect upon the skin in the form of short-wave light, which has to activate the precursor of the vitamin, is responsible. How much the phosphorus and calcium intake, or, to be accurate, their quantitative proportion, (being very active in calcification processes of the bones in young growing rats), is of import to man, cannot be clearly surveyed at this time. The entire Vitamin D research is based on the observations of McCollum and Mellanby, assigning the cause of evolution of rachitis to the lack of a fat-soluble vitamin in the food. It is found abundantly in cod liver oil and may be separated by suitable means from the associated Vitamin A.

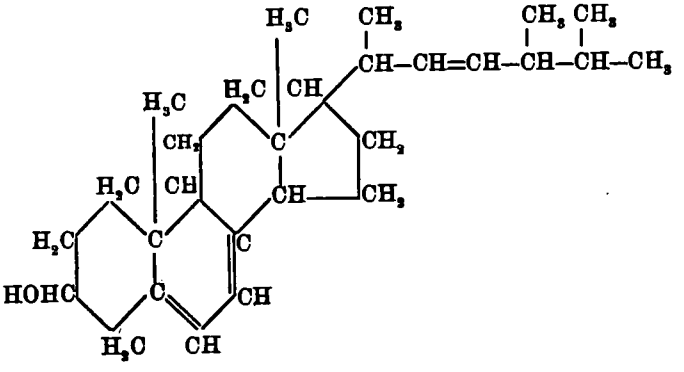
Chemistry. That the studies of the chemical nature of Vitamin D were finally crowned with success rests upon two discoveries of decisive importance. First, Huldschinsky, a pediatrician in Berlin, showed that artificial ultraviolet irradiation would cure infantile rachitis. Second, the observation of American investigators is that anti-rachitically inactive animal and vegetable tissues, after having been irradiated with ultraviolet light, would cure rachitis (Alfred F. Hess and coworkers). After long continued and laborious investigations in which chemists and physicists participated equally, the substance was found at last in ergosterol, a stearin present in fungi and ergot, being a contamination of cholesterol, which on irradiation becomes even in small doses a highly potent antirachitic

(Windaus). By ultraviolet irradiation of certain wave lengths—256-313 μμ (optimal 290 μμ), there finally resulted highly potent crystallizations equal to Vitamin D, or calciferol (British). Later it appeared, however, that these crystallizations were not yet pure Vitamin D, but a molecular compound of the pure Vitamin D and an inactive lumistearin. By continued work with the substance the pure Vitamin D was finally obtained and also Vitamin D_2 called "Calciferol New" (Windaus et al, Bourdillon). Between the theory of environment and the view that rachitis was a deficiency disease a bridge was built in a manner never anticipated. From irradiation of ergosterol not only Vitamin D but a series of chemically related transitional- and by-products arises, which Windaus has arranged as follows:

ERGOSTEROL
|
LUMISTEARIN
|
TACHYSTEARIN
|
VITAMIN D

SUPRASTEARIN I — TOXISTEARIN — SUPRASTEARIN II

Vitamin D has the same gross formula as the ergosterol, of which it is to be regarded as an isomeric product. The gross formula is C_{28} $H_{44}O$ and the structural formula of ergosterol is as follows:



Ergosterol

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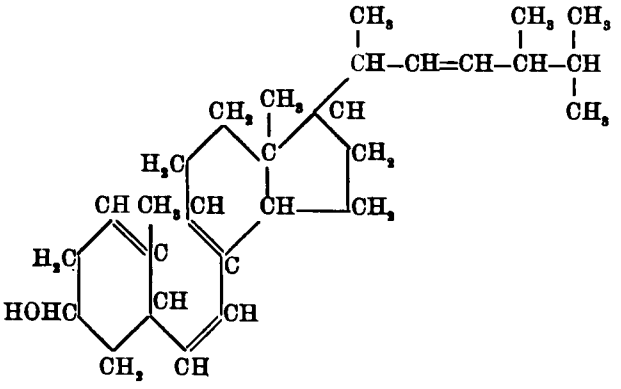

Vitamin D differs from ergosterol by showing only three rings, but possesses four double bonds. During the irradiation of ergosterol, ring-opening takes place. Vitamin D has the above constitutional formula.

The pure Vitamin D is a well crystallized substance with a melting point of 115°–117° and [a] $\frac{20}{D} = +102.50°$. In contrast to its mother substance, the ergosterol, pure Vitamin D is not precipitated by digitonin. It is soluble in acetone, chloroform, benzine and alcohol. It is very resistant to high temperatures. The ultraviolet irradiated substances do not lose their antirachitic effect by cooking or baking. Mineral acids destroy the Vitamin D only slowly.

Determination of Vitamin D. At present there are no positive methods of determination, either chemical or physical, for Vitamin D. The colorimetric methods described ever and anon are of no use, being nonspecific, and, therefore giving inaccurate values. The only method at our disposal to ascertain Vitamin D is the biological test. It is based upon the property of the vitamin to prevent or cure the bone changes of rats fed on a rachitogenic diet. There are, therefore, two methods of Vitamin D testing to choose from—the prophylactic and the curative, which are of equal value with sufficiently large animal material to work with and a correspondingly large experience. The curative methods rest upon the fact that rachitic rats following treatment with Vitamin D-containing substances show in the distal ends of their rachitic bones healing processes in proportion to the dose administered. The stepwise manner of these changes may readily be discerned (McCollum et al). In the so-called "line test" the degree of healing is ascertained by putting a bone in a nitrate of silver solution and exposing it to natural or artificial light. By this method the freshly deposited calcium becomes nicely visible, being blackened by the colloidal silver. According to the breadth of the calcified zone the varying degrees

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of healing are estimated. The roentgenological method which may be employed as well in a prophylactic as in a curative sense has continued to prove reliable. By means of a scale the grade of rachitis and the extent of the healing processes at the epiphyseal lines may be read in an X-ray film of the bone endings (Windaus, Scheunert, Schieblish, Holtz, Laquer, Kreitmair and Moll). Another method of ascertaining the curative effect of Vitamin D is the examination of the ash content of bones of young rats fed on a rachitogenic diet. The substance to be determined is fed on a basis of a fixed dosage. Its effect is read out of the bone-ash-content of the test animals. A controlling series of animals, which have been fed a standardized preparation of the vitamin, serves as comparison. The ash-content of the bones stands in direct relation to the Vitamin D content of the diet (Hume-Pickersgill-Gaffikin). Still another method of determination is very interesting; it is based upon a change of the pH value of the feces at the beginning of recovery from rachitis from slightly alkaline to slightly acid. Of all the methods the roentgenological examination has been given preference. It is done incomparably quicker, for example, than the determination of the ash content of bones, and by maintaining a fixed method as shown chiefly by the work of Windaus and his school, it produces sufficiently accurate values. All of the methods demand a large experience and must be studied in the respective text books.

Vitamin D Units. The Vitamin D standard set up by the International Vitamin Conference is a 0.01% solution of irradiated ergosterol in olive oil. Designated as International Unit Vitamin D, it is that quantity of Vitamin D which possesses the antirachitic power of 1 mg. of the standard solution. This amount of standard solution corresponds to 1/10,000 mg. (equals 0.1 γ of ergosterol, which was employed originally to make the standard solution). The biological unit ever and anon referred to in the literature is that smallest quantity of Vitamin D, which supplied daily for 14 days to young rats fed on a fixed diet, completely protects them against rachitis. The clinical unit equals 100 biological units (equals 12.5–17 International Units).

Commercial Preparations. In Germany pure Vitamin D is on the market as Vigantol, and that in the form of Vigantol oil or of Chocolate tablets, Vigantol cod liver oil and Vigantol salve. The oil represents a 1% solution in olive oil, 5 drops corresponding to 10 clinical units. The chocolate tablets contain a like amount. The Vigantol cod liver oil and the preparation known as "detavit" include Vitamin D as well as Vitamin A, in standardized form. The dose for nurslings and small children is ½ to 1 teaspoonful; for larger children 1-2 dessert spoonfuls, and for adults 1-2 teaspoonfuls once a day. The Vigantol ointment must always be freshly made; it contains 0.5%–1% of Vigantol. A strong Vitamin D-containing ointment is on the market under the name of Unguentolan. Foreign commercial preparations are Viosterol and Radiosterol. There are a number of standardized cod liver oils for sale under various names.

Occurrence of Vitamin D. Compared to other vitamins, Vitamin D is scarce in Nature. Main sources of Vitamin D or its precursor in our food are: butter, milk, egg yolk, yeast. There are only traces of it in vegetables,

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if any. Indeed some cereals may, at least in rats, by their low phosphorous content (the phytin phosphorus in vegetable matter the organism cannot metabolize) have direct rachitogenic activity. On the other hand our customary edible mushrooms have clearly demonstrable quantities of Vitamin D, and the same is true for certain grain germs. The Vitamin D content of animal foodstuff depends on the fodder with which the animals have been nourished. By irradiation with sun or ultraviolet light the antirachitic value of the food may rise considerably. Cow's milk abounding in phosphorus and calcium has far greater antirachitic value, than its low Vitamin D content would indicate.

Exceedingly rich in Vitamin D are the various fish-liver oils, of which the best known and most used therapeutically, is the cod liver oil. However, the Vitamin D content of it is not constant, fluctuating between 0 and 20 biological units per gram. The livers of other fish, for example, halibut and shark, also have a high vitamin content, while the liver oils of whale and dogfish have much less of the specific substance. There are species of fish, the liver oils of which hold many times the Vitamin D content of cod liver oil. Comparing the vitamin content of butter, for instance, a good cod liver oil contains 20 to 400 times as much Vitamin D as an equal quantity of butter. Just why so much Vitamin D should be stored in the fish livers has caused a good deal of brain work. The kind of feed of the fish cannot explain the abundance of vitamin present (Bliss, Hess). Today it is assumed that the Vitamin D factor is formed in great quantities in the fish livers by a so-far-unknown synthesis. The assumption has not been substantiated. Equally undecided is the question whether the antirachitically active substance of the fish livers is identical with the Vitamin D obtained by irradiation of ergosterol or not, though their biological behavior is alike (Dalmer, von Werder and Moll).

Lack of Vitamin D in the nutriment is offset by the exceedingly frequent occurrence of the provitamin, and by the possibility of a photochemical synthesis of Vitamin D in the skin of man and animal.

Vitamin D Requirement. Contrary to Vitamin C, which is synthesized by most animals themselves, almost all laboratory animals depend upon their food for their supply of Vitamin D. The Vitamin D requirement of a healthy little child amounts to 12-15 International Units (about 1 clinical unit daily), while to recover a rachitic child needs at least 5 clinical units per day. Quite similar as with the other vitamins, these figures only indicate a rough average since the requirement is never the same, but dependent upon diverse circumstances. For instance, the relation of calcium to phosphorus in the food which plays a pace-making role, at least, in test animals (McCollum and co-workers) must be emphasized. And also, the very frequently observed appearance of rachitic symptoms following infections speak for the fact that infections and the defense against them raise the Vitamin D requirement of the organism. It happens likewise in cases of certain diseases of the gastrointestinal tract, for example, celiac disease and choledochus obstruction (Heyman), conditions, in which probably because of faulty absorption of the vitamin in the gastrointestinal tract, despite a sufficient supply, a tendency to rachitis appears. The consumption

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of Vitamin D is increased during pregnancy and puberty, when extension of longitudinal growth sets in. Concerning the question of the need of Vitamin D, of great importance is the recently demonstrated storage of Vitamin D in various organs, for example, in the brain, adrenal, thymus, liver, kidney and in the skin (Goldblatt, Soames and Page). In experimental rachitis a relation of time between the onset of the disease and the duration of the consumption of the vitamin depot has been observed long since (Hess et al). To what extent, however, nurslings may be protected by supplying the pregnant and nursing mother with suitable Vitamin D doses has not been established with certainty. In view of the peculiar susceptibility of prematures to rachitis it has been considered that they in contrast to mature children possess no vitamin depots, as they receive them from the mother during the last weeks before delivery.

Manifestations of Avitaminosis D. Chief symptoms of avitaminosis D are the well-known changes of the skeletal system in the form of an impeded calcification at the epi-diaphyseal margins of the long bones, and the resulting interruption of longitudinal growth. In microscopical sections of bone the disappearance of the characteristic zone of calcification at the epiphyseal lines is specifically impressive. An uncalcified osteoid is formed showing on longitudinal section a characteristic goblet-shaped excavation. As the disease progresses all sorts of bendings of bone appear. One of the first signs is the rachitic rosary, excrescence of the ribs at the bone-cartilage margins. These symptoms of rachitis are assumed to be a disturbance of the mineral metabolism running a natural course in several phases, which is often manifest in a lowered blood-phosphorus level before clinical symptoms arise. Thus, in growing rats the serum phosphorus may drop from the value of 7–8.5 mg.% to 2.8 mg.%. At a later period the calcium balance becomes also deteriorated. However, the calcium level in the serum is far less changed than the phosphorus level. With the onset of healing processes the phosphorus level improves first and then the calcium balance. The question of origin of the phosphatemia in rachitis is still not clarified, but it is assumed as certain that the interruption of ossification in avitaminosis D is not a primary disease of the bone, but a sequence of a disordered mineral metabolism. There are several theories to explain its occurrence. In the theory of absorption it is assumed that the phosphoric acid in the gastrointestinal tract is insufficiently absorbed, whereby the phosphorus level of the serum sinks and the ossification suffers. Another theory points to a dysfunction of incretory glands as a cause of the disease. As a matter of fact there are certain reciprocations between Vitamin D and individual hormones, so that hormonal disturbances may have rachitogenic effect. Some eminent investigators like Mellanby are considering the possible role of toxic substances, so-called toxamines, which are supposed to arise from the food or from metabolism. More recent investigation seems to afford a better understanding of the processes involved in the evolution of rachitis. It was established that bone formation is contingent upon an absorbable calcium-phosphorus complex in the blood, which is absent in rachitis, and its quantity is independent of the total calcium and phosphorus in the serum (Hess). It was conceivable,

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therefore, that Vitamin D served as a sort of catalyst for the formation of certain calcium-phosphorus complexes, necessary in the process of ossification. Yet to be mentioned is a so-called renal rachitis in children, developing sometimes into chronic nephritis and presenting in the blood an inorganic phosphorus content above normal. A remarkable feature of this disease is that it reacts negatively toward a Vitamin D supply.

Vitamin D Pharmacology. I. Toxicology. Very soon after discovery of antirachitically highly potent irradiation products of ergosterol, toxic effects of these substances in large doses was reported (Bamberger, Degkwitz, Pfannenstiel, Kreitmair and Moll). The conception that the injuries incited were not due to Vitamin D proper, but to associated substances present proved erroneous, for later it was found that in large doses Vitamin D also showed toxic effects. Pure Vitamin D is merely less toxic than the irradiated ergosterol. The antirachitic action of the latter cannot be separated from the toxic effect ascribed to the so-called calcinosis-factor. That factor is measured by toxic marginal doses, and they are that smallest daily dose which, under certain conditions, produces reduction of weight or death of the test animal (the mouse in this case) (Holtz). As first sign of overdosage there appears in omnivera, a marked hypercalcemia; in herbivora, an equally pronounced hyperphosphatemia. Outstanding changes may be named; rough hide, weight loss, gastrointestinal manifestations, such as anorexia and diarrhea. After a supermineralization of the bones at the outset, it finally comes to a decalcification of the subepiphyseal spongiosa with calcium deposits in various organs as, for instance, in the large vessels, heart, kidneys, and further to nephritis and uremic symptoms, supposed to be due to a toxicosis from protein disintegration. Under calcium-poor, or calcium-free feeding, the organic calcification and the hypercalcemia are less marked, but still evident, which proves that the superfluous blood calcium comes from the bones. Another symptom of hypervitaminosis D is an action upon the fat metabolism resulting in emaciation, lipoid infiltration of liver, arterial wall and endocrine glands (Collazo). From hypodermic injection of larger doses of Vitamin D local calcification may develop as a specific effect of the vitamin (von Brand, Holtz). All of the organ calcifications, even the grave ones, are capable of reabsorption according to experiences hitherto obtained (Demole). Of great importance is another observation—that the hypervitaminosis D sets in later and less intensively, if at all, when other vitamins, particularly those of the B-complex and Vitamin A are simultaneously supplied (Harris, Moore, Jusatz).

Hypervitaminosis D is already of great interest for the reason that it constitutes the first instance of a toxic action of large vitamin doses. However, merely for practical purposes it is scarcely of any importance, since the therapeutic spread of Vitamin D, meaning the proportional difference between the antirachitic and the toxic marginal value, is uncommonly great. In animal tests the toxic dose is one thousand times the curative. At any rate a 40 or several 100 fold of a therapeutic dose was given for weeks without disturbances having appeared. The approximate border line dose, from which by its daily administration for weeks symptoms arise, amounts to about 200 times the normal dose. The tolerability of Vitamin D in chil-

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dren depends upon the degree of the Vitamin D deficit of the organism. Rachitic children tolerate far greater amounts than the healthy. In the few cases where an hypervitaminosis D in man was observed at all, the overdosage showed itself in anorexia, loss of weight, digestive disturbances and nephritic symptoms. At any rate to prevent overdosing, the use of the pure Vitamin D must be restricted to those cases where it is strictly indicated.

II. Pharmacological properties. Vitamin D is according to Rominger "that organic substance" which may remove in smallest doses the rachitic disturbance of the mineral metabolism in man and animal, and prevent it even in the presence of continued rachitogenic injury. In high dosage it causes calcium deposits, cachexia and death of the test animals, and in this respect it is a poison for man as well. Influencing all bony changes concomitant with rachitis and those in a larger sense related to it, it fulfills all the postulates of an antirachitic specificum. In the course of investigations for the purpose of getting conversant with the working mechanism of Vitamin D in the economy, a series of pharmacological effects were met with. In a general way it may be said that the oxidative processes of the organism are increased by physiological quota of Vitamin D. This is supported, among other things, by the observation that the blood catalases rise in test animals fed Vitamin D, and are lowered by overdosage (Jusatz). Following Vitamin D administration the "carbohydrate/lactic acid" quotient rises in the blood in a like manner. In Vitamin D poisoning the decrease of glutathione is looked upon as an expression of a disturbance of the oxidative metabolism (Hesse). The phosphatase content of rats, if worked up entirely, is increased by irradiated ergosterol and the serum cholesterol as well. According to recent work of Alfred F. Hess the rachitogenic-curing effect of Vitamin D, as mentioned, must be ascribed to its ability of building up the absorbable calcium-phosphorus complex necessary for bone formation. Results have been published by investigators regarding the influence of Vitamin D upon blood pressure. By daily dosing with irradiated ergosterol it was essentially increased in dogs. In the intestinal channel Vitamin D may raise the permeability of the gut cells for calcium and phosphoric acid (Drummond, Bond) and may activate the phosphate-splitting ferments. It's quite certain that the raising of the blood calcium level is connected with the blood-clotting effect of the pure Vitamin D (Selye).

Reciprocations between Vitamin D and Parathyroid and Thyroid Activity. The relations to the hormones proved for all vitamins may be assured to a special high degree for Vitamin D. From the start it seemed obvious to consider a connection between Vitamin D and the parathyroid, which has a controlling part in the regulation of calcium metabolism. The difference in action of the parathormone and Vitamin D consists in the fact that the former regulates the calcium phosphoric acid elimination at the expense of the bones, while administration of Vitamin D allows adsorption of calcium and phosphorus by the bones, raising the blood calcium level, for instance, in tetany, by effecting a better utilization of the calcium offered in the food. Nevertheless in large doses Vitamin D may also develop parathormone activity (Demole, Christ). Both, the irradiated ergosterol and

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the parathormone are able to raise the calcium content of serum, for example, in parathyroidectomized dogs. It is possible, however, that this effect of Vitamin D in the food is indispensable for development of hypercalcemia by the parathormone. Therefore, in the treatment of rachitis Vitamin D may never be substituted by the parathormone (Soos). However, it is possible to influence the parathyroprival tetany by giving large doses of Vitamin D.

According to other studies Vitamin D may become active by inciting thyroid function. The experimental, as well as the spontaneous human rachitis according to von Nitschke's investigation (not confirmed by others, for example, Fasold) may be relieved of all of its symptoms by feeding thyroid substance. Typical histological changes of the thyroid found in rachitis and improved by the vitamin, speak for a connection between thyroid and Vitamin D. Of thyreogenic origin is supposed to be the sinking of the basal metabolic rate, which is seen in Vitamin D deficiency resulting from a decrease of oxidation. The typical rachitis observed in young thyroidectomized rabbits despite a normal diet, is not curable by Vitamin D, but is with thyroid, which might also speak for a Vitamin D effect by way of thyroid function. It is worthy of note that rachitic rats have been successfully treated by injections of thymus extracts, pointing toward certain relations of thymus and Vitamin D. A more intensive study of the conditions seems urgently desired.

Elimination. The elimination has been studied in the cow. Upon feeding 300 gm. (equals 60,000 biological units) of irradiated yeast, 25% of the Vitamin D fed was eliminated with the feces. In the urine no Vitamin D could be found, but the antirachitic value of the milk had increased considerably, and the relative Vitamin D content moved in inverse ratio to the milk-fat production (Hess et al). Moreover, when Vitamin D has been given, it is also eliminated in the bile (Hefke).

Clinical Application of Vitamin D.*

Rachitis. Research on the pathogenesis of rachitis which reached its crowning success in the elucidation of constitution and in the synthesis of the pure Vitamin D naturally had a bearing upon the treatment of avitaminosis D. The observation that sunlight and artificial quartz light were apt to cure rachitis in entirely the same manner as cod liver oil became intelligible, as explained above, when it was established that the action of short wave light transferred the ergosterol ever present in the skin into Vitamin D. In the treatment with cod liver oil, active vitamin is put into the body from outside. So the chief causes of rachitis are either a deficient supply of Vitamin D in the nourishment or inadequate exposure to sunlight. When this was recognized, new and unforeseen possibilities were disclosed for the prevention and treatment of rachitis. By determination of constitution and the production of Vitamin D in pure form it became possible to really express in terms of weight the Vitamin D requirement of the organism.

By an adequate supply of Vitamin D, either by improving hygienic conditions (light and sun) or by immediate addition of Vitamin D to the food, or by treatment with isolated vitamin, rachitis may be prevented or

* Among others see Merck's Annual Reports, 1929-1934. Guggisberg: Die Bedeutung der Vitamine fuer das Weib., 1935.

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cured with assurance. That sunshine and artificial quartz light can cure rachitis by synthesizing Vitamin D in the skin is of great importance for the reason that for the first time a photosynthesis of a vital substance in the skin has been demonstrated. By this discovery the necessity to train the child to be accustomed to fresh air and the great advantage of sports in the free air received an entirely new appreciation. Moreover, the prevention and cure of rachitis were uncommonly facilitated by the possibility of manufacture of highly concentrated, standardized Vitamin D preparations. Up to the time that such were available, cod liver oil was the remedy of choice, and without doubt, it is still an excellent medicament for rachitis. There was a disadvantage, however, in that the vitamin content of the usual preparations on the market fluctuated within pretty wide limits, so that in recent years the liver oils have been standardized. Other objections to the liver oils are the taste and that they are not always absorbed well in the gastrointestinal tract. Of the commercial preparations containing pure Vitamin D Vigantol is the best known in Germany. This is a preparation which has proven exceedingly potent in the prevention and cure of rachitis, and compared to the irradiated food mixtures, it has the advantage that accurate doses may be given.

As mentioned, prematures have a very special tendency to rachitis, which is explained by the vitamin depots being lacking in children. In a general way it may be said that hereditary and congenital evolution of rachitis has not been proven even with nutritional deficiency in the mother. However, while the mother's economy is inadequately supplied with Vitamin D, the infant lives in a condition of latent rachitis. Holding no appreciable Vitamin D reserves the child will succumb to a rachitis on the least provocation. So the prophylaxis may begin with the mother, but a sufficient provision of the necessary vitamins after the birth of the child remains the most important postulate (Guggisberg). In women treated with Vigantol during pregnancy the placenta shows up a great deal of Vitamin D. A like result may surely be obtained by dietetic measures and proper exposure to sunlight. To prevent rachitis in prematures immediate administration of Vigantol has been recommended, three drops twice daily. When vitality is markedly low, smaller doses are feasible, 1 to 2 drops daily of Vigantol. The same dosage is applied in small children for the prevention of rachitis during sunless periods. The vitamin is given for a month with pauses of six weeks. As soon as secondary manifestations arise, for example, diarrhea, the dose must be reduced and Vigantol may be given every second or third day. In florid rachitis of older infants much larger doses are needed, up to 20 drops a day. There has not been any harm observed following these high doses. It must be mentioned that these, and even still larger doses, do not suffice if the florid rachitis is complicated by an infectious disease.

Osteomalacia. As a result of careful anatomical studies the idea has increasingly persisted that osteomalacia, like rachitis, must be referred to as a lack of Vitamin D. In sequence late rachitis and early osteomalacia are entirely identical diseases. It may be said that rachitis, osteomalacia and osteoporosis denote clinical terms corresponding to the different ages of life, but of the same metabolic disturbance. Puerperal osteomalacia,

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however, has to be assigned to a place of its own. It is very difficult to explain the result obtained by castration in puerperal osteomalacia, which very likely develops because of withdrawal of calcium and Vitamin D by the fetus. At any rate, it is a fact that the Vitamin D therapy in osteomalacia has rendered excellent results. Vigantol has proven especially reliable, and if given in doses of 6-10 drops daily, it may cure the disease in a few weeks.

Tetany. The third disease, similar to rachitis and osteomalacia, associated with a disturbance of calcium metabolism, is tetany. This metabolic disorder of tetany finds its expression in constant hypocalcemia, though it may be of different origin. Under the heading of "relations of parathyroid and Vitamin D", the parathyroprival tetany was mentioned, which could be influenced by large doses of Vitamin D. In this case the given remedy is the parathormone of Collip. Lately a modified irradiated product of ergosterol, the so-called A. T. 10 (Holtz), has been used. In proper dosage it raised the blood-calcium level for a long time. The genesis of puerperal tetany does not seem to be quite uniform. If the disease is a disturbance of the vitamin metabolism or if a hypofunction of the adrenal is a factor, it may often be decided only ex juvantibus. In parathyroprival tetany many authors recommend Vitamin D itself as a supporting measure. In larger doses (5-10 times the antirachitic) it may wholly replace parathormone. The formerly so-called idiopathic tetany, which may develop without injury to the parathyroid, is looked upon by many students as merely a certain phase in the course of avitaminosis D. It may appear as a complication of recovery from rachitis, in which, as indicated, the improved phosphorus balance preceeds the rise of the blood-calcium level. Out of this so-called spring crisis manifest by a hyperphosphatemia and hypocalcemia associated with an alkalosis (contrary to osteomalacia, in which an acidosis is found), the syndrome of tetany may then develop. The remedy of choice for this kind of tetany is naturally Vitamin D. It is of specific importance that the rather rare cases of rachitis, arising from a disturbed absorption in the gastrointestinal tract, as, for example, celiac disease and biliary obstruction, may be treated parenterally with Vitamin D in the form of Vigantol either intramuscularly or intravenously. The dosage must be adjusted to the quantities given in peroral administration.

Vitamin D and the Bony and Dental System. The close relationship between Vitamin D and calcium metabolism was impressively elucidated by observations during the War of the increase in the number of fractures in children nourished chiefly with margarine and of the sudden decrease of them when butter was again available. Vitamin D may, however, act not only as a preventive, but also, according to clinical and experimental investigations, it has a promoting action upon callus formation and calcium infiltration following fractures. By administration of 3-5 drops of Vigantol daily the healing time of fractures may be shortened even in old people. A careful dosage is imperative, however, since toxic doses may provoke demineralization and thus have an opposite effect.

Generally known is the importance of Vitamin D in the formation of teeth in children. Rachitic teeth, which give evidence throughout life of

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recovery from an avitaminosis, are not so rarely seen. Purely by experimental means a very rapid regeneration of the supercalcified dentine has been observed with local application of Vigantol. Aside from Vitamin D the value of other vitamins has been stressed and that of Vitamin C in particular.

Vitamin D in Allergic Diseases. Vigantol is recommended furthermore, either alone or with calcium in all diseases in which an increase of the blood calcium level is desired. The rise of this level continues longer if Vigantol is given at the same time. Very good results have been reported from combined calcium-Vigantol treatment in allergic diseases such as bronchial asthma and hay fever. In diseases of the vegetative-endocrine system, as in the thyrotoxicoses and in asthenic patients with more or less hyperthyrotic tendencies, the results of this treatment are allegedly entirely satisfactory. In all of these cases intravenous injections of calcium are given with 5 drops of Vigantol per os. In allergic conditions, action may be obtained with Vigantol alone if toxic doses are given.

Vitamin D and Tuberculosis. There has been much contention about the Vitamin D effect in tuberculosis, in which recently, a disturbance of the mineral metabolism was also discovered. As a supporting measure Vigantol in doses of 3-5 drops is said to exert a favorable general effect in every form of tuberculosis, appearing specifically in increase of weight and improved appetite. Moreover, some authors have reported that pure Vitamin D may act favorably in preventing pulmonary hemorrhages and in promoting calcification of progressive processes. Especially in tuberculosis too large doses must be cautioned against, for by overdosage it may easily come to an undesired demineralization. Of very little uniformity are the experiences made by investigating the relations between Vitamin D and the resisting forces of the organism against infections. While some workers have seen an increased resistance of the test animals against certain infections following treatment with Vitamin D others have not been convinced of a protecting effect of the vitamin. However, perusal of the work submitted seems to indicate that Vitamin D, especially in combination with the Vitamin B complex may effect a rise of resistance. In veterinary medicine, in which the Vigantol treatment generally plays a large role, the protective action of Vitamin D has been made use of extensively.

Vigantol Treatment of Leucorrhea. The Vigantol treatment of fluor albus is well spoken of by gynecologists as a supporting agent. With cautious dosage and in combination with calcium and general dietetic measures Vigantol is supposed to act favorably, especially in non-specific leucorrhea in smaller girls.

Vigantol Treatment of Eczema. In eczema of children Vigantol ointment has been quite effective, but improvement has also been obtained with the same treatment in adults. In acne rosacea the results of parenteral administration of Vigantol are said to be similar to those of the cod liver oil injections of Unna (Strafke).

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VITAMIN D CONTENT OF SOME FOODSTUFFS

(in γ per 100 gm. of substance; 1 γ equals 0.001 milligrams).

Sea Food	
Herring	0.14
Sardines	0.14
Herring, smoked	0.14
Sprats	0.14
Oysters	0.16
Eggs	
Egg yolk	20.00
Milk—Butter	
Cow's milk	0.2 - 0.4
Butter	0.4 - 20.0
Fats and Oils	
Cod liver oil	40 -400.0
Edible Fungi	
Mushrooms	0.14
Morels	0.14
Puff Balls	0.14

BIBLIOGRAPHY FOR VITAMIN D

Bills, Journal of Biological Chemistry, 72, 751, 1927.
Bond, Lancet II, 328, 1929.
Bourdillon, Proceeding of the Royal Society, 108, 340, 1931.
Bourdillon, Proceeding of the Royal Society, 109, 488, 1932.
v. Brandt and Holtz, Z. f. Physiol. Chem., Bd. 185, S. 217, 1929.
Brockmann, Hoppe-Seylers, Zschr., Bd. 241, H. 1, 2, and 3, S. 104, 1936.
Brockmann and Chen, Hoppe-Seylers, Zschr., Bd. 241, H. 1, 2 and 3, S. 129, 1936.
Collazo, Paidoterapia Nr. 113, S. 575, 1931.
Dalmer, v. Werder and Moll, Mercks Jahresbericht 1934.
Degkwitz and Bamberger, Gesdh. f. Kindesalt. 3, 181, 1928.
Demole, Christ, Arch. exp. Path. 146, 361, 1929.
Drummond, Biochemical Journal 20, 1229, 1926.
Fasold, Mschr. Kinderh. 62, 28-32, 1934.
Flinn, Journal of the American Medical Association 21, September 1935.
Goldblatt and Soames, Biochemical Journal 17, 294, 297, 1923.
Guggisberg, Die Bedeutung der Vitamine fur das Weib., 1935.
Harnapp, Klin. Wschr., II, 1043, 1936.
Harris and Moore, Biochemical Journal 5, H. 22, S. 1461.
Hess, Alfred F. et al, Journal of Biological Chemistry 27-55, 100, 1933.
Hess, Alfred F. et al, Journal of Biological Chemistry, 97, 369.
Hesse, Klin W., Nr. 12, 1933.
Heymann, Z. f. Kinderh. 49, 748, 1930.
Holtz, D. m. W., Nr. 15, S. 560 and Nr. 48, S. 1830, 1934.
Huldschinsky, D. m. W., 45, 712, 1919.
Hume, Pickersgill, Gaffikin, Biochem. J. 26, 488, 1932.
Kreitmaier and Moll, N. m. W., Nr. 40, S. 1688, 1931.
Laquer, Klin. W., Nr. 23, S. 1072 and Nr. 33, S. 1542, 1931.
Laquer, D. m. W., Nr. 6, S. 243, 1931.
Mellanby, Journal of the American Medical Association, 96, 325, 1931.
Nitschke, Z. f. Kinderh. 52, 668, 1932.
Nitschke, Z. f. Kinderh. 54, 1933.
Nitschke, Z. f. exp. Med., 65, 1929.
Page, Biochem. Z. 220, 420, 1930.
Rygh, Bull. Soc. Chim. biol. Paris 18, 1091-1096, 1936.
Scheunert, Schieblich, Klin. W. I, 699, 1929.
Soós, Arb. ung. biol. Forsch.—inst., 4, 515, 1931.
Windaus et al, Nachr. Ges. Wiss. Gottingen, Math.—Physik. Kli. 1932.
Windaus et al, Ann. Chem., 481, 120, 1930.
Windaus et al, Ann. Chem., 25, 483, 1930.
Windaus et al, Ann. Chem., 266, 489, 1931.
Windaus et al, Klin. W. 753, 1933.

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CHAPTER FIVE

VITAMIN E

Introduction. For normal function of the sexual organs and attainment of optimal fertility in rats provision of a specific vitamin—the antisterility Vitamin E—is necessary. That information was published in 1923 by Sure and Evans, but if this vitamin is also required by man, it has not been established with certainty. Manifestations of a Vitamin E deficiency are not known in man. Though it has been demonstrated in recent years that Vitamin E concentrates in various diseases of the genital sphere, definitely not due primarily to vitamin deficiency, have obvious curative effect, that is not proof of a vital importance of this vitamin for the human organism, for the vitamins are not only (at least for part of the mammals) essential accessory foodstuffs, but independently thereof exert curative activity even in diseases which are not avitaminoses. This second mode of action appears to be present in Vitamin E in a marked form. The nonexistence of human avitaminoses E may possibly be connected with the fact that this vitamin is more extensively dispersed in Nature and that it is more resistant to the effects of Kitchen-processing than other vitamins. Whatever we know today of the physiology of Vitamin E and of the symptoms of avitaminosis E, we are chiefly indebted to the extensive investigations of Evans (1926-1928). Biological research of the Vitamin E problem has not made any essential progress, except that recent studies seem to indicate that Vitamin E consists of two divisional factors, one being indispensable to the male and the other to the female organism.

Chemistry. Vitamin E in the purest form so far produced exhibits a colorless, or pale yellow viscous oil, soluble in alcohol and ether, but not in water. Its chemical composition corresponds best to the formula $C_{29}H_{50}O_2$ (eventually $C_{28}H_{48}O_2$) (Drummond-Singer-MacWalter). Its properties indicate that it is a polycyclic alcohol which approaches the triterpenes (lanostearin and amyrin $C_{30}H_{50}O$, betulin $C_{30}H_{50}O_2$). Amyrin frequently accompanies Vitamin E at its natural sources. Vitamin E is very resistant to heat (200°); and by alkalies and acids, catalytic hydration (even under greatest pressures) it is not destroyed; neither is it destroyed in pure state by oxygen, but it is decomposed if the fats in which it is held in solution become rancid (Olcott) or if heavy metals are present in lipoid-soluble form (Waddell-Steenbock). Against this inactivation Vitamin E is protected in Nature by "antioxygenetic" associated substances of a phenol character (Cummings-Mattill). Its molecule contains probably three double compounds and one OH group. Vitamin E acetate and benzoate are equally effective as the unesterizd vitamin and moreover insensitive to

rancidity. In Nature Vitamin E very likely occurs also in this esterized form. Contrary to older perceptions it has no relation to xanthophyll.

Determination. The difficulty of the determination of the Vitamin E content of foodstuffs is aggravated by the inadequacy of the test methods so far worked out. Specific chemical reactions are not known. The biological determination is round about and time-consuming, extending of necessity over two generations, the Vitamin E depots of the organs being very slowly depleted and then because of the widely spread results, it yields suitable values only when applied to animal material. The usual test procedures are curative and prophylactic. In the classic curative test of Evans, female rats are fed Vitamin E-free diets until resorption sterility occurs. Thereafter on the day of a mating a single dose of the substance to be investigated is fed and the course of gestation is observed. One may also try to ascertain the prophylactic quantity which guarantees a normal gestation and a normal number of offspring (Evans) or prevents paralysis (Ringsted). To frame a term for the Vitamin E unit has not been possible as yet. At present it must suffice to indicate the Vitamin E content of foodstuffs by the quantity necessary to prevent sterility.

Occurrence. The following table shows the occurrence of Vitamin E in Nature.

Material	Relative Vitamin E Activity*
Beef Muscle	20
Beef Liver	10
Placenta	25-100
Hypophysis, Anterior Lobe	25-100
Lard	20
Egg Yolk	17
Water Cress (at least)	50
Green lettuce	40
Green Vegetables	40
Peas	25
Peanuts, raw	100
Wheat Germs, dry	400
Bananas	3
Yeast	0-20

Vitamin E is also found in barley, oats, rice, coconut, cotton seed, palm linseed and soja oils, butter and milk. Flour is Vitamin-E free.

Requirement of Man. The kinds of animals in which proof of indispensability of Vitamin E has been established are rats, mice, chickens (Gard, Ender). The honey bee develops into a queen only when it receives Vitamin E-containing food. Larvae of the working bee are nourished Vitamin E free (Hill-Burdet). Since the tendency to abortion in cattle, sheep and swine may be removed by Vitamin E concentrates, there must exist an E requirement in these animals also; it has not been definitely proven, however. In rats a daily supplement of 0.1 mg. (in form of the highly purified

* Relative Vitamin E activity equals 100/sterility-preventing minimum doses in grams.

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preparations of Drummond-Singer-MacWalter) suffices to maintain normal fertility. About the magnitude of the human requirement nothing is known. A hypervitaminosis E is unknown.

Behavior of Vitamin E in the Organism. The supplied Vitamin E is stored in the organs, most in those pertaining to the female sexual sphere (placenta, hypophysis, anterior lobe) and then in muscle, pancreas, spleen, less in liver, not in kidney and brain. According to Zagami also testes and semen contain Vitamin E. Depletion of these depots proceeds very slowly in Vitamin E deficiency, but in fully developed avitaminosis E these organs are Vitamin E-free. The assumption that Vitamin E might be a precursor of prolan is lacking in proof so far.

Symptoms of Avitaminosis E. The manifestations of Vitamin E deficiency are fundamentally different in both sexes. In the male histologically demonstrable lesions appear quite early, becoming irreparable when the avitaminosis is fully developed. Manifest organic changes (except increase of basophilic cells in the hypophysis) in the female have not been observed and the disturbances in the course of gestation may be relieved at any time by supplementing Vitamin E. In the male sexual organs the beginning of avitaminosis E is presaged by azoospermia and degeneration of the spermatozoon. Later atrophy of the seminal tubules occurs leading to sterility. Finally, it comes to an irreparable loss of spermatid nuclei, with formation of giant cells and liquefaction. The Vitamin E-free-fed female always remains conceptive, carrying out the first gestation normally, providing the conception occurs at the beginning of the avitaminosis; however, even in this case, the rearing of the young is often refused. Sometimes in the first gestation stillbirths appear; in the second, only a few dead young ones are brought forth; in the third, intrauterine resorption of the fetus and placenta occurs. Spontaneous deciduomata have been observed. Outside of the sexual sphere avitaminosis E manifests itself in muscular dystrophies (C. Mueller —Pappenheimer) and paralysis of the extremities (Ringsted). Young Vitamin E fed female rats may also exhibit pareses (Evans-Burr). In the stomach wall an undefined cell growth resembling malignancy has been seen by Adamstone.

Commercial Preparations. The following preparations are highly concentrated and have been tested in animal experiment and in the clinic and may be given perorally or parenterally: The German "Vitamin E Promonta", the English Feritol (Vitamin Lts., London W4) and the Danish "Fertilan MCO". A schedule of dosage cannot be submitted.

Clinical Application of Vitamin E. Experiences gathered thus far from the therapeutic application of Vitamin E in man do not allow of definite conclusions in any direction and may only be looked upon as guides. That deficient nutrition is liable to give rise to menstrual disturbances, sterilities and genital hypoplasias, has been shown by Bauer and Macomber, but these manifestations off hand may not be referred to as E deficiency, Vitamin A likewise being required for normal function of the sexual organs. Juhász-Schaeffer have obtained good results with Vitamin E concentrates in sexual weakness, azoospermia, sterility in man, and then in hypogalactia and especially evident in retarded menarche, but none in menstrual disorders.

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The discoveries of Juhász-Schaeffer and Vogt Möller made on a relatively large clinical group give promising prospects for Vitamin E in the prophylaxis and therapy of habitual abortion and in the treatment of primary sterilities of women. Gierhake has recommended Vitamin E treatment in the tendency to premature births and generally in functional disturbances of propagation, especially if an alimentary deficit is suspected.

BIBLIOGRAPHY FOR VITAMIN E

Albrecht, M. m. W., 1319, 1936.
Evans et al, Journal of Biological Chemistry, 113, 319, 1936.
Evans et al, Science, 83, 421, 1936.
Eymer, M. m. W., 1940, 1936.
Gierhake, Klin. W., 220, 1936.
Guggisberg, Die Bedeutung der Vitamine für das Weib., Berlin-Wien, 1935.
Juhász-Schaeffer, Erg. inn. Med. 45, 129, 1933.
Quiraud, Nodet, Paris Médical, II, 199, 1936.
Saphir, Endocrinology 20, 107, 1936.
Simonnet, Monde médl., 810, 1936.
Vogt-Möller, Hospital Tidings, 621, 1933.
Vogt-Möller, Klin. W., 1883, 1936.
Watson, Canadian Medical Association Journal, 34, 134, 1936.
Watson, Tew, American Journal of Obstetrics & Gynecology, 31, 352, 1936.

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CHAPTER SIX

VITAMIN H

Introduction. First discovered in 1927 by Miss Boas under the name of "Factor X", it was recognized by Györgyi (1931) as an essential factor in the diet of man and designated by him as "skin factor". Judging from what little is known, it is an indispensable accessory factor for the child in particular, differing essentially as to properties as well as to physiological action from other vitamins. Vitamin H is required for the normal evaluation of fats and certain protein bodies, and in the metabolism of these substances it has to fulfill certain functions, the nature of which are not known in detail.

Chemistry. Vitamin H is distinguished from other accessory factors in that in its natural state of occurrence it is insoluble in water as well as in ether, alcohol and fats, but is firmly fixed to the insoluble organic basal substance of foodstuffs (probably to protein). Only the proteolytic-splitting processes in the intestine, or the papain hydrolysis in vitro, effect a liberation of the Vitamin H factor from its compound and make possible its absorption. Thus, it is explained that extracts of untreated raw material containing Vitamin H (liver or yeast extracts) do not develop Vitamin H activity. The manufacture of pure Vitamin H has not been successful as yet, but may be expected in the near future, since highly potent extracts extensively freed of ballast matter are available. Vitamin H (freed according to Lease-Parsons by papain digestion of residue of extracts of liver) is itself heat-resisting, soluble in water, but not in alcohol and benzine, contains nitrogen, but no sulphur. Its chemical nature is unknown; it is perhaps an amino acid (Gorter).

Determination. The determination of the Vitamin H content of food is obtained by the curative rat test. When animals fed on a certain deficiency diet of much egg white and olive oil for 4 to 6 weeks have developed a status seborrheicus, they receive each day the same supplementary dose of the substance to be investigated. Hypodermic injection of the material is also possible, providing it is previously subjected to a proteolytic exfoliation. On the administration of the substance under observation if Vitamin H is present, crusts and scales are thrown off in a short time, spots of skin with secondary infection clear up, and the skin becomes smooth and hair starts growing. The newly grown hide usually contains more pigment, is stronger and more shiny than the old. This curative effect is so constant that a standardization of the Vitamin H factor is made possible. A rat unit (preliminary) is designated as that quantity of bio-

logically active substance, which by being administered every day subcutaneously to rats ill of an avitaminosis H, has the power to cure them completely within 4 weeks. The purest preparations of Györgyi contain 1 rat unit in 5 Greek gamma (= .000005 gm.) of substance. It has been learned that on the average the requisite peroral dose is five times greater than the corresponding subcutaneous one.

Occurrence. The following table will give information on the Vitamin H content of some foodstuffs.

Material	Subcutaneous Rat Units per 100 gm. Fresh Substance (after Györgyi)*
Liver (beef, hog)	1000
Kidney, beef	1000
Kidney, hog (cooked)	2000**
Yeast	200-250
Mother's milk	25
Cow's Milk, summer	50-100
Cow's Milk, winter	25
Potato Meal	160-250
Casein	160-250
Brain	160
Bananas	100-125
Muscle, thymus, spleen, skin, wheat flour, rice, corn	0

Vitamin H factor is also found in fair quantity in green vegetables, spinach and cabbage, in blood serum (Boas) and egg yolk (Gorter). Pork and linseed oil are Vitamin H free (Parsons). So is whey (Heiman) and all commercial liver and yeast extracts [(Campolon, Lilly 343) Cenovis extract, Marmite, Vitox]. The usual household cooking increases the Vitamin H content in liver and kidney (Parsons-Lease-Kelly). In the potato the vitamin is bound to the starch; there is none in the juice. Compared to cow's milk, the low Vitamin H content in mother's milk is noteworthy. The distribution of Vitamin H, as the table shows, is rather limited.

Requirement of Man. The Vitamin H requirement rises proportionately with the body weight, and therefore does not present a constant magnitude. According to Györgyi it amounts to about 50 subcutaneous rat units per kilogram weight. Prophylactic and therapeutic doses appear to be the same, so the Vitamin H requirement of adults is about 3500 units daily. In view of this high value and the sparse occurrence of the Vitamin H factor in Nature, it was suggested that the conditions of Vitamin H deficiency were wider spread than it was so far assumed to be. It must be considered on the other hand that the Vitamin H requirement varies parallel with the supply of egg white and fat and that it is probably less with a fat-free diet as indicated. Up to the present an avitaminosis H is not known, although the Vitamin H factor is indispensable not only for man and the rat, but also for the chicken (Norris-Ringrose).

* The number of subcutaneous units were calculated from the daily curative unit with peroral administration based upon the fact that 1 subcutaneous unit equals 5 peroral units.

** According to Parson-Lease-Kelly.

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Behavior in the Organism. From the abundant Vitamin H content of liver and kidney it follows that the Vitamin H consumed is stored solely in both of these organs. The absence of the skin-factor H in the skin is worthy of note. Diarrheas and dyspeptic phenomena, impeding the proteolytic liberation and assimilation of Vitamin H, predispose to manifestations of Vitamin H deficiency (status seborrheicus). The fetal organism at birth does not contain any Vitamin H reserves and so it is explained that manifestations of a Vitamin H deficiency are observed immediately after birth. The vitamin also is allegedly percutaneously resorbable.

Manifestations of Vitamin H Deficiency. That an absolute or relative Vitamin H deficiency occurs in Vitamin H-poor nourished rats has been frequently observed by English and American authors during the past decade. For example, with an over-feeding of egg white, inflammatory, in part pellagra-like, skin changes develop. However, it is to the credit of Györgyi to have established the fact in 1931 that the clinical syndrome of avitaminosis H in the rat had nothing to do with pellagra, but was in every respect analagous to the human status seborrheicus. The first signs of Vitamin H deficiency in the rat are cutaneous inflammations about the mouth, blepharitis, intertrigo-like spots in the axillae, inguinal folds and urethra, prurigo and loss of hair, then redness appears and oozing of the skin, formation of scales and spreading of crusty yellow masses. Finally there is added a fine scaly desquamation over the whole body in the form of a "jacket of scales". Secondarily, as in the equivalent human disease, pyodermatoses, mucous and skin ulcers, septo-pyemic disease, pneumonias, and even keratomalacia may develop. The histological picture exactly likens the seborrhea of man. The differentiation between pellagrous and Vitamin-H-avitomotic skin symptoms, usually plain in the rat, does not obtain in the chicken. Vitamin B_6 and Vitamin H deficiency symptoms appear the same in the chicken, and may be distinguished only by therapeutic results (Lease-Parsons). This, and the fact that Vitamin B_6 and Vitamin H deficiencies are often superimposed, has led to errors and wrong conclusions in the investigations of water-soluble vitamins.

Physiology of Vitamin H. The human status seborrheicus is in every respect like the experimental rat seborrhea and must thus be interpreted as a manifestation of Vitamin H deficiency. It represents a pathologically changed-state of reaction. Its nature consists in an increase and abnormal composition of the sebaceous secretion and in a fatty degeneration of the superficial horny stratum of the epidermis, predisposing to development of skin infections. The disturbance of fat metabolism of the skin fundamental to seborrhea may be caused by a "too little" of Vitamin H, as well as by "too much" of egg white in the food, and moreover may be aggravated by a generous supply of fat. There are then close reciprocations between the avitaminosis H, the skin-fat-metabolism, and, as demonstrated in the rat and the human infant, the toxic effect of egg white. Thus, Vitamin H is concerned immediately with neutralizing the toxicity of egg white in the nutriment and later with the maintenance of a normal skin-fat-metabolism. Its function is enhanced by the fact that the skin-fat-metabolism is afforded relief by reduction of the fat supply. In regard to

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the avitaminosis H problem it is of interest that Bateman as early as 1916 has warned against too generous a supply of egg white in the human diet.

In what manner the detoxication of the toxic factor of egg white occurs is not evident, nor is there anything known of the nature of the toxic factor. It is apparently of a protein character, since egg white is no longer toxic after being heated, acid denatured or proteolytically predigested. Precipitation with alcohol does not destroy it, but it is not identical with egg albumen.

Vitamin H has (perhaps because of the normalization of the changed "terrain") a pronounced anti-infections action (Gundel-Györgyi-Pagel). Besides, it seems to possess growth promoting faculties, for it is apparently identical with the "insoluble rat factor R" of Williams-Lewis and Hunt.

Commercial Preparations. Vitamin H preparations are not on the market as yet. Some German firms, however, have made available for test purposes highly purified Vitamin H concentrates in ampules (a 2 cc. ampule containing 1000 subcutaneous rat units) for intramuscular (also peroral and hypodermic) application. Dosage: 1 ampule daily for several weeks.

Indications for Vitamin H Therapy. 1. Status seborrheicus. The pronounced form of avitaminosis H and thereby the main field of application of Vitamin H therapy is the status seborrheicus of the nursing age—the first trimenon—with both of its types of manifestations, the dermatitis seborrheicus and erythematosa, and the generalized form of erythematous type, the erythrodermia desquamatosa (Leiner). Pityriasis, intertrigo and dermatitis lichenoides must be included under phenomena of Vitamin H deficiency as specific manifestations of the nursling's seborrhea. The common base of all these disease manifestations is the seborrheic "change of terrain", consisting of a metabolic fault in the skin, disturbing the fat metabolism and the processes of cornification. 80% of all cases of seborrhea affect nursing children, because mother's milk contains less of the Vitamin H factor than cow's milk. However, seborrheic conditions may occur in bottle-fed children if they are undernourished or suffer from dyspepsias impeding the assimilation of the Vitamin H supplied. According to Moro there is a toxic egg-white effect associated with the development of avitaminosis H of the nursling. Particularly during the first three months of life a great permeability of the intestinal wall for uncatabolized egg white has been demonstrated.* Another form of seborrhea, likewise to be considered as a sign of a lack of Vitamin H, appears after the first trimenon and has been seen in children up to 10 years of age. This is the psoriasoid of Jadassohn and Tachau (seborrhoid-psoriasoid type of dermatitis seborrheica) which is often not properly diagnosed. It may result from inadequate nutrition (deficiency form) or it may be due perhaps to an endocrine imbalance in the sense of a diminished fat-tolerance and a correspondingly increased Vitamin H requirement (the constitutional form).

* In the nursling the egg white may not only act from within the intestine as a specific toxin, but also as a nonspecific agent. The frequent association of status seborrheicus and the genuine (allergic) eczema is thus explained.

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The latter is closely related to the genuine psoriasis. Therapeutically Vitamin H is administered either through injections of pure Vitamin H concentrates, from the use of which Györgyi has seen good results, or through Vitamin H rich foods. And here liver has a prominent place, 25-30 gm. of cooked hog or beef liver is given daily to a nursing child. At the same time generous allowances of easily digestible albumen (in the form of casein, larosan, plasmon, but not of meat or egg white) should be made, because it serves as a Vitamin H carrier and checks diarrheas which inhibit Vitamin H resorption. In animal tests the Vitamin H treatment not only cures seborrhea, but also conditions resulting from it (especially pyogenic skin infections, keratitides), as well as incipient pneumonia and keratomalacias, which in this manner prove themselves as true symptoms of Vitamin H deficiency. Yeast has also been used successfully, but it must be given in very large quantities. The well-known results from yeast treatment of acne and furunculosis, conditions consequential to the seborrheic state of reaction, are based essentially upon the Vitamin H content of the yeast. Both affections are favorably influenced by injection of Vitamin H concentrates. In the adult the formation of baldness, providing it may be attributed to a basic seborrhea, belongs to the range of application of the Vitamin H factor. Experiences with Vitamin H treatment in these cases, however, are quite limited.

2. In older children from the status seborrheicus morphologic and genetic relations lead to psoriasis, relations justifying therapeutic application of Vitamin H. There is with it, as with the seborrhea, a disturbance of the skin-fat metabolism (Buerger, Gruetz) coupled with an unexplained toxic effect (intolerance) of the nutrient egg white ("dysproteinosis") (Samberger, Pular). That the two-fold metabolic disorder is present points to a deficit of Vitamin H. In the hands of Mancorps and Györgyi injections of Vitamin H concentrates have shown as good results in psoriasis as has administration of cooked liver as the Vitamin H source (350 gm. several times a week). As an adjuvant of this treatment a reduction of fat supply is to be advised (Gruetz).

3. In the etiology of pellagra, aside from the lack of the pellagra-protecting substance, there is a poisonous effect of certain toxins arising in spoiled foodstuffs, particularly in corn (Chick). This indicates that in the genesis of pellagra Vitamin H deficiency is also of importance, particularly because the pellagra-protecting factor and Vitamin H usually coexist, and because the foodstuffs successfully used in the treatment of pellagra (liver, yeast, cow's milk) are likewise good sources of Vitamin H. In animal experiments the possibility of superposition of Vitamin B_2 complex and Vitamin H avitaminoses is also frequently presented (Györgyi). Thus, perhaps is explained the fact that occasionally egg-white dermatitis has been confused with rat pellagra. At least, it is commendable in pellagra, not only to supply an abundance of foodstuffs containing Vitamin H given anyhow for their Vitamin B_2 complex content, but also to resort to parenteral application of Vitamin H concentrates when intestinal disturbances obtain, impeding Vitamin H assimilation.

4. The diverse successes reported from injection treatment with Vita-

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min H concentrates in alopecia areata and genuine (allergic) eczema are without any theoretical foundation. From animal tests it is evident furthermore that the parenteral Vitamin H therapy may also be drawn upon to support local treatment of parasitic skin diseases. The curative action of the Vitamin H factor in all these skin affections confirms the truth of the statement that the vitamins are not only accessory supporting substances, but may also exert curative effects in lesions of a non-avitaminotic nature (Stepp).

In all cases where Vitamin H therapy is to be practiced in adults, attention must be paid to support the parenteral with a dietetic supply of Vitamin H (in the form of liver, kidney—twice weekly 250 mg., milk and vegetables) and to restrict meat, fat and egg consumption.

BIBLIOGRAPHY FOR VITAMIN H

Finkelstein in Pfaundler—Schlossmann, Handb. Kinderheilk., Berlin, 10, 464, 1935.
Goodman, Burr, Archives of Pediatrics, 53, 790, 1936.
Gorter, Z. Vitaminf. 1, 5, 1936.
György in Pfaundler—Schlossmann, Handb. Kinderheilk., Berlin, 10, 45, 1935.
Lease, Z. Vitaminf. 5, 110, 1936.
Lease, Biochemical Journal, 31, 424, 1937.
Milbradt, Dermat. Wschr., 1376, 1402, 1936.
Moncorps, Med. Kl., 1517, 1935.
Moncorps, Dermat. Wschr. 1230, 1936.
Schmid, Archives of Dermatology, 175, 344, 1937.
Schreus, Dermat. Wschr., 1231, 1936.
Schubert, ebenda.
Schultz, Medzin u. hemie, 3, 143, 1936.

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CHAPTER SEVEN

VITAMINS AND HUMAN NUTRITION

Only a few years ago there was relatively little known about the import of the vitamins for the human economy. Many results of investigation in vitamin research of recent times seemed to hold more of experimental interest than of importance for human dietetics. Very soon therefore after the discovery of vitamins and even more in recent years overestimating the value of vitamins has been warned against, from various sides. Thus it was maintained that with an ordinary mixed diet the danger of an avitaminosis did not exist in any manner whatsoever. Purity and synthesis of the most important vitamins having been established, there resulted not only an insight into the essence of the vitamins, but also new possibilities of a rational treatment or prevention of deficiency diseases came to hand.

Another advantage not to be underestimated practically consists in the opportunity to express the food content not only in biological units, but also plainly in weight, at least in reference to the vitamins already set up in pure form. The objection that the rarity of avitaminoses, even in patients on a limited diet, speaks for an adequate supply of vitamins, is invalidated by the newly gained knowledge of the nature and frequency of hypovitaminoses, previously discussed under the separate vitamins.

Clinical syndromes of indefinite character arise when the supply of vitamins or vitamin does not proceed in proportions or quantity corresponding to optimal conditions. Under such circumstances the classical signs of the known avitaminoses do not appear, but the relative vitamin deficiency makes itself noticeable in numerous frequently ill-defined disturbances. Very recently Frederiksen examining a series of school children in Copenhagen has found, for example, a remarkably frequent appearance of latent scurvy. The only symptoms of a hypovitaminosis C he often found were anorexia and an insignificant hematuria.

According to Castle and Strauss there are relations between pernicious anemia and the B_2-complex. Also in all probability it more frequently comes to a hypovitaminosis with B_2-complex, because of the great spread between the merely adequate and the optimal provision of the necessary vitamin quantities, as has been generally assumed. Finally it has been pointed out by Stepp, that a deficient vitamin supply might only manifest itself in the offspring, as M. B. Schmidt has demonstrated in mice with an iron-poor diet. That mutations may develop must also be thought of. Hence it appears from these suggestions that in the future still more

clinical syndromes will be counted as belonging to the range of hypovitaminoses, the relations of which to the vitamins are still unknown today. One difficulty, however, consists in the fact that with uncharacteristic symptoms of the hypovitaminoses the connections are often hard to clarify, since a diagnosis ex juvantibus is not satisfactory.

It is therefore not so important to obtain exact information as to intake of vitamins in figures, as it is imperative that the quantities be in keeping with certain optimal proportions of the total quantity of the food. This dependence is proven especially for B_1, the supply of which must be more generous, the greater the quantity of carbohydrates taken up with the nourishment. Matters are similar in regard to relation of vitamins and mineral metabolism. It is known that in case of rickets the requirement of Vitamin D is the greater the more the proportion of phosphoric acid and calcium is removed from the normal.

The conditions which may favor development of a hypovitaminosis or avitaminosis, even if the food is not particularly vitamin-poor, are therefore quite numerous. It is self-evident that a primary vitamin deficiency in the nutriment plays a role in bringing them about. Too little notice has been taken of the fact that every bland diet also presents a limited nutrition, because many vitamin containing food-stuffs must be discarded for their incompatibility to the patients. In fact during long continued restricted diets avitaminoses have occurred. Morawitz, for instance, has observed the appearance of scurvy in a typhoid patient, who was fed almost solely on mush and gruel. In cases of dysentery, gastric ulcer, fistula and colitis avitaminoses have been seen. How much an adequate provision of vitamin is warranted, is unknown. To progress with this question it is necessary to learn, at least approximately, the vitamin content of a diet. Such a calculation was done by us for the most commonly used diet forms. In the main those diets were considered, which are employed at the first medical clinic of the hospital l.d.I. in Munich.

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CHAPTER EIGHT

DAILY VITAMIN REQUIREMENT FOR MAN

Vitamin A minimal 1 mg. carotin
optimal 3—5 mg. carotin (not exactly known)

Vitamin B_1 minimal 0.25—0.5 mg. crystalline B_1
optimal 1.00—2.0 mg. crystalline B_1

Vitamin B_2 minimal 1 mg. crystalline lactoflavine
optimal 2—3 mg. crystalline lactoflavine (in presence of Vitamin B_4)
Requirement of the rest of the B-factors unknown

Vitamin C minimal (and at the same time the lower border of the optimum)
nursing infant 2.5 mg. crystalline ascorbic acid
adults 20-50 mg. crystalline ascorbic acid

Vitamin D Nursling and infant
minimal 0.002 mg. crystalline D_2 (calciferol new)
optimal (minimum in rickets) 0.01 mg. D_2
Adult requirement unknown, not much higher however

Vitamin E Requirement unknown

Aided by this table indicating the approximate vitamin requirement of normal man, we find it possible to judge whether a vitamin deficit exists in one of the diets presented. With these figures it is well to consider that they afford only an approximate indication pertaining to a healthy individual.

Since special diets are applied to sick people, these matters deserve particular consideration. There are two factors to be considered, first restricted vitamin supply in the diet, second increased vitamin consumption due to the disease, either one in itself being apt to produce vitamin deficiency. It must be conceded, therefore, that a diet of a vitamin content rated as just sufficient normally must be considered inadequate in a certain disease.

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CONTENT OF ESSENTIAL VITAMINS IN VARIOUS DIETS

The quota of vitamin provided daily in the different forms of diet

Diets	Vitamin A mg. carotin Min. 1 mg. Opt. 3-5 mg.	Vitamin B_1 γ Min. 250-500 Opt. 1000-2000	Vitamin B_2 mg. Min. 1 mg. Opt. 2-4 mg.	Vitamin C mg. Min. 20-59 mg.	Vitamin D γ Min. 2 Opt. 10
Bland diet Krankenhaus 1.d.I	11-67	250-480	1-2	5.2-6.5	41-51
Transduodenal feeding	4.6-56	190-340	1.1-1.8	15-30	21-22
Gastritis diet Krankenhaus 1.d.I	9-66	250-320	3.5-5.5	38.5-65	41-45
Ulcer diet Kalk 4th day	0.15-1	20-30	0.1-0.15	0.5-1	0.2-0.4
5th day	0.3-2	40-60	0.2-0.3	1-2	0.4-0.8
6th day	3.5-28	160-280	0.2-1.5	1.5-3	20
7th day	6.3-53	260-440	1.3-2.5	1.5-3	40
8th day	6.5-53	280-500	1.3-2.5	2-4	40
15th day	11-152	520-760	2-4	10.5-20	61-72
23-27th day	22-100	660-840	6-9.5	25-40	61-72
Ulcer diet Leube-Ewald					
1st day	12-8	160-220	1	4-8	1.6-3.2
2nd day	1.5-10	200-280	1-1.6	5-10	2-4
3rd day	1.7-12.5	200-280	1-1.5	5-10	2-6
4th day	1.8-14	200-280	1-1.5	25-35	2-6
5th day	5.40	280-480	2	40-65	22-28
6th day	8-65	400-680	2-3	40-65	42-48
7th day	11-93	520-880	3-4	5-10	62-70
8-15th day	11-93	520-880	4	11-27	62-70
Dyspepsy fermentative 2 period	10-76	320-620	1.5-3		60
3 & 4 period	13-101	360-660	1.2-1.4	172-241	60-65
Ketogenic diet acidotic	4-37	140-240	3-4.5		20-30
Cystopyelitis alkalotic	5-15	240-640	1.2-2.4	172-241	1.2-2.4

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Nephritic diet Karrel	1-8	160-220	1	4-8	1.6-3.2
" Nonnenbruch	9-50	140-220	0.6-1	185-217	1.2-21.6
Vollhard	8-77.5	300-520	4-6.5	22-28	45-70
" v. Norden 1	1.0-27.5	40-70	0.5-1	122-248	5-30
" " 11	14-87	160-240	0.8-1.8	152-288	5-30
Mushfruit days Schlayer	0.9-6	120-160	0.7-1.4	13-60	1.2-2.4
Raw food days	26-240	600-920	1.7-3.3	450-550	1.2-2.4
Diet Gerson	93-350	1200-1600	2.4-4.6	440-510	90-200
Diet Hermannsdorfer	16-75	120-400	6-10	170-190	2.4-24
Apple diet			0.2-0.8	25-150	
Banana diet	7.4-54	300-520	2.5-4	61-82	80
Reducing diet Umber	10-27	300-330	7.3-11.3	82-147	0.1-0.2
" " Richter	5.4-29	330-500	5.3-9	69-131	20
" " Branting	2-4.5	250-260	11-17	77-85	
Forced alimentation					
High caloric Pariser	29-193	440-2880	5.3-8	175-356	83-126
High Caloric Bormtraeger-Schall	39-61	1600-3800	6.6-11.3	170-353	200-224
Diet for pernicious anemia Minot & Murphy	36-150	360-640	5.3-8	175-356	20-30
Diet cholesterol free					
Krankenhaus 1.d.I	13-36	130-200	0.2-0.7	240-290	
Vegetable fat diet Petren	13-55	160-280	0.6-1.3	90-110	0.8-40
Oatmeal cure v. Norden	4.5-75			10-20	1.2-60
Diabetes-Falta soup diet	3-50	60-70	0.2-0.4	11-15	0.8-40
" -flour fruit diet	3.5-55	45-50	0.1-0.2	10-16	0.8-40
"-flour fruit vegetable	15-91	170-230	0.5-0.7	74-90	0.8-40
Hyperthyroidism Abelin diet	21-120	840-1280	3.8-5	132-210	63-86
Gen. diet weekly average					
from July 22 to July 27	7.5-20	160-220	2.7-4.2	44-58	10-20
from Dec. 30 to Jan. 5	4-23	190-250	3.9-4.7	33-53	10-20
from Sept. 16 to Sept. 22	6-33	200-270	3-5	36-58	10-20
from Mar. 4 to Mar. 10	6-28	240-340	2.3-3.7	30-44	10-20

From a comparison of the vitamin content of different kinds of diet with the daily minimum human requirement of essential vitamins, as visualized by the table, it is evident that many forms of diet do not supply the organism with sufficient vitamins. A more detailed analysis indicates that Vitamin A and Vitamin D are abundantly represented in every diet. Only in some ulcer and nephritic diets, and then only during the first days when provision of calories per se is light, the values for Vitamin A and Vitamin D move below the normal line. A Vitamin C deficiency appears in the dietary far more frequently. In the beginning of all ulcer cures and in the regime of fermentative and flatulent dyspepsia an inadequate provision of Vitamin C may be demonstrated. The same holds true of the Karrel cure for the acidotic part of the ketogenic diet in cystopyelitis. In almost all forms of dietary the provision of the necessary vitamins of the B-complex is very deficient. Pronounced especially are the low values of Vitamin B_1, which very rarely rise above the minimum requirement. Vitamin B_2 is better provided for. In the general diet 3rd. class Krankenhaus 1.d.I Munich all vitamins except B_1 are present in sufficient quantities, the reason being that potatoes and meat, the main sources of Vitamin B_1 in our nutrition, must be supplied in pretty large quantities to cover the daily need of this vitamin.

It is remarkable that the Vitamin C requirement in the general ward diet is made up almost entirely by potatoes. It is generally known that a large part of our population is providing its need of Vitamin C with potatoes, thus living on the borderline of the minimum supply. It is evident that this limitation is fraught with certain danger. Indeed, in the past and also very recent times, epidemics of scurvy have been observed in connection with potato crop failures.

Another question is whether a diet with too low a value in vitamins might prove harmful to health if provided for a short time only. It is self-evident that the magnitude of the vitamin deficit and also the quantitative proportion of all vitamins play a role. Of guinea pigs it is known that after 8 days of C-free feeding they show histological changes in the teeth, even though clinically demonstrable signs of scurvy are absent.

It is evident that a general survey, as offered by the table, may only function as a guide for providing vitamins for the organism in the diet forms cited. Disregarding the fact that the exact vitamin requirement of a healthy man is not known as yet, the vitamin consumption is subject to great fluctuations in the different diseases. At any rate the calculations might suggest which of the dietary forms should be rearranged or supplemented in food respecting vitamins. The supply of the vitamin requirement is facilitated by the opportunity to apply them in their isolated form.

In view of the newly acquired knowledge of the frequency of hypovitaminoses and of the susceptibility of patients with avitaminoses to all sorts of diseases, the importance of a sufficient vitamin supply must not be underestimated in our patients. Concerning the nourishment of children it is of significance that through insufficient supply of vitamins injuries may arise in the organism, presumably never to be corrected, and that

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many disturbances of health at a later age have their origin in an inadequate nutrition of the growing organism.

There is no doubt that the provision of sufficient quantities of vitamin in child and adult represents an essential aid in securing and maintaining complete health and optimal growth, which is the final goal of dietetics.

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CHAPTER NINE

THE ANTAGONISM OF THE VITAMINS AND ITS IMPORTANCE IN VITAMIN THERAPY

In the discussion of the separate vitamins of the previous chapters the antagonism of the vitamins has been referred to ever and again. These relations are, as may be stated with assurance today, not only interesting theoretically, but also of greatest significance practically. Thus what is most important in the co- and counterplay of the vitamins will be briefly presented in the following.

To begin with, we know of an antagonism between the group of fat-soluble vitamins on the one side and the group of the water-soluble vitamins on the other. If rats, for instance, kept on a certain standard diet well suited for breeding purposes, receive a larger dose of cod liver oil daily, they grow ill, and additions of yeast remove the harmful effects of the oil (F. G. Hopkins). If guinea pigs on a scurvy-producing diet are protected against it by supplementing fruit juice, additions of cod liver remove the antiscorbutic action of the fruit juice (Mouriquand and Michel; von Euler).

When the opportunity to work with pure substances was realized during the recent years of advances in the manufacture of pure vitamins, these results were reinvestigated in detail. Thereby it became quite evident that the observation of Hopkins depended upon an antagonism between Vitamin A and the vitamins of the B complex. However, in detail one was forced to be convinced that the harmful action of an additional feeding of larger quantities of the pure Vitamin A could only be removed, if besides the Vitamin B Complex, Vitamin C were also given. Conversely it was demonstrated that the effect of the Vitamin B group could be impeded by a simultaneous administration of Vitamin A, and the action of Vitamin C entirely abolished by Vitamin A. These findings are in complete harmony with the tests of Mouriquand and Michel; von Euler. Furthermore, it is worthy of note that the toxic action of large doses of Vitamin D may be reduced by the Vitamin B Complex.

However, there exists an antagonism not only between the fat- and water-soluble vitamins but also within the group of the fat-soluble vitamins themselves. For instance it has been shown successfully that hypervitaminosis D may be prevented by simultaneous administration of large quantities of Vitamin A substances, and conversely, that signs of Vitamin

A deficiency may be provoked by an over abundant supply of Vitamin D. If the quantities of Vitamin A and Vitamin D substances remain within physiological limits, an antagonism is not debatable, indeed one may best justify the actual observations by speaking of a synergism in this case. There is no doubt that the apposition of calcium in the bones under the influence of Vitamin D is improved if small quantities of Vitamin A are added at the same time.

Thus in the relations between the vitamins the quantitative factor is directly of decisive importance. Looking about in Nature we find the ideal equilibrium realized between Vitamin A and Vitamin D in the natural product, namely cod liver oil, which proves the richest source of both these fat-soluble vitamins.

However, in liver oils that have been subjected to extensive chemical refining processes this proportion may be disrupted, because the more labile Vitamin A is destroyed easier than the more stable Vitamin D. It will be the problem of the future to study the quantitative connections of the vitamins in pure natural products. However, cod liver oil, little changed by chemical processes in refining, is perhaps superior to the artificial combinations of the pure vitamins solely for the reason that the resorptive conditions in the natural products are suitable. Of course, artificial products like Detavit, representing a mixture of Vitamin A and Vitamin D, may be so constituted that they satisfy the ideal postulate. Practical experience has proven Detavit to be eminently useful.

From the fact just stated, that there exists a vitamin equilibrium in the natural products, it seems imperative not to overestimate the existence of an antagonism. In addition, account must be taken, in these and other conditions, of the possibility that a diet may be poor in several vitamins at the same time. In such cases it is necessary to assay with great care to learn to know the specific deficiency of the nutriment in detail, procuring relief by adding the indicated vitamins. At any rate a more or less thoughtless "shot gun" treatment, as Americans express it, must be declined. Furthermore, in the question of the correlation of the vitamins or vitamin antagonism, it is of import that the vitamin requirement is not of a constant magnitude, but dependent in great measure, first upon the minerals contributed by the food (this holds especially for Vitamin D), and then upon the quantity of the main nutrients metabolized. It has been known for a long time that the Vitamin B_1 requirement rises with the quantity of carbohydrates metabolized, fat evincing a sparing effect. Evidently these interrelations are very important not only for the consumption of vitamins, but also for their activity and their reciprocations among each other. Still another phenomenon has to be considered—that there exists very close and weighty connections between the vitamins and hormones. Chiefly during recent years these connections have been most carefuly studied. It is known, that the vitamins not only react upon the activity of the hormonal glands, but also influence the effect of the hormones, at times in a sense of synergism and then in that of antagonism. Best known is the antagonism between Vitamin A and thyroxin. It is

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evident at once that with disturbances in the endocrine system the action of the vitamins may be entirely changed.

All these connections are of great practical importance or import for the reason that there is a possibility of doing harm with vitamin combinations not only in animal experiments but in bedside treatment as well. How easily a well-meant "too much" may do injury is shown by a report from America about scurvy appearing in children, whose mothers, desiring to make the provision of vitamins most generous, administered orange juice and cod liver oil mixed.

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APPENDIX

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For the convenience of those who desire to make a study of any special phase of known deficiency reactions, we offer a recently compiled Vitamin Chart with detailed bibliography following (references up to October 1937).

By the publisher of the English Edition.

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VITAMIN A

Apparent Function:

1. Necessary to normal function and integrity of—
— Tissues of epiblastic origin;
— Epithelial tissues (Wound healing hastened, resistance to infections raised);
— Nervous system.
2. Necessary to maintenance of normal cell metabolism, such as:
— Cell respiration;
— Blood cell generation (Platelets).
3. Necessary to formation and integrity of periodontal tissue.
4. Promotes growth, feeling of well-being and longevity.
5. Essential to successful reproduction.
6. Prevents keratinization of tissues.

Possible Results of Deficiency:

7. Retarded appetite, growth and development (due to interference with assimilation).
8. Disturbed dental and bone development (atrophy).
9. Susceptibility to infections as well as slow healing of the following:
— Reticulo-endothelium;
— Epithelium, due to degenerative change in structures of skin and mucosa.
10. Presence (due to lowered resistance) of—
— Infections of eye (corneal ulcers) and degeneration of eyes (xerophthalmia, keratomalacia, night blindness, total blindness);
— Infections of ear (otitis media);
— Infections of genitourinary tract;
— Infections of mucous tract (tonsilitis);
— Infections of respiratory tract (pneumonia, tuberculosis);
— Infections of gastrointestinal tract (diarrhea);
— Infections of sinuses.

11. Presence of keratinizations and metaplasia of—
— Epithelium;
— Genitourinary tract (making for difficult delivery of young);
— Mucous tract;
— Respiratory tract;
— Glands.
12. Interference with successful reproduction and lactation (loss of sex impulse);
— Sterility in the female by failure of ovulation or resorption of fetus;
— Sterility in the male by temporary injury to seminiferous epithelium;
— Prolonged gestation, retained and diseased placenta, difficult delivery.
13. Development of—
— Pernicious anemia;
— Secondary anemia;
— Rickets (in conjunction with Vitamin D deficiency);
— Gastritis;
— Bronchitis;
14. Development of kidney and bladder disorders (metaplasias) and renal dysfunction;
— Formation of stones (calculi);
— Nephritis;
— Cystitis;
15. Excessive growth of lymphoid tissue.
16. Degeneration of the nervous system—dulling or perversion of special senses.

Results of Absence:

17. Atrophy of organs and glands (testes, liver, spleen, thyroid, pituitary and salivary).
18. Degenerative skeletal muscle lesions develop.
19. Ophthalmia, xerophthalmia, keratomalacia, conjunctivitis or keratoconjunctivitis.
20. Death.

Bibliography for Vitamin A on pages 137-141

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VITAMIN B

Apparent Function:

1. Stimulates and promotes appetite and normal digestion.
2. Promotes optimal growth (increases height and vigor).
3. Necessary to maintenance of normal metabolic processes such as:

— Carbohydrate metabolism (lactic acid excesses);
— Cell respiration;
— Tissue respiration.

4. Necessary to normal pregnancy and lactation.
5. Maintains nervous function.
6. Stimulates digestive secretions, including insulin.
7. Necessary to maintenance of muscle tonus.
8. Prevents toxicosis from protein components in high meat diets.

Possible Results of Deficiency:

9. Susceptibility to infections due to lowered resistance.
10. Disturbed carbohydrate metabolism (Diabetes Mellitus) (lactic acid excesses, slow or labored respiration).
11. Functional disorders, atrophy or pathological enlargement of adrenals, brain, gonads, heart (heart block and bradycardia), kidneys, liver, ovaries, pancreas, pituitary gland, spleen, testes, thymus and thyroid glands—goiter.
12. Tendency to functional gastrointestinal disorders (Intestinal immobility, loss of tonus, constipation, lack of gastric secretions, ulcers, impaired appetite [anorexia] and digestion).
13. Tendency to muscle paralysis (loss of tone).
14. Loss of weight and vigor, stunted growth and emaciation.
15. Tendency to edematous conditions.
16. Fall in body temperature.
17. Degeneration of central nervous system (impaired nerve function, convulsions, tetany).
18. Anemia.

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19. Disturbances of reproductive cycle (sterility — atrophy of seminiferous tubules, loss of libido, anestrus—hemorrhage at partus and abortions).
20. Dental caries.
21. Predisposes to allergic conditions.

Results of Absence:

22. Beriberi.
23. Peripheral and other forms of neuritis (polyneuritis).
24. Death.

Bibliography for Vitamin B on pages 143-149

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VITAMIN C

Apparent Function:

1. Essential to health and integrity of endothelial tissues (raises resistance to infections).
2. Essential to proper development of teeth.
3. Essential to oxygen metabolism.
4. Regeneration of blood cells.
5. Maintains proper blood-clotting time.

Possible Results of Deficiency:

6. Tendency to structural tissue changes:

— (a) Diseases of blood vessels and capillaries (fragility, hemorrhages, tendency to bruise easily, "black and blue spots," purpura hemorrhagica), (varicosities).
— (b) Diseases of gums (hemorrhages, sore gums), (pyorrhea).
— (c) Tooth degeneration (Necrosis, caries).
— (d) Joint and bone changes (Decalcification, friability).
— (e) Mucous membrane hemorrhages.
— (f) Destruction of bone marrow.

7. Tendency to epithelial lesions (ulcerations of mouth, intestine, etc.).
8. Increased susceptibility or reduced resistance to infections.
9. Retarded growth and loss of weight.
10. Physical weakness, depression and irritability.
11. Rapid respiration and heart action.
12. Blood degeneration (Tendency to certain types of anemia, reduced hemoglobin, destruction of bone marrow).
13. Development of heart weakness.
14. Increased weight and enlargement of spleen, liver, stomach, intestines and kidneys.
15. Atrophy or hypertrophy of glands:
    (a) Reduced secretion of adrenals;
    (b) Morbid secretion of thyroid (toxic goiter).
16. Development of arthritis (Rheumatic tendency).

17. Development of edematous conditions.
18. Complications of pregnancy and lactation as well as ill effects to new born (Abortions).
19. Tendency to raised temperature.
20. Possible Sterility.
21. Lowered glucose tolerance.
22. Cataract.
23. Predisposes to allergic conditions.

Results of Absence:

24. Scurvy.
25. Sprue.
26. Death.

Bibliography for Vitamin C on pages 151-154

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VITAMIN D

Apparent Function:

1. Essential to proper mineral metabolism; absorption from alimentary tract, utilization (health and calcification of bone and teeth) (Antirachitic action) and excretion of calcium and phosphorus.
2. Necessary to successful pregnancy and lactation.
3. Necessary for normalizing and reducing time of labor.
4. Necessary to maintain blood platelets at normal level.
5. Maintains normal coagulation time of blood.
6. Maintains growth (longitudinal bone growth).
7. Aids in maintaining muscle tone.
8. Increases strength of capillaries.
9. Related to hormonal function.
10. Increases resistance to infections (especially against tuberculosis).
11. Necessary to normal respiratory function.

Possible Results of Deficiency:

12. Rickets and osteomalacia (improper calcification of bone).
13. Growth retarded.
14. Enlargement of liver, kidney and spleen.
15. Instability and irritability of nervous system and tissues.
16. Decreases resistance to infections.
17. Muscular weakness, constipation and reduced motility of gastrointestinal tract.
18. Increased tendency to dental caries and defective teeth (improper calcification) (pyorrhea).
19. Parathyroid dysfunction (Enlargement).
20. Menstrual disorders, cessation of ovulation, uterine atrophy, difficult childbirth due to deformities in pelvic development.

Results of Absence:

21. Osteoporosis.
22. Rickets.

Bibliography for Vitamin D on
pages 155-159

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VITAMIN E

Apparent Function:

1. Necessary to reproduction in both male and female (necessary to prevent irreparable sterility in male)
2. Necessary to maintenance of mental alertness.
3. Necessary to growth and vigor.
4. Possibly to prevent carcinoma.
5. Necessary to resistance to infections.
6. Possibly to prevent paralysis of young (from E-deficient mothers).
7. Vermifuge (possibly due to associated principles).
8. Some influence on the endocrines (pituitary, anterior pituitary).

Possible Results of Deficiency:

9. Loss of weight, retarded growth, weakness.
10. Wasting of muscles, paralysis.
11. Lowered resistance in infections (particularly to infantile paralysis).
12. Sterility (Temporary in female — interference with placental function), (Permanent in male—irreparable seminiferous epithelial injury).

Results of Absence:

13. Severe paralysis.
14. Disturbances of latter stages of pregnancy producing sterility (fetal resorption and habitual abortion).
15. Roughness, falling out (alopecia) and altering of the texture of the hair.
16. Possible tendency to malignancies.

Bibliography for Vitamin E on pages 161-164

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VITAMIN F

Apparent Functions:

1. Necessary to healthy epidermis (Protection against infection).
2. Maintains normal growth and reproduction.
3. May be necessary to maintain normal blood sugar (Possibly related to Insulin secretion).
4. Necessary to cell respiration.
5. Necessary to hair health.
6. Necessary to brain function and probably to function of other nerve tissue.

Possible Results of Deficiency:

7. Epidermal manifestations (Ridged and split fingernails, eczematous conditions, dermatitis—infantile and allergic, scurf, dandruff and hemorrhagic spots on the skin).
8. Brittleness and falling out of hair (Alopecia).
9. Involvement of endocrine glands (pituitary in particular).
10. Involvement of visceral organs (particularly kidneys).
11. Lowers resistance to allergies.
12. Susceptibility to Vitamin D poisoning.
13. Loss of sex instinct.
14. Lowered resistance to infections (Tuberculosis in particular).

Results of Absence:

15. Cessation of growth and subsequent death.
16. Severe renal manifestations (Hematuria, albuminaria and severe nephritis).
17. Sterility (Impaired and irregular ovulation with interference with mechanism of labor in the female), (Loss of sex potentia with eventual sterility in the male).

Bibliography for Vitamin F on pages 165-168

VITAMIN G

Apparent Function:

1. Necessary to growth and development.
2. Necessary to cell respiration.
3. As growth stimulus promotes normal repair processes and thereby delays senility.
4. Necessary to blood regeneration.

Possible Results of Deficiency:

5. Underdevelopment and retarded growth from malnutrition.
6. Eye disorders (conjunctivitis).
7. Incipient pellagra.
8. Abnormally slow regeneration of erythrocytes (secondary anemia).
9. Cutaneous changes (pellagric symptoms, mild dermatitis).
10. Nerve lesions and irritability (Neuritis).
11. Loss of hair (alopecia).
12. Sprue.
13. Interferes with normal skin respiration.
14. Alimentary tract disorders (Gastroenteritis, stomatitis, digestive disturbances).
15. Fatty infiltration and degeneration of the liver.
16. Renal manifestations (Cystitis, Hemorrhagic conditions of the urine, stones—renal calculi).

Results of Absence:

17. Gastrointestinal disturbances (Gastroenteritis, stomatitis, ulcerative colitis, diarrhea, nausea, vomiting, achlorhydria).
18. Cessation of growth.
19. Eye disorders (keratinization, severe conjunctivitis, ophthalmia, cataracts).
20. Severe pellagra.

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21. Severe nerve and spinal degeneration (Mental disorders, hyperirritability).
22. Death.

Bibliography for Vitamin G on pages 169-173

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BIBLIOGRAPHY FOR VITAMIN A

1. Gardner, E. and Gardner, F., *American Journal of Diseases of Children*, 47:1261, 1934.
— Harris, L. J., *Vitamins in Theory and Practice*, page 158, Cambridge University Press, 1935.
— Journal of the American Medical Association, *Editorial*, 97:783, 1931.
— Mathews, Albert P., *Principles of Biochemistry*, page 411, William Wood & Co., Baltimore, 1936.
— Medical Research Council, *Vitamins: A Survey of Present Knowledge*, page 90, London, 1932.
— Mellanby, E. and Green, H. H., *British Medical Journal*, 1929.
— Quigley, Daniel Thomas, *Notes on Vitamins and Diets*, page 16-17, 43, Consolidated Book Publishers, Inc., Chicago, 1933.
— Sherman, H. C., and Smith, S. L., *The Vitamins*, Second Edition, Monograph Series, No. 6, pages 280, 282, The Chemical Catalog Co., Inc., New York, 1931.
— Shibata, M., *Jap. Journal of Experimental Medicine*, 9:21, 1931.
— Stepp, W., Kuhnau, J. and Schroeder, H., *The Vitamins and Their Clinical Application*, Ferdinand Enke, Stuttgart, Germany, 1936.
— United States Department of Agriculture *Circular No. 84.*
— Washington (D. C.) Star, *Vitamin A Lack Held Stone Cause*, January 11, 1935.

2. Mathews, Albert P., *Principles of Biochemistry*, page 411, William Wood & Co., Baltimore, 1936.
— McCollum, E. V., and Simmonds, N., *The Newer Knowledge of Nutrition*, Fourth Edition, pages 495-496, The MacMillan Co., New York, 1929.
— Stepp, W., Kuhnau, J. and Schroeder, H., *The Vitamins and Their Clinical Application*, Ferdinand Enke, Stuttgart, Germany, 1936.

3. Macleod, J. J. R., *Physiology in Modern Medicine*, Seventh Edition, page 752, C. V. Mosby Co., St. Louis, 1935.
— Medical Research Council, *Vitamins: A Survey of Present Knowledge*, page 90, London, 1932.
— Shibata, M., *Jap. Journal of Experimental Medicine*, 9:21, 1931.

4. Eddy, W. H. and Dalldorf, G., *The Avitaminoses*, pages 31, 64, The Williams and Wilkins Co., Baltimore, 1937.
— Howell, William H., *A Textbook of Physiology*, Twelfth Edition, Revised, pages 967, 968-969, W. B. Saunders Co., Philadelphia, 1933.
— Mathews, Albert P., *Principles of Biochemistry*, page 411, William Wood & Co., Baltimore, 1936.
— McClendon, J. F., *A Manual of Biochemistry*, page 3, John Wiley & Sons, Inc., New York, 1934.

— Sherman, H. C., and Smith, S. L., *The Vitamins*, Second Edition, Mono graph Series, No. 6, pages 287, 292, The Chemical Catalog Co., Inc. New York, 1931.
— Sure, Barnett, *The Vitamins in Health and Disease*, page 23, The Wil liams and Wilkins Co., Baltimore, 1933.

5. Eddy, W. H. and Dalldorf, G., *The Avitaminoses*, page 64, The William: and Wilkins Co., Baltimore, 1937.
— Mathews, Albert P., *Principles of Biochemistry*, page 411, Willian Wood & Co., Baltimore, 1936.
— McClendon, J. F., *A Manual of Biochemistry*, page 3, John Wiley & Sons, Inc., New York, 1934.
— Sherman, H. C. and Smith, S. L., *The Vitamins*, Second Edition, Mono graph Series, No. 6, page 291, The Chemical Catalog Co., Inc., New York, 1931.
— United States Department of Agriculture, *Circular No. 84.*

6. McClendon, J. F., *A Manual of Biochemistry*, page 3, John Wiley & Sons, Inc., New York, 1934.
— Stepp, W., Kuhnau, J. and Schroeder, H., *The Vitamins and Their Clinical Application*, Ferdinand Enke, Stuttgart, Germany, 1936.

7. Barborka, Clifford J., *Diet and Preventive Dentistry*, Journal of the American Dental Association, 23, 6:977-985, June, 1936.
— Eddy, W. H. and Dalldorf, G., *The Avitaminoses*, page 54, The Williams and Wilkins Co., Baltimore, 1937.
— Howell, William H., *A Textbook of Physiology*, Twelfth Edition, Revised, page 968, W. B. Saunders Co., Philadelphia, 1933.
— Macleod, J. J. R., *Physiology in Modern Medicine*, Seventh Edition, pages 730-731, C. V. Mosby Co., St. Louis, 1935.
— Mathews, Albert P., *Principles of Biochemistry*, pages 416-417, William Wood & Co., Baltimore, 1936.
— Medical Research Council, *Vitamins: A Survey of Present Knowledge*, page 25, London, 1932.
— Sherman, H. C. and Smith, S. L., *The Vitamins*, Second Edition, Monograph Series, No. 6, pages 273-274, 278, The Chemical Catalog Co., Inc., New York, 1931.
— United States Department of Agriculture, *Circular No. 84.*

8. Eddy, W. H. and Dalldorf, G., *The Avitaminoses*, page 52, The Williams and Wilkins Co., Baltimore, 1937.
— Medical Research Council, *Vitamins: A Survey of Present Knowledge*, page 192, London, 1932.
— Smith, M. C. and Lantz, E. M., *Journal of Home Economics*, 25:411, 1935.
— Stepp, W., Kuhnau, J. and Schroeder, H., *The Vitamins and Their Clinical Application*, Ferdinand Enke, Stuttgart, Germany, 1936.

9. Barborka, Clifford J., *Diet and Preventive Dentistry*, Journal of the American Dental Association, 23, 6:977-985, June, 1936.
— Eddy, W. H. and Dalldorf, G., *The Avitaminoses*, pages 59-60, The Williams & Wilkins Co., Baltimore, 1937.
— Green and Mellanby, *British Medical Journal*, ii, 691, 1928.
— Howell, William H., *A Textbook of Physiology*, Twelfth Edition, Revised, page 968, W. B. Saunders Co., Philadelphia, 1933.

Posted for noncommercial historical preservation and educational use only by seleneriverpress.com

— Medical Research Council, *Vitamins: A Survey of Present Knowledge*, page 33, London, 1932.
— Sherman, H. C. and Smith, S. L., *The Vitamins*, Second Edition, Monograph Series, No. 6, pages 274, 280, 281, 287, The Chemical Catalog Co., Inc., New York, 1931.
— Stepp, W., Kuhnau, J. and Schroeder, H., *The Vitamins and Their Clinical Application*, Ferdinand Enke, Stuttgart, Germany, 1936.

10. Eddy, W. H. and Dalldorf, G., *The Avitaminoses*, pages 33, 34, 38-39, 40, 57, 258, The Williams & Wilkins Co., Baltimore, 1937.
— Macleod, J. J. R., *Physiology in Modern Medicine*, Seventh Edition, page 731, 732, C. V. Mosby Co., St. Louis, 1935.
— Mathews, Albert P., *Principles of Biochemistry*, pages 415-416, William Wood & Co., Baltimore, 1936.
— Quigley, Daniel Thomas, *Notes on Vitamins and Diets*, pages 16, 98, Consolidated Book Publishers, Inc., Chicago, 1933.
— Rosslene, A. H., *Journal of Nutrition*, 8:75, 1934.
— Sherman, H. C. and Smith, S. L., *The Vitamins*, Second Edition, Monograph Series, No. 6, pages 274, 278, 286-287, The Chemical Catalog Co., Inc., New York, 1931.
— Sure, Barnett, *The Vitamins in Health and Disease*, page 23, The Williams and Wilkins Co., Baltimore, 1933.

11. Eddy, W. H. and Dalldorf, G., *The Avitaminoses*, pages 47, 51, 258, The Williams and Wilkins Co., Baltimore, 1937.
— Harris, L. J., *Vitamins in Theory and Practice*, page 158, Cambridge University Press, 1935.
— Howell, William H., *A Textbook of Physiology*, Twelfth Edition, Revised, page 968, W. B. Saunders Co., Philadelphia, 1933.
— Macleod, J. J. R., *Physiology in Modern Medicine*, Seventh Edition, page 732, C. V. Mosby Co., St. Louis, 1935.
— Mathews, Albert P., *Principles of Biochemistry*, page 411, William Wood & Company, Baltimore, 1936.
— McClendon, J. F., *A Manual of Biochemistry*, page 3, John Wiley & Sons, Inc., New York, 1934.
— Medical Research Council, *Vitamins: A Survey of Present Knowledge*, pages 29, 33, London, 1932.
— Sherman, H. C. and Smith, S. L., *The Vitamins*, Second Edition, Monograph Series, No. 6, pages 280, 289, The Chemical Catalog Co., Inc., New York, 1931.
— Stepp, W., Kuhnau, J., and Schroeder, H., *The Vitamins and Their Clinical Application*, Ferdinand Enke, Stuttgart, Germany, 1936.

12. Eddy, W. H. and Dalldorf, G., *The Avitaminoses*, pages 49, 50, 51, 64-65, The Williams and Wilkins Co., Baltimore, 1937.
— Howell, William H., *A Textbook of Physiology*, Twelfth Edition, Revised, pages 968, 974, W. B. Saunders Co., Philadelphia, 1933.
— Mason, K. E., *Differences in Testis Injury and Repair After Vitamin A Deficiency, Vitamin E Deficiency, and Inanition*, American Journal of Anatomy, 52:153—240, 1933.
— Mason, K. E., *Reproductive Function in Female Rats on Low Levels of Vitamin A*, Anatomical Record, 58, 4, Suppl. 80, 1934.
— McClendon, J. F., *A Manual of Biochemistry*, page 3, John Wiley & Sons, Inc., New York, 1934.

Posted for noncommercial historical preservation and educational use only by seleneriverpress.com

— Medical Research Council, *Vitamins: A Survey of Present Knowledge*, pages 33-34, 112, London, 1932.
— Sherman, H. C. and Smith, S. L., *The Vitamins*, Second Edition, Monograph Series, No. 6, pages 289, 336, The Chemical Catalog Co., Inc., New York, 1931.
— Stepp, W., Kuhnau, J. and Schroeder, H., *The Vitamins and Their Clinical Application*, Ferdinand Enke, Stuttgart, Germany, 1936.
— Sure, Barnett, *The Vitamins in Health and Disease*, page 23, The Williams and Wilkins Co., Baltimore, 1933.
— United States Department of Agriculture, *Circular No. 84.*

13. DeSanctis, Adolph and Craig, John D., *A Five-Year Clinical Study of the Prophylactic Value of Antirachitic Agents*, New York State Journal of Medicine, 34, 16:712-714, 1934.
— Eddy, W. H. and Dalldorf, G., *The Avitaminoses*, page 34, The Williams and Wilkins Co., Baltimore, 1937.
— Mathews, Albert P., *Principles of Biochemistry*, pages 415-416, William Wood & Co., Baltimore, 1936.
— McCollum, E. V., and Simmonds, N., *The Newer Knowledge of Nutrition*, Fourth Edition, page 495, The MacMillan Co., New York, 1929.
— Stepp, W., Kuhnau, J. and Schroeder, H., *The Vitamins and Their Clinical Application*, Ferdinand Enke, Stuttgart, Germany, 1936.

14. Berglund, Medes, Huber, Longcope and Richards, *The Kidney in Health and Disease*, pages 147-149, 253-255, Lea & Febiger Co., Philadelphia, 1935.
— Eddy, W. H. and Dalldorf, G., *The Avitaminoses*, pages 34, 49, 56, 64, 258, The Williams and Wilkins Co., Baltimore, 1937.
— Fujimaki, *Jap. Med. World*, vi, 29, 1926.
— Mathews, Albert P., *Principles of Biochemistry*, page 417, William Wood & Company, Baltimore, 1936.
— McCarrison, R., *British Medical Journal*, 1:717, 1927.
— McCarrison, R., *Ibid*, 2:159-160, 1927-1928.
— Medical Research Council, *Vitamins: A Survey of Present Knowledge*, page 237, London, 1932.
— Sherman, H. C. and Smith, S. L., *The Vitamins*, Second Edition, Monograph Series, No. 6, pages 278, 292, The Chemical Catalog Co., Inc., New York, 1931.
— Washington (D. C.) Star, *Vitamin A Lack Held Stone Cause*, January 11, 1935.

15. Eddy, W. H. and Dalldorf, G., *The Avitaminoses*, page 54, The Williams & Wilkins Co., Baltimore, 1937.
— McCollum, E. V., and Simmonds, N., *The Newer Knowledge of Nutrition*, Fourth Edition, page 495, The MacMillan Co., New York, 1929.

16. Eddy, W. H. and Dalldorf, G., *The Avitaminoses*, pages 41-42, 52-53, The Williams and Wilkins Co., Baltimore, 1937.
— Harris, L. J., *Vitamins in Theory and Practice*, pages 166-167, Cambridge University Press, 1935.
— Macleod, J. J. R., *Physiology in Modern Medicine*, Seventh Edition, page 732, C. V. Mosby Co., St. Louis, 1935.

Posted for noncommercial historical preservation and educational use only by seleneriverpress.com

— Mathews, Albert P., *Principles of Biochemistry*, pages 415-416, William Wood and Company, Baltimore, 1936.
— Stepp, W., Kuhnau, J. and Schroeder, H., *The Vitamins and Their Clinical Application*, Ferdinand Enke, Stuttgart, Germany, 1936.

17. Eddy, W. H. and Dalldorf, G., *The Avitaminoses*, page 51, The Williams and Wilkins Co., Baltimore, 1937.

18. Eddy, W. H. and Dalldorf, G., *The Avitaminoses*, page 54, The Williams and Wilkins Co., Baltimore, 1937.

19. Eddy, W. H. and Dalldorf, G., *The Avitaminoses*, pages 34, 40, The Williams and Wilkins Co., Baltimore, 1937.
— Howell, William H., *A Textbook of Physiology*, Twelfth Edition, Revised, page 968, W. B. Saunders Co., Philadelphia, 1933.
— Jeghers, H., *Night Blindness Due to Vitamin A Deficiency: A Consideration of Its Importance in Traffic Problems*, New England Journal of Medicine, 216:51-56, January 14, 1937.
— Mathews, Albert P., *Principles of Biochemistry*, page 411, William Wood & Co., Baltimore, 1936.
— McClendon, J. F., *A Manual of Biochemistry*, page 3, John Wiley & Sons, Inc., New York, 1934.
— Sherman, H. C. and Smith, S. L., *The Vitamins*, page 274, Second Edition, Monograph Series, No. 6, The Chemical Catalog Co., Inc., New York, 1931.
— Stepp, W., Kuhnau, J. and Schroeder, H., *The Vitamins and Their Clinical Application*, Ferdinand Enke, Stuttgart, Germany, 1936.

20. Macleod, J. J. R., *Physiology in Modern Medicine*, Seventh Edition, page 731, C. V. Mosby Co., St. Louis, 1935.
— Mathews, Albert P., *Principles of Biochemistry*, pages 416-417, William Wood & Co., Baltimore, 1936.
— Medical Research Council, *Vitamins: A Survey of Present Knowledge*, pages 25, 29, London, 1932.
— Sherman, H. C. and Smith, S. L., *The Vitamins*, Second Edition, Monograph Series, No. 6, pages 273-274, The Chemical Catalog Co., Inc., New York, 1931.

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BIBLIOGRAPHY FOR VITAMIN B

1. Eddy, W. H. and Dalldorf, G., *The Avitaminoses*, pages 79, 115, The Williams and Wilkins Co., Baltimore, 1937.
— McClendon, J. F., *A Manual of Biochemistry*, page 4, John Wiley & Sons, Inc., New York, 1934.
— Sherman, H. C. and Smith, S. L., *The Vitamins*, Second Edition, Monograph Series, No. 6, pages 72, 73, The Chemical Catalog Co., New York, 1931.
— Sure, Barnett, *Vitamins in Health and Disease*, pages 39, 41, The Williams and Wilkins Co., Baltimore, 1933.

2. Eddy, W. H. and Dalldorf, G., *The Avitaminoses*, page 79, The Williams and Wilkins Co., Baltimore, 1937.
— Howell, William H., *Textbook of Physiology*, Twelfth Edition, Revised, page 969, W. B. Saunders Co., Philadelphia, 1933.
— Medical Research Council, *Vitamins: A Survey of Present Knowledge*, pages 128-129, London, 1932.
— Morgan, A. F. and Barry, M. M., *American Journal of Diseases of Children*, 39:933, 1930.
— Quigley, D. T., *Notes on Vitamins and Diets*, page 41, Consolidated Book Publishers, Inc., Chicago, 1933.
— Ross, J. R. and Summerfeldt, P., *American Journal of Diseases of Children*, 49:1185, 1935.
— Summerfeldt, P., American Journal of Diseases of Children, 45:284, 1932.
— Sure, Barnett, *Vitamins in Health and Disease*, page 39, The Williams and Wilkins Co., Baltimore, 1933.

3. Eddy, W. H. and Dalldorf, G., *The Avitaminoses*, pages 81-82, The Williams and Wilkins Co., Baltimore, 1937.
— Howell, Wm. H., *Textbook of Physiology*, Twelfth Edition, Revised, page 101, W. B. Saunders Co., Philadelphia, 1933.
— Macleod, J. J. R., *Physiology in Modern Medicine*, Seventh Edition, page 744, C. V. Mosby Company, St. Louis, 1935.
— Mathews, Albert P., *Principles of Biochemistry*, pages 56, 58, 429, William Wood and Co., Baltimore, 1936.
— Medical Research Council, *Vitamins: A Survey of Present Knowledge*, page 133, London, 1932.
— Quigley, D. T., *Notes on Vitamins and Diets*, page 54, Consolidated Book Publishers Co., Inc., Chicago, 1933.
— Stepp, W., Kuhnau, J. and Schroeder, H., *The Vitamins and Their Clinical Application*, Ferdinand Enke, Stuttgart, Germany, 1936.
— Wiggers, Carl J., *Physiology in Health and Disease*, page 961, Lea and Febiger Co., Philadelphia, 1934.

4. Eddy, W. H. and Dalldorf, G., *The Avitaminoses,* pages 111, 112, 117, 119, The Williams and Wilkins Co., Baltimore, 1937.
— Mathews, Albert P., *Principles of Biochemistry,* page 420, William Wood & Co., Baltimore, 1936.
— Medical Research Council, *Vitamins: A Survey of Present Knowledge,* pages 132-133, 136, London, 1932.
— Quigley, D. T., *Notes on Vitamins and Diets,* pages 36-39, The Consolidated Book Publishers Co., Inc., Chicago, 1933.
— Sherman, H. C. and Smith, S. L., *The Vitamins,* Second Edition, Monograph Series, No. 6, The Chemical Catalog Co., New York, 1931.
— Stepp, W., Kuhnau, J. and Schroeder, H., *The Vitamins and Their Clinical Application,* Ferdinand Enke, Stuttgart, Germany, 1936.

5. Chicago Tribune, *Find Way to Synthesize Second Vitamin: Aid to Insanity,* January 28, 1935.
— Eddy, W. H. and Dalldorf, G., *The Avitaminoses,* page 105, The Williams and Wilkins Co., Baltimore, 1937.
— Gildea, M. C. L., Castle, W. B., Gildea, E. F., and Cobb, S., *Neuropathology of Experimental Vitamin Deficiency,* American Journal of Pathology, 11, 65:669, July, 1935.
— Quigley, Daniel Thomas, *Notes on Vitamins and Diets,* page 43, Consolidated Book Publishers Co., Inc., Chicago, 1933.
— Schuler, R., *Chemistry and Physiology of Vitamin B,* Drug & Cosmetic Industry, 39, 2:180, August, 1936.

6. Mathews, Albert P., *Principles of Biochemistry,* page 59, William Wood & Co., Baltimore, 1936.
— Webster and Armour, *Proceedings of Society for Experimental Biology and Medicine,* January, 1934.

7. Pemberton and Osgood, *Chronic Arthritis,* Macmillan Co., 1934.
— Stepp, W., Kuhnau, J. and Schroeder, H., *The Vitamins and Their Clinical Application,* Ferdinand Enke, Stuttgart, Germany, 1936.

8. Mathews, Albert P., *Physiological Chemistry,* Fourth Edition, page 855, William Wood & Co., Baltimore, 1925.
— Ruskin, S. L., *Nucleic Acid and Nucleotide Therapyin Nasal Diseases,* Archives of Otolaryngology, 22:172-181, August, 1935.

9. Eddy, W. H. and Dalldorf, G., *The Avitaminoses,* page 264, The Williams and Wilkins Co., Baltimore, 1937.
— Mathews, Albert P., *Principles of Biochemistry,* page 421, William Wood & Co., Baltimore, 1936.
— McCollum, E. V. and Simmonds, Nina, *The Newer Knowledge of Nutrition,* Fourth Edition, page 499, Macmillan Co., New York, 1929.
— Medical Research Council, *Vitamins: A Survey of Present Knowledge,* page 137, London, 1932.

10. Eddy, W. H. and Dalldorf, G., *The Avitaminoses,* pages 81, 116, 117, The Williams and Wilkins Co., Baltimore, 1937.
— Harris, L. J., *Vitamins in Theory and Practice,* pages 64-67, Cambridge University Press, London, 1935.
— Howell, William H., *A Textbook of Physiology,* Twelfth Edition, Revised, page 970, W. B. Saunders Co., Philadelphia, 1933.
— Labbe, Nepveux and Gringoire, *Bull. Acad. de Med., Paris,* 109:689-702, 1933.

Posted for noncommercial historical preservation and educational use only by seleneriverpress.com

— Macleod, J. J. R., *Physiology in Modern Medicine*, Seventh Edition, page 744, C. V. Mosby Co., St. Louis, 1935.
— Mathews, Albert P., *Principles of Biochemistry*, page 57, William Wood & Co., Baltimore, 1936.
— McCollum, E. V. and Simmonds, Nina, *The Newer Knowledge of Nutrition*, Fourth Edition, page 223, Macmillan Co., 1929.
— Medical Research Council, *Vitamins: A Survey of Present Knowledge*, pages 133-134, London, 1932.
— Schrader, G. A., *Alabama Agricultural Experiment Station*, Forty-second Annual Report, page 35, 1931.
— Sherman, H. C. and Smith, S. L., *The Vitamins*, Second Edition, Monograph Series, No. 6, pages 70, 81, The Chemical Catalog Co., Inc., New York, 1931.
— Stepp, W., Kuhnau, J. and Schroeder, H., *The Vitamins and Their Clinical Application*, Ferdinand Enke, Stuttgart, Germany, 1936.
— Sure, B., *Vitamins in Health and Disease*, page 41, The Williams and Wilkins Co., Baltimore, 1933.
— Vorhaus, M. G., Williams, R. R. and Waterman, R. E., *Studies on Crystalline Vitamin B_1: Observations in Diabetes*, American Journal of Digestive Diseases and Nutrition, 2, 9:541-557, November, 1935.
— Wiggers, Carl J., *Physiology in Health and Disease*, page 961, Lea and Febiger, Philadelphia, 1934.

11. Barborka, C. J., *Diet and Preventive Dentistry*, Journal of the American Dental Association, 23, 8:977-985, June, 1936.
— Eddy, W. H. and Dalldorf, G., *The Avitaminoses*, pages 84, 106-107, The Williams and Wilkins Co., Baltimore, 1937.
— Harris, L. J., *Vitamins in Theory and Practice*, pages 65-67, Cambridge University Press, London, 1935.
— Howell, W. H., *A Textbook of Physiology*, Twelfth Edition, Revised, page 970, W. B. Saunders Co., Philadelphia, 1933.
— Macleod, J. J. R., *Physiology in Modern Medicine*, Seventh Edition, pages 744-745, C. V. Mosby Co., St. Louis, 1935.
— Mathews, Albert P., *Principles of Biochemistry*, pages 58, 59, 421, William Wood & Co., Baltimore, 1936.
— McCollum, E. V. and Simmonds, Nina, *The Newer Knowledge of Nutrition*, Fourth Edition, pages 231-232, Macmillan Co., 1929.
— Medical Research Council, *Vitamins: A Survey of Present Knowledge*, pages 134-137, London, 1932.
— Sherman, H. C. and Smith, S. L., *The Vitamins*, Second Edition, Monograph Series, No. 6, pages 70, 81, 82, The Chemical Catalog Co., Inc., New York, 1931.
— Stepp, W., Kuhnau, J. and Schroeder, H., *The Vitamins and Their Clinical Application*, Ferdinand Enke, Stuttgart, Germany, 1936.
— Sure, Barnett, *Vitamins in Health and Disease*, page 41, The Williams and Wilkins Co., Baltimore, 1933.
— Tohoku Journal of Experimental Medicine, page 184, 1935.
— Vorhaus, M. G., Williams, R. R. and Waterman, R. E., *Studies on Crystalline Vitamin B_1: Observations in Diabetes*, American Journal of Digestive Diseases and Nutrition, 2, 9:541-557, November, 1935.
— Wiggers, C. J., *Physiology in Health and Disease*, page 960, Lea & Febiger Co., Philadelphia, 1934.

Posted for noncommercial historical preservation and educational use only by seleneriverpress.com

12. Barborka, C. J., *Diet and Preventive Dentistry*, Journal of the American Dental Association, 23, 6:977-985, June, 1936.
— Eddy, W. H. and Dalldorf, G., *The Avitaminoses*, pages 79-80, 94, 105-106, 112-114, 116, The Williams and Wilkins Co., Baltimore, 1937.
— Fitts, J. B., *Motor and Secretory Dysfunction of the Gastro-intestinal Tract and the Vitamin B Factor: A Clinical Study*, Southern Medical Journal, 28:920-923, October, 1935.
— Howell, W. H., *Textbook of Physiology*, Twelfth Edition, Revised, page 970, W. B. Saunders Co., Philadelphia, 1933.
— Marks, H. E., *Medical Journal and Record*, March 2, 1932.
— Mathews, Albert P., *Principles of Biochemistry*, page 423, William Wood & Co., Baltimore, 1936.
— McCollum, E. V. and Simmonds, Nina, *The Newer Knowledge of Nutrition*, Fourth Edition, pages 227, 231-232, Macmillan Company, 1929.
— Medical Research Council, *Vitamins: A Survey of Present Knowledge*, pages 131, 134-135, 137, London, 1932.
— Rowlands, M. J. and Browning, E., *Lancet*, 1:180, 1928.
— Sherman, H. C. and Smith, S. L., *The Vitamins*, Second Edition, Monograph Series, No. 6, pages 70-71, 74-75, The Chemical Catalog Co., Inc., New York, 1931.
— Sparks, M. I. and Collins, E. N., *The Role of Vitamin B_1 in Tonus of the Large Intestine*, American Journal of Digestive Diseases and Nutrition, 2, 10:618-620, December, 1935.
— Stepp, W., Kuhnau, J. and Schroeder, H., *The Vitamins and Their Clinical Application*, Ferdinand Enke, Stuttgart, Germany, 1936.
— Sure, B., *Vitamins in Health and Disease*, page 40, The Williams and Wilkins Co., Baltimore, 1933.
— Wiggers, Carl J., *Physiology in Health and Disease*, pages 961-962, Lea & Febiger Co., Philadelphia, 1934.

13. Collazo, J. A., *Biochem. Ztschr.*, 134:194-214, 1922.
— Drummond, J. C. and Marrian, G. F., *The Physiological Role of Vitamin B_1, the Relation of Vitamin B to Tissue Oxidation*, Biochemical Journal, 20:1229-1255, 1926.
— Eggleton, R. and Gross, L., *A Note on the Blood Sugar Levels of Rats Fed With Complete Diets and Diets Deficient in Vitamin B.*, Biochemical Journal, 19:633-637, 1925.
— McCollum, E. V., and Simmonds, Nina, *The Newer Knowledge of Nutrition*, Fourth Edition, page 493, Macmillan Co., 1929.
— Sherman, H. C. and Smith, S. L., *The Vitamins*, Second Edition, Monograph Series, No. 6, page 83, The Chemical Catalog Co., Inc., New York, 1931.
— Stepp, W., Kuhnau, J. and Schroeder, H., *The Vitamins and Their Clinical Application*, Ferdinand Enke, Stuttgart, Germany, 1936.
— Sure, B., *Vitamins in Health and Disease*, page 40, The Williams and Wilkins Co., Baltimore, 1933.

14. Barborka, C. J., *Diet and Preventive Dentistry*, Journal of the American Dental Association, 23, 6:977-985, June, 1936.
— Eddy, W. H. and Dalldorf, G., *The Avitaminoses*, page 80, The Williams and Wilkins Co., Baltimore, 1937.
— Howell, William H., *Textbook of Physiology*, Twelfth Edition, Revised, page 970, W. B. Saunders Co., Philadelphia, 1933.

Posted for noncommercial historical preservation and educational use only by seleneriverpress.com

— Marks, H. E., *Medical Journal and Record,* March 2, 1932.
— Mathews, Albert P., *Principles of Biochemistry,* page 421, William Wood & Co., Baltimore, 1936.
— Medical Research Council, *Vitamins: A Survey of Present Knowledge,* page 129, London, 1932.
— Sherman, H. C. and Smith, S. L., *The Vitamins,* Second Edition, Monograph Series, No. 6, pages 70, 72, 83, The Chemical Catalog Co., Inc., New York, 1931.
— Shipley, P. G., McCollum, E. V. and Simmonds, N., *Studies in Experimental Rickets, IX. Lesions in the Bones of Rats Suffering from Uncomplicated Beriberi,* Journal of Biological Chemistry, 49:399-410, 1921.
— Stepp, W., Kuhnau, J. and Schroeder, H., *The Vitamins and Their Clinical Application,* Ferdinand Enke, Stuttgart, Germany, 1936.
— Sure, B., *Vitamins in Health and Disease,* pages 53-54, The Williams and Wilkins Co., Baltimore, 1933.
— Wiggers, Carl J., *Physiology in Health and Disease,* pages 961-962, Lea & Febiger Co., Philadelphia, 1934.

15. Delafield, F. and Prudden, T. M., *Textbook of Pathology,* Fifteenth Edition, page 496, William Wood & Co., New York, 1931.
— Mathews, Albert P., *Principles of Biochemistry,* page 423, William Wood & Co., Baltimore, 1936.
— Stepp, W., Kuhnau, J. and Schroeder, H., *The Vitamins and Their Clinical Application,* Ferdinand Enke, Stuttgart, Germany, 1936.

16. Howell, William H., *Textbook of Physiology,* Twelfth Edition, Revised, page 970, W. B. Saunders Co., Philadelphia, 1933.
— Macleod, J. J. R., *Physiology in Modern Medicine,* Seventh Edition, page 744, C. V. Mosby Co., St. Louis, 1935.
— Medical Research Council, *Vitamins: A Survey of Present Knowledge,* page 131, London, 1932.
— Sherman, H. C. and Smith, S. L., *The Vitamins,* Second Edition, Monograph Series, No. 6, page 70, The Chemical Catalog Co., Inc., New York, 1931.
— Stepp, W., Kuhnau, J. and Schroeder, H., *The Vitamins and Their Clinical Application,* Ferdinand Enke, Stuttgart, Germany, 1936.

17. Delafield, F. and Prudden, T. M., *Textbook of Pathology,* page 496, Fifteenth Edition, William Wood & Co., Baltimore, 1931.
— Eddy, W. H. and Dalldorf, G., *The Avitaminoses,* pages 103-105, The Williams and Wilkins Co., Baltimore, 1937.
— Gildea, M. C. L., Castle, W. B., Gildea, E. F. and Cobb, S., *Neuropathology of Experimental Vitamin Deficiency,* American Journal of Pathology, 11, 65:669, July, 1935.
— Harris, L. J., *Vitamins in Theory and Practice,* page 67, Cambridge University Press, London, 1935 .
— Howell, William H., *Textbook of Physiology,* Twelfth Edition, Revised, page 970, W. B. Saunders Co., Philadelphia, 1933.
— Mathews, Albert P., *Principles of Biochemistry,* pages 59, 419-420, William Wood and Co., Baltimore, 1936.

Posted for noncommercial historical preservation and educational use only by seleneriverpress.com

— Sherman, H. C. and Smith, S. L., *The Vitamins,* Second Edition, Monograph Series, No. 6, page 70, The Chemical Catalog Co., Inc., New York, 1931.
— Stepp, W., Kuhnau, J. and Schroeder, H., *The Vitamins and Their Clinical Application,* Ferdinand Enke, Stuttgart, Germany, 1936.
— Wiggers, C. J., *Physiology in Health and Disease,* pages 960-962, Lea & Febiger Co., Philadelphia, 1934.

18. Haden, R., *American Journal of Digestive Diseases and Nutrition,* 1:628, 1934.
— Hutter, A. M., Middleton, Wm. S., and Steenbock, H., Journal of the American Medical Association, 101:1305, 1935.
— Macleod, J. J. R., *Physiology in Modern Medicine,* Seventh Edition, pages 744-745, C. V. Mosby Co., St. Louis, 1935.
— McCollum, E. V. and Simmonds, Nina, *The Newer Knowledge of Nutrition,* Fourth Edition, page 223, Macmillan Co., 1929.
— Medical Research Council, *Vitamins: A Survey of Present Knowledge,* page 137, London, 1932.

19. Eddy, W. H. and Dalldorf, G., *The Avitaminoses,* page 107, The Williams and Wilkins Co., Baltimore, 1937.
— Frank, R. T., *The Female Sex Hormone,* page 123, Charles C. Thomas, Baltimore, 1929.
— Hitsuko, Chin., Journal Chosen Medical Association, 23:968.
— Mathews, Albert P., *Principles of Biochemistry,* page 423, William Wood & Co., Baltimore, 1936.
— Macleod, J. J. R., *Physiology in Modern Medicine,* Seventh Edition, page 745, C. V. Mosby Co., St. Louis, 1935.
— Medical Research Council, *Vitamins: A Survey of Present Knowledge,* page 136, London, 1932.
— Moore, Carl R. and Samuels, L. J., American Journal of Physiology, 96:278, 1931.
— Sherman, H. C. and Smith, S. L., *The Vitamins,* Second Edition, Monograph Series, No. 6, page 82, The Chemical Catalog Co., Inc., New York, 1931.
— Stepp, W., Kuhnau, J. and Schroeder, H., *The Vitamins and Their Clinical Application,* Ferdinand Enke, Stuttgart, Germany, 1936.

20. Stepp, W., Kuhnau, J. and Schroeder, H., *The Vitamins and Their Clinical Application,* Ferdinand Enke, Stuttgart, Germany, 1936.

21. Mathews, Albert P., *Physiological Chemistry,* pages 918-919, William Wood & Co., Baltimore, 1925.

22. Barborka, Clifford J., *Diet and Preventive Dentistry,* Journal of the American Dental Association, 23, 6:977-985, June, 1936.
— Cutter, Irving S., *How to Keep Well: Scurvy and the Onset of Arthritis,* Chicago Daily Tribune, January 21, 1936.
— Eddy, W. H. and Dalldorf, G., *The Avitaminoses,* pages 79, 90, 97, The Williams and Wilkins Co., Baltimore, 1937.
— Mathews, Albert P., *Principles of Biochemistry,* page 419, William Wood & Co., Baltimore, 1936.
— Medical Research Council, *Vitamins: A Survey of Present Knowledge,* page 127, London, 1932.

Posted for noncommercial historical preservation and educational use only by seleneriverpress.com

23. Delafield, F. and Prudden, T. M., *Textbook of Pathology,* page 496, Fifteenth Edition, William Wood & Co., Baltimore, 1931.
— Eddy, W. H. and Dalldorf, G., *The Avitaminoses,* pages 89, 103-105, The Williams and Wilkins Co., Baltimore, 1937.
— Mathews, Albert P., *Principles of Biochemistry,* pages 419-420, William Wood & Co., Baltimore, 1937.

24. Gildea, M. C. L., Castle, W. B., Gildea, E. F., and Cobb, S., *Neuropathology of Experimental Vitamin Deficiency,* American Journal of Pathology, 11, 65:669, July, 1935.
— Mathews, Albert P., *Principles of Biochemistry,* pages 419-420, William Wood & Co., Baltimore, 1936.
— Medical Research Council, *Vitamins: A Survey of Present Knowledge,* page 129, London, 1932.
— Sherman, H. C. and Smith, S. L., *The Vitamins,* Second Edition, Monograph Series, No. 6, page 83, The Chemical Catalog Co., Inc., New York, 1931.

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BIBLIOGRAPHY FOR VITAMIN C

1. Eddy, W. H. and Dalldorf, G., *The Avitaminoses*, page 169, The Williams and Wilkins Co., Baltimore, 1937.
— Findlay, G. M., *The Relation of Vitamin C to Bacterial Infection*, Journal of Pathology and Bacteriology, 26:1-18, 1923.
— Hess, A. F., American Journal of Diseases of Children, November, 1927.
— Medicine, 13:205, 1934.
— Proceedings of Society of Experimental Biology and Medicine, page 1157, April, 1935.
— Quigley, Daniel Thomas, *Notes on Vitamins and Diets*, page 126, Consolidated Book Publishers, Inc., Chicago, 1933.
— Wiggers, C. J., *Physiology in Health and Disease*, page 987, Lea & Febiger, Philadelphia, 1934.

2. Eddy, W. H. and Dalldorf, G., *The Avitaminoses*, page 169, The Williams and Wilkins Co., Baltimore, 1937.
— Medical Research Council, *Vitamins: A Survey of Present Knowledge*, page 102, London, 1932.
— Vitamin D Milk, 2, 1:2, January, 1935.

3. Eddy, W. H. and Dalldorf, G., *The Avitaminoses*, pages 168-169, 185, The Williams and Wilkins Co., Baltimore, 1937.
— Harris, L. J., *Vitamins in Theory and Practice*, page 106, Cambridge University Press, 1935.
— Wiggers, C. J., *Physiology in Health and Disease*, pages 967-968, Lea & Febiger, Philadelphia, 1934.

4. Stepp, W., Kuhnau, J. and Schroeder, H., *The Vitamins and Their Clinical Application*, Ferdinand Enke, Stuttgart, Germany, 1936.

5. Stepp, W., Kuhnau, J. and Schroeder, H., *The Vitamins and Their Clinical Application*, Ferdinand Enke, Stuttgart, Germany, 1936.

6. Barborka, C. J., *Diet and Preventive Dentistry*, Journal of the American Dental Association, 23, 6:977-985, June, 1936.
— Delafield, F. and Prudden, T. M., *A Textbook of Pathology*, Fifteenth Edition, page 495-496, William Wood & Co., New York, 1931.
— Drummond, J. C. and Marrian, G. F., *The Physiological Role of Vitamin B., I. The Relation of Vitamin B to Tissue Oxidation*, Biochemical Journal, 20:1229-1255, 1926.
— Eddy, W. H. and Dalldorf, G., *The Avitaminoses*, pages 169, 175, 178, 185, The Williams and Wilkins Co., Baltimore, 1937.
— Findlay, G. M., *The Blood and Blood Vessels in Guinea Pig Scurvy*, Journal of Pathology and Bacteriology, 24:446-454, 1921.
— Hanke, M. T., Journal of Nutrition, 3, 4:448, January, 1931.

— Harris, L. J., *Vitamins in Theory and Practice,* pages 106, 212-213, Cambridge University Press, 1935.
— Journal of the American Medical Association, 103, 13:1022, September 29, 1934.
— Macleod, J. J. R., *Physiology in Modern Medicine,* Seventh Edition, pages 747, 749, C. V. Mosby, St. Louis, 1935.
— McClendon, J. F., *A Manual of Biochemistry,* pages 4, 87, John Wiley & Sons, Inc., New York, 1934.
— Medical Research Council, *Vitamins: A Survey of Present Knowledge,* pages 90, 102, 192-193, London, 1932.
— Plimmer, R. H. B. and Plimmer, V. G., *Foods, Health, Vitamins,* Third Edition, page 18, Longmans Green & Co., New York, 1928.
— Quigley, Daniel Thomas, *Notes on Vitamins and Diets,* pages 120, 126-127, Consolidated Book Publishers, Inc., Chicago, 1933.
— Quigley, D. T., *Vitamin Chart,* Consolidated Book Publishers, Inc., Chicago, 1933.
— Sherman, H. C., *Chemistry of Food & Nutrition,* Fifth Edition, page 441, The Macmillan Co., New York, 1937.
— Sherman, H. C. and Smith, S. L., *The Vitamins,* Second Edition, Monograph Series, No. 6, pages 162-163, 164, 166, 172, The Chemical Catalog Co., Inc., New York, 1931.
— Stepp, W., Kuhnau, J. and Schroeder, H., *The Vitamins and Their Clinical Application,* Ferdinand Enke, Stuttgart, Germany, 1936.
— Sure, B., *Vitamins in Health and Disease,* page 79, The Williams and Wilkins Co., Baltimore, 1933.
— Wiggers, C. J., *Physiology in Health and Disease,* pages 967-968, Lea & Febiger, Philadelphia, 1934.

7. Archives of Internal Medicine, 51:426.
— Quigley, D. T., *Notes on Vitamins and Diets,* page 43, Consolidated Book Publishers, Inc., Chicago, 1933.

8. Drug Trade News, 10, 9:35, April, 1935.
Eddy, W. H. and Dalldorf, G., *The Avitaminoses,* page 177, The Williams & Wilkins Co., Baltimore, 1937.
— Proceedings of Society of Experimental Biology and Medicine, page 1089, April, 1935.
— Sherman, H. C. and Smith, S. L., *The Vitamins,* Second Edition, Monograph Series, No. 6, pages 163-164, The Chemical Catalog Co., Inc., New York, 1931.
— Stepp, W., Kuhnau, J. and Schroeder, H., *The Vitamins and Their Clinical Application,* Ferdinand Enke, Stuttgart, Germany, 1936.
— Wiggers, C. J., *Physiology in Health and Disease,* page 969, Lea & Febiger, Philadelphia, 1934.

9. Eddy, W. H. and Dalldorf, G., *The Avitaminoses,* page 177, The Williams and Wilkins Co., Baltimore, 1937.
— Sherman, H. C. and Smith, S. L., *The Vitamins,* Second Edition, Monograph Series, No. 6, pages 171-172, The Chemical Catalog Co., Inc., New York, 1931.
— Stepp, W., Kuhnau, J. and Schroeder, H., *The Vitamins and Their Clinical Application,* Ferdinand Enke, Stuttgart, Germany, 1936.
— Wiggers, C. J., *Physiology in Health and Disease,* page 967, Lea & Febiger, Philadelphia, 1934.

Posted for noncommercial historical preservation and educational use only by seleneriverpress.com

10. Eddy, W. H. and Dalldorf, G., *The Avitaminoses,* page 175, The Williams and Wilkins Co., Baltimore, 1937.
— Quigley, D. T., *Vitamin Chart,* Consolidated Book Publishers, Inc., Chicago, 1933.

11. Eddy, W. H. and Dalldorf, G., *The Avitaminoses,* page 175, The Williams and Wilkins Co., Baltimore, 1937.
— Quigley, D. T., *Vitamin Chart,* Consolidated Book Publishers, Inc., Chicago, 1933.
— Wiggers, C. J., *Physiology in Health and Disease,* page 968, Lea & Febiger, Philadelphia, 1934.

12. Archives of *Diseases of Childhood,* 8:117-144, 1933.
— Delafield, F. and Prudden, T. M., *A Textbook of Pathology,* Fifteenth Edition, pages 495-496, William Wood & Co., New York, 1931.
— Eddy, W. H. and Dalldorf, G., *The Avitaminoses,* page 179, The Williams and Wilkins Co., Baltimore, 1937.

13. Quigley, D. T., *Notes on Vitamins and Diets,* page 126, Consolidated Book Publishers, Inc., Chicago, 1933.
— Stepp, W., Kuhnau, J. and Schroeder, H., *The Vitamins and Their Clinical Application,* Ferdinand Enke, Stuttgart, Germany, 1936.

14. Berglund, Medes, Huber, Longcope and Richards, *The Kidney in Health and Disease,* pages 150-151, Lea & Febiger Co., Philadelphia, 1935.
— Eddy, W. H. and Dalldorf, G., *The Avitaminoses,* page 190, The Williams and Wilkins Co., Baltimore, 1937.
— Medical Research Council, *Vitamins: A Survey of Present Knowledge,* pages 192-193, London, 1932.
— Sherman, H. C. and Smith, S. L., *The Vitamins,* Second Edition, Monograph Series, No. 6, page 166, The Chemical Catalog Co., Inc., New York, 1931.

15. Eddy, W. H. and Dalldorf, G., *The Avitaminoses,* pages 190, 202, The Williams and Wilkins Co., Baltimore, 1937.
— Medical Research Council, *Vitamins: A Survey of Present Knowledge,* pages 192-193, London, 1932.
— Sherman, H. C. and Smith, S. L., *The Vitamins,* Second Edition, Monograph Series, No. 6, page 166, Chemical Catalog Co., Inc., New York, 1931.

16. Cutter, Irving S., *How to Keep Well:* Chicago Daily Tribune, Chicago, January 21, 1936.
— Eddy, W. H. and Dalldorf, G., *The Avitaminoses,* pages 176-178, 274-275, The Williams and Wilkins Co., Baltimore, 1937.
— Rinehart, James F., *Annals of Internal Medicine,* December, 1935.

17. Eddy, W. H. and Dalldorf, G., *The Avitaminoses,* page 177, The Williams and Wilkins Co., Baltimore, 1937.

18. Eddy, W. H. and Dalldorf, G., *The Avitaminoses,* pages 203-204, The Williams and Wilkins Co., Baltimore, 1937.
— Journal of the American Medical Association, 103:78, 1934.

Posted for noncommercial historical preservation and educational use only by seleneriverpress.com

— Medical Research Council, *Vitamins: A Survey of Present Knowledge,* page 194, London, 1932.
— Sherman, H. C. and Smith, S. L., *The Vitamins,* Second Edition, Monograph Series, No. 6, Chemical Catalog Co., Inc., New York, 1931.
— Stepp, W., Kuhnau, J. and Schroeder, H., *The Vitamins and Their Clinical Application,* Ferdinand Enke, Stuttgart, Germany, 1936.

19. Eddy, W. H. and Dalldorf, G., *The Avitaminoses,* pages 175, 177-178, The Williams and Wilkins Co., Baltimore, 1937.

20. Eddy, W. H. and Dalldorf, G., *The Avitaminoses,* page 190, The Williams and Wilkins Co., Baltimore, 1937.

21. Sigal, A. and King, C. G., *The Relationship of Vitamin C to Glucose Tolerance in the Guinea Pig,* Journal of Biological Chemistry, 116, 2:489-492, December 1936.

22. Josephson, E., *Ascorbic Acid in Cataract,* Science, 82:222-223, September 6, 1935.

23. Mathews, Albert P., *Physiological Chemistry,* pages 918-919, William Wood & Co., Baltimore, 1925.

24. Barborka, C. J., *Diet and Preventive Dentistry,* Journal of the American Dental Association, 23, 6:977-985, June, 1936.
— Eddy, W. H. and Dalldorf, G., *The Avitaminoses,* pages 174-184, The Williams and Wilkins Co., Baltimore, 1937.
— Quigley, D. T., *Notes on Vitamins and Diets,* page 98, Consolidated Book Publishers, Inc., Chicago, 1933.
— Stepp, W., Kuhnau, J. and Schroeder, H., *The Vitamins and Their Clinical Application,* Ferdinand Enke, Stuttgart, Germany, 1936.

25. Stepp, W., Kuhnau, J. and Schroeder, H., *The Vitamins and Their Clinical Application,* Ferdinand Enke, Stuttgart, Germany, 1936.

26. Eddy, W. H. and Dalldorf, G., *The Avitaminoses,* pages 47, 175, 185, The Williams and Wilkins Co., Baltimore, 1937.
— Macleod, J. J. R., *Physiology in Modern Medicine,* Seventh Edition, page 747, C. V. Mosby Co., St. Louis, 1935.
— Quigley, D. T., *Notes on Vitamins and Diets,* page 126, Consolidated Book Publishers, Inc., Chicago, 1933.

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BIBLIOGRAPHY FOR VITAMIN D

1. Becker, J. E., *Journal of the American Dietetic Association,* 10:391, 1935.
— Eddy, W. H. and Dalldorf, G., *The Avitaminoses,* page 269, The Williams and Wilkins Co., Baltimore, 1937.
— Harris, L. J., *Lancet,* No. 222, 1031, 1932.
— Harris, L. J., *Vitamins in Theory and Practice,* pages 122, 140-141, Cambridge University Press, London, 1935.
— Howell, W. H., *Textbook of Physiology,* Twelfth Edition, Revised, page 972, W. B. Saunders Co., Philadelphia, 1933.
— Kay, H. D. and Guyatt, B. L., *Nature,* 131:468, 1933.
— Macleod, J. J. R., *Physiology in Modern Medicine,* Seventh Edition, pages 734, 749, C. V. Mosby Co., St. Louis, 1935.
— Mathews, Albert P., *Principles of Biochemistry,* pages 417, 439-440, William Wood and Co., Baltimore, 1936.
— McCollum, E. V., *Safeguarding the Growing Child,* No. 5.
— McGowan, J. P., *Journal of Biological Chemistry,* 26:1138, 1933.
— Medical Research Council, *The Influence of Diet on Caries on Children's Teeth,* pages 129-130, 132, London, 1936.
— Medical Research Council, *Vitamins: A Survey of Present Knowledge,* pages 48, 93, 100, 242, London, 1932.
— Orr, W. J., Holt, L. E., Jr., Wilkins, L. and Boone, F. G., *The Calcium and Phosphorus Metabolism in Rickets,* with special reference to ultraviolet ray therapy, American Journal of Diseases of Children, 26:362, 1923.
— Orr, W. J., Holt, L. E., Jr., Wilkins, L. and Boone, F. G., *The Relation of Calcium and Phosphorus in the Diet to the Absorption of These Elements from the Intestine,* American Journal of Diseases of Children, 28:574, 1924.
— Quigley, D. T., *Notes on Vitamins and Diets,* pages 19-20, 127, Consolidated Book Publishers, Inc., Chicago, 1933.
— Schabad, J. A., Arch. f. Kinderh., 52:68, 1910.
— Schloss, E., Ergebn. inn. Med. Kinderh., 15:55, 1917.
— Sherman, H. C. and Smith, S. L., *The Vitamins,* Second Edition, Monograph Series, No. 6, pages 298-299, The Chemical Catalog Co., Inc., New York, 1931.
— Stearns, G. and Jeans, P. C., *Proceedings of the American Society of Biological Chemistry,* 114, c, 1936.
— Stepp, W., Kuhnau, J. and Schroeder, H., *The Vitamins and Their Clinical Application,* Ferdinand Enke, Stuttgart, Germany, 1936.
— Sure, B., *Vitamins in Health and Disease,* page 114, The Williams and Wilkins Co., Baltimore, 1933.
— Telfer, S. V., *Studies on Calcium and Phosphate Metabolism, Part I; The Excretion of Calcium and Phosphorus,* Quarterly Journal of Medicine, 16:45, 1922-1923.
— Telfer, S. V., *Studies on Calcium and Phosphate Metabolism, Part II;*

The Metabolism of Calcium and Phosphorus in Rickets, Quarterly Journal of Medicine, 16:63, 1922-1923.
— Telfer, S. V., *Studies on Calcium and Phosphate Metabolism, Part III; The Absorption of Calcium and Phosphorus and Their Function in the Skeleton,* Quarterly Journal of Medicine, 17:245, 1924.
— Wiggers, C. J., *Physiology in Health and Disease,* pages 967, 971, 1031, Lea & Febiger, Philadelphia, 1934.

2. Harris, L. J., *Vitamins in Theory and Practice,* page 122, Cambridge University Press, London, 1935.
— Medical Research Council, *Vitamins: A Survey of Present Knowledge,* pages 242, 269, London, 1932.
— Wiggers, C. J., *Physiology in Health and Disease,* page 969, Lea & Febiger, Philadelphia, 1934.

3. Richardson, G. C., *Illinois Medical Journal,* 65:367, 1934.

4. Gunn, F. D., *Proceedings of the Society of Experimental Biology and Medicine,* 24:120, 1926.
— Laurens, H. and Sooy, J. W., *Proceedings of the Society of Experimental Biology and Medicine,* 22:114, 1924.
— Sanford, H. N. Gastever, R. H. and Wyat, L., *American Journal of Diseases of Children,* 43:566, 1922.

5. Gunn, F. D., *Proceedings of the Society of Experimental Biology and Medicine,* 24:120, 1926.
— McNealy, R. W., Shapiro, P. F., and Milnick, P., *Surgery, Gynecology and Obstetrics,* 60:785, 1935.
— Phillips, R. A., Robertson, D. F., Corson, W. C., and Irwin, G. F., *Annals of Internal Medicine,* 4:1134, 1934.
— Richardson, G. C., *Illinois Medical Journal,* 65:367, 1934.
— Sanford, H. N. Gastever, R. H. and Wyat, L., *American Journal of Diseases of Children,* 43:566, 1922.
— Stepp, W., Kuhnau, J. and Schroeder, H., *The Vitamins and Their Clinical Application,* Ferdinand Enke, Stuttgart, Germany, 1936.

6. Jeans, P. C. and Stearns, G., *Proceedings of the Society of Experimental Biology and Medicine,* 31:1159, 1934.
— Jeans, P. C. and Stearns, G., *Proceedings of the Society of Experimental Biology and Medicine,* 32:1464, 1935.
— Medical Research Council, *Vitamins: A Survey of Present Knowledge,* page 48, London, 1932.
— Quigley, D. T., *Notes on Vitamins and Diets,* page 21, Consolidated Book Publishers, Inc., Chicago, 1933.
— Sherman, H. C. and Smith, S. L., *The Vitamins,* Second Edition, Monograph Series, No. 6, page 320, The Chemical Catalog Co., Inc., New York, 1931.
— Stearns, G., Jeans, P. C. and Vandecar, V., *Journal of Pediatrics,* 9:1, 1936.
— Stearns, G. and Jeans, P. C., *Proceedings of the American Society of Biological Chemistry,* 114, c, 1936.
— Stepp, W., Kuhnau, J. and Schroeder, H., *The Vitamins and Their Clinical Application,* Ferdinand Enke, Stuttgart, Germany, 1936.

Posted for noncommercial historical preservation and educational use only by seleneriverpress.com

— Wiggers, C. J., *Physiology in Health and Disease*, page 969, Lea & Febiger, Philadelphia, 1934.

7. Richardson, G. C., *Illinois Medical Journal*, 65:367, 1934.

8. Vitamin D Milk, 3, 7:27, October, 1936.

9. Harrow, B. and Sherwin, C. P., *The Chemistry of the Hormones*, pages 31-32, The Williams and Wilkins Co., Baltimore, 1934.
— Medical Research Council, *The Influence of Diet on Caries in Children's Teeth*, pages 129-130, London, 1936.
— Stepp, W., Kuhnau, J. and Schroeder, H., *The Vitamins and Their Clinical Application*, Ferdinand Enke, Stuttgart, Germany, 1936.
— Wolf, William, *Endocrinology in Modern Practice*, page 367, W. B. Saunders Co., Philadelphia, 1936.

10. Eddy, W. H. and Dalldorf, G., *The Avitaminoses*, page 269, The Williams and Wilkins Co., Baltimore, 1937.
— Quigley, D. T., *Notes on Vitamins and Diets*, pages 20, 43-44, 88, 127, Consolidated Book Publishers, Inc., Chicago, 1933.
— Sure, B., *The Vitamins in Health and Disease*, page 188, The Williams and Wilkins Co., Baltimore, 1933.

11. Mathews, Albert P., *Principles of Biochemistry*, page 442, William Wood & Co., Baltimore, 1936.
— Presnell, A. K., *The Relation of Vitamin D to Skin Respiration*, Journal of Biological Chemistry, 121, 1:5-8, October, 1937.

12. Barborka, D. J., *Diet and Preventive Dentistry*, Journal of the American Dental Association, 23, 6:977-985, 1936.
— Cantarow, A., *Calcium Metabolism and Calcium Therapy*, Lea & Febiger, Philadelphia, 1931.
— Eddy, W. H. and Dalldorf, G., *The Avitaminoses*, pages 218-219, The Williams and Wilkins Co., Baltimore, 1937.
— Harris, L. J., *Vitamins in Theory and Practice*, Footnote page 127, Cambridge University Press, London, 1935.
— Mathews, Albert P., *Principles of Biochemistry*, pages 439-440, William Wood & Co., Baltimore, 1936.
— Medical Research Council, *Vitamins: A Survey of Present Knowledge*, pages 48-49, 73, 239, London, 1932.
— Quigley, D. T., *Notes on Vitamins and Diets*, page 43, Consolidated Book Publishers, Inc., Chicago, 1933.
— Stepp, W., Kuhnau, J. and Schroeder, H., *The Vitamins and Their Clinical Application*, Ferdinand Enke, Stuttgart, Germany, 1936.
— Wiggers, C. J., *Physiology in Health and Disease*, pages 971, 987, Lea & Febiger, Philadelphia, 1934.

13. Macleod, J. J. R., *Physiology in Modern Medicine*, Seventh Edition, page 734, C. V. Mosby Co., St. Louis, 1935.
— Mathews, Albert P., *Principles of Biochemistry*, page 439, William Wood & Co., Baltimore, 1936.
— Stearns, G., Jeans, P. C. and Vandecar, V., *Journal of Pediatrics*, 9:1, 1936.
— Stepp, W., Kuhnau, J. and Schroeder, H., *The Vitamins and Their Clinical Application*, Ferdinand Enke, Stuttgart, Germany, 1936.

Posted for noncommercial historical preservation and educational use only by seleneriverpress.com

14. Berglund, Medes, Huber, Longcope and Richards, *The Kidney in Health and Disease,* page 151, Lea & Febiger, Philadelphia, 1935.
— Mathews, Albert P., *Principles of Biochemistry,* page 439, William Wood & Co., Baltimore, 1936.

15. Barborka, C. J., *Diet and Preventive Dentistry,* Journal of the American Dental Association, 23, 6:977, 985, June, 1936.
— Quigley, D. T., *Notes on Vitamins and Diets,* page 89, Consolidated Book Publishers, Inc., Chicago, 1933.
— Rhinehart, B. A., Radiology, 24:1, 1933.

16. Eddy, W. H. and Dalldorf, G., *The Avitaminoses,* page 269, The Williams and Wilkins Co., Baltimore, 1937.
— Medical Research Council, *Vitamins: A Survey of Present Knowledge,* page 54, London, 1932.
— Quigley, D. T., *Notes on Vitamins and Diets,* pages 20, 43-44, 88, 98, 127, Consolidated Book Publishers, Inc., Chicago, 1933.
— Sherman, H. C. and Smith, S. L., *The Vitamins,* Second Edition, Monograph Series, No. 6, page 388, The Chemical Catalog Co., Inc., New York, 1931.
— Stepp, W. Kuhnau, J. and Schroeder, H., *The Vitamins and Their Clinical Application,* Ferdinand Enke, Stuttgart, Germany, 1936.

17. Barborka, C. J., *Diet and Preventive Dentistry,* Journal of the American Dental Association, 23, 6:977-985, June, 1936.
— Harris, R. S. and Bunker, J. W. M., *American Journal of Roentgenology and Radium Therapy,* 33:25-30, 1935.

18. Barborka, C. J., *Diet and Preventive Dentistry,* Journal of the American Dental Association, 23, 6:977-985, June, 1936.
— East, Bion R., *Vitamin D Milk: Its Significance to the Public Health and to the Milk Industry,* Journal of Medicine, 418-423, October, 1934.
— Eddy, W. H. and Dalldorf, G., *The Avitaminoses,* page 269, The Williams and Wilkins Co., Baltimore, 1937.
— Macleod, J. J. R., *Physiology in Modern Medicine,* Seventh Edition, pages 734, 749-750, C. V. Mosby Co., St. Louis, 1935.
— Mathews, Albert P., *Principles of Biochemistry,* page 439, William Wood & Co., Baltimore, 1936.
— McCollum, E. V., *Relationship Between Diet and Dental Caries,* Journal of Dental Research.
— Quigley, D. T., *Notes on Vitamins and Diets,* page 19, Consolidated Book Publishers, Inc., Chicago, 1933.
— Sure, B., *Vitamins in Health and Disease,* page 109, The Williams and Wilkins Co., Baltimore, 1933.
— Vitamin D Milk, 2, 1:2, January, 1935.

19. Hamilton, B. and Schwartz, C. J., *Journal of Clinical Investigation,* 11:817, 1932.
— Trumper, and Cantarow, *Biochemistry in Internal Medicine,* page 150, W. B. Saunders Co., Philadelphia, 1933.
— Vitamin D Milk, *Parathyroid Enlargement as Related to Sunshine and Vitamin D,* 3, 4:16, April, 1936.

Posted for noncommercial historical preservation and educational use only by seleneriverpress.com

20. Dworzak, H., *Med. Klinik.*, January, 1936.
— East, Bion R., *Vitamin D Milk: Its Significance to the Public Health and the Milk Industry,* Journal of Medicine, page 419, October, 1934.

21. Eddy, W. H. and Dalldorf, G., *The Avitaminoses,* page 220, The Williams and Wilkins Co., Baltimore, 1937.
— Macleod, J. J. R., *Physiology in Modern Medicine,* Seventh Edition, page 734, C. V. Mosby Co., St. Louis, 1935.

22. Macleod, J. J. R., *Physiology in Modern Medicine,* Seventh Edition, page 734, C. V. Mosby Co., St. Louis, 1935.

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Posted for noncommercial historical preservation and educational use only by seleneriverpress.com

BIBLIOGRAPHY FOR VITAMIN E

1. Dryerre, H., *Vitamins and the Prevention of Abortion in Sheep*, Nature, 132:751, 1933.
— Eddy, W. H. and Dalldorf, G., *The Avitaminoses*, pages 248, 250, The Williams and Wilkins Co., Baltimore, 1937.
— Evans, H. M., *Journal of the American Medical Association*, 99:469-474, 1932.
— Howell, W. H., *A Textbook of Physiology*, Twelfth Edition, Revised, page 974, W. B. Saunders Co., Philadelphia, 1933.
— Mathews, A. P., *Principles of Biochemistry*, pages 443-445, William Wood & Co., Baltimore, 1936.
— Mattill, H. A. and Clayton, M. M., *Vitamin E and Reproduction on Synthetic and Milk Diets*, Journal of Biological Chemistry, 68:665-685, 1926.
— Medical Research Council, *Vitamins: A Survey of Present Knowledge*, page 117, London, 1932.
— Pacini, A. J., *Wheat Germ Oil—Vitamin E*, pages 23-24, The American Physician, Inc., New York, 1935.

2. Eddy, W. H. and Dalldorf, G., *The Avitaminoses*, page 248, The Williams and Wilkins Co., Baltimore, 1937.
— Pacini, A. J., *Wheat Germ Oil—Vitamin E*, pages 17-18, The American Physician, Inc., New York, 1935.
— Pacini, A. J., *Why We Need Vitamin E*, Health Culture Magazine, January, 1936.

3. Blumberg, H. A., *Growth Deficiency Disease Curable by Wheat Germ Oil*, Journal of Biological Chemistry, 108, 1:227-238, January, 1935.
— Eddy, W. H. and Dalldorf, G., *The Avitaminoses*, page 248, The Williams and Wilkins Co., Baltimore, 1937.
— Pacini, A. J., *Wheat Germ Oil—Vitamin E*, pages 12-13, The American Physician, Inc., New York, 1935.
— Sure, B., *The Vitamins in Health and Disease*, page 123, The Williams and Wilkins Co., Baltimore, 1933.

4. Davidson, J. R., *An Attempt to Inhibit the Development of Tar Carcinoma in Mice*, Canadian Medical Association Journal, 32:364-366, 1935.
— Eddy, W. H. and Dalldorf, G., *The Avitaminoses*, pages 248, 254-255, The Williams and Wilkins Co., Baltimore, 1937.
— Mathews, A. P., *Principles of Biochemistry*, page 445, William Wood & Co., Baltimore, 1936.
— Pacini, A. J., *Wheat Germ Oil—Vitamin E*, pages 10, 39, The American Physician, Inc., New York, 1935.

5. Pacini, A. J., *Wheat Germ Oil—Vitamin E*, page 15, The American Physician, Inc., New York, 1935.

6. Olcott, H. S., *Paralysis in the Young of Vitamin E Deficient Female*

Rats, Journal of Biological Chemistry, Scientific Proceedings of the American Society of Biological Chemists, 119, 1:lxxiv, June, 1937.
— Pacini, A. J., *Wheat Germ Oil—Vitamin E,* pages 15-16, The American Physician, Inc., New York, 1935.

7. McGonigle, G. C. M., Illinois Medical Journal, page 212, March, 1935 *(Health Department, Stockton-on-Tees, England).*

8. Blumenfeld, C. M., *Weight Changes in the Suprarenal Glands of Albino Rats on Vitamin E Deficient and Fat Deficient Diets,* Endocrinology, 18:367-381, 1934.
— Eddy, W. H. and Dalldorf, G., *The Avitaminoses,* pages 248, 250, The Williams and Wilkins Co., Baltimore, 1937.
— Gierhake, *Experimental Studies on Vitamin E,* Arch. F. Gynekol., 156: 348-350, 1933.
— Mathews, A. P., *Principles of Biochemistry,* page 445, William Wood & Co., Baltimore, 1936.
— McQueen-Williams, M., *Increased Gonadotropic Content of Anterior Hypophysis from Vitamin E Deficient Female Rats,* Anatomical Record, 58, No. 4, Suppl. 77, 1934.
— Medical Research Council, *Vitamins: A Survey of Present Knowledge,* page 109, London, 1932.
— Nelson, W. O., *Studies on the Anterior Hypophysis, III; The Anterior Hypophysis in Vitamin E Deficient Rats, Anatomical Record,* 56:241-253, 1933.
— Pacini, A. J., *Wheat Germ Oil—Vitamin E,* page 20, The American Physician, Inc., New York, 1935.
— Verzar, F., *The Action of Vitamin E, Magyar Orvosi,* Arch., 32:273-292, 1931.
— Verzar, F., *Hypertrophy of the Uterus and Vitamin E. Internal Secretion and Avitaminosis,* Pflugers Arch., 227:491-510, 1931.
— Verzar, F., Arch. Ges. Physiol. Mensch u. Tiere, *The Action of Vitamin E on the Hypertrophy of the Uterus,* 227, 4:499-510, 1931.
— Verzar, F., *The Anti-Sterility or Fertility Vitamin,* Ztschr. f. vitaminforsch, 1:116-134, 1932.
— Verzar, F., *Vitamin and Internal Secretions,* Schweiz. Med. Wochenschr., 62:57-60, 1932.
— Verzar, F., Arvay, A. and Kokas, E. von, *Basal Metabolism of Vitamin E Deficient Rats and the Correction of the Vitamin E Deficiency by Means of the Anterior Pituitary Hormone, Internal Secretion and Avitaminosis,* Biochem. Ztschr., 240:19-27, 1931.
— Verzar, F. and Kokas, E. von, *The Action of Vitamin E, Deficiency on the Hair Growth of Rats,* Pflugers Arch. Ges. Physiol., 227, 4:511-516, 1931.

9. Blumberg, H. A., *A Growth Deficiency Disease Curable by Wheat Germ Oil,* Journal of Biological Chemistry, 108, 1:227-238, January, 1935.
— Medical Research Council, *Vitamins: A Survey of Present Knowledge,* pages 107-108, London, 1932.
— Pacini, A. J., *Wheat Germ Oil—Vitamin E,* page 10, The American Physician, Inc., New York, 1935.
— Sure, B., *The Vitamins in Health and Disease,* page 123, The Williams and Wilkins Co., Baltimore, 1935.

Posted for noncommercial historical preservation and educational use only by seleneriverpress.com

10. Evans, H. M. and Burr, G. O., *Journal of Biological Chemistry*, 76:273-297, 1928.
— Medical Research Council, *Vitamins: A Survey of Present Knowledge*, page 107, London, 1932.
— Pacini, A. J., *Wheat Germ Oil—Vitamin E*, page 15, The American Physician, Inc., New York, 1935.

11. Evans, H. M. and Burr, G. O., *Journal of Biological Chemistry*, 76:273-297, 1928.
— Pacini, A. J., *Wheat Germ Oil—Vitamin E*, page 15, The American Physician, Inc., New York, 1935.

12. Adamstone, F. B. and Card, L. E., *The Effects of Vitamin E Deficiency on the Testis of Male Fowl*, Journal of Morphology, 56:339-359, 1934.
— Eddy, W. H. and Dalldorf, G., *The Avitaminoses*, pages 247, 250-251, The Williams and Wilkins Co., Baltimore, 1937.
— Evans, H. M., *Vitamin E*, Journal of the American Medical Association, 99:469-474, 1932.
— Evans, H. M. and Burr, G. O., *The Anti-Sterility Vitamin Fat-Soluble E*, Proceedings of the National Academy of Science, 11:334-341, 1925.
— Evans, H. M. and Burr, G. O., *Journal of Biological Chemistry*, 76:273-297, 1928.
— Macleod, J. J. R., *Physiology in Modern Medicine*, page 742, C. V. Mosby Co., St. Louis, 1935.
— McCollum, E. V. and Simmonds, N., *The Newer Knowledge of Nutrition*, Fourth Edition, pages 368-369, The Macmillan Co., New York, 1929.
— Medical Research Council, *Vitamins: A Survey of Present Knowledge*, page 112, London, 1932.
— Pacini, A. J., *Wheat Germ Oil—Vitamin E*, pages 19, 23, 25, 38, The American Physician, Inc., New York, 1935.
— Stepp, W., Kuhnau, J. and Schroeder, H., *The Vitamins and Their Clinical Application*, Ferdinand Enke, Stuttgart, Germany, 1936.

13. Ringsted, A., *A Preliminary Note on the Appearance of Paresis in Adult Rats Suffering from Chronic Avitaminosis E*, Biochemical Journal, 29:788, 1936.
— Sherman, H. C. and Smith, S. L., *The Vitamins*, Second Edition, Monograph Series, No. 6, page 344, The Chemical Catalog Co., Inc., New York, 1931.
— Stepp, W., Kuhnau, J. and Schroeder, H., *The Vitamins and Their Clinical Application*, Ferdinand Enke, Stuttgart, Germany, 1936.
— Sure, B., *The Vitamins in Health and Disease*, page 123, The Williams and Wilkins Co., Baltimore, 1933.

14. Eddy, W. H. and Dalldorf, G., *The Avitaminoses*, pages 241, 250-251, The Williams and Wilkins Co., Baltimore, 1937.
— Evans, H. M. and Burr, G. O., *The Anti-Sterility Vitamin Fat-Soluble E*, Proceedings of the National Academy of Science, 11:334-341, 1925.
— Ewing, P. V., The Hog Breeder, 10, 3, 1935.
— Gass, H. and Schmidt, C. L. A., *Calcium and Phosphorus Metabolism in Rats During Pregnancy and Lactation and the Influence of the Reaction of the Diet Thereon*, Journal of Biological Chemistry, 86, 1:417, 1930.

Posted for noncommercial historical preservation and educational use only by seleneriverpress.com

— Harris, L. J., *Vitamins in Theory and Practice,* page 179, Cambridge University Press, 1935.
— Howell, W. H., *A Textbook of Physiology,* Twelfth Edition, Revised, page 973, W. B. Saunders Co., Philadelphia, 1933.
— Juhasz-Schaffer, *Vitamin E. VI, Sterility in Female Rats in Avitaminoses E.,* Virchow's Arch., 282:662-679, 1931.
— Macleod, J. J. R., *Physiology in Modern Medicine,* pages 742, 974, C. V. Mosby Co., St. Louis, 1935.
— Marchesi, F., *Vitamin E and Reproductive Function in Albino Rats,* Sperimentale, 89:119-165, 1935.
— Mason, K. E., *Differences in Testis Injury and Repair After Vitamin A Deficiency, Vitamin E Deficiency and Inanition,* American Journal of Anatomy, 52:153-240, 1933.
— Mathews, A. P., *Principles of Biochemistry,* pages 443-445, William Wood & Co., Baltimore, 1936.
— McCollum, E. V. and Simmonds, N., *The Newer Knowledge of Nutrition,* Fourth Edition, pages 368-369, The Macmillan Co., New York, 1929.
— Medical Research Council, *Vitamins: A Survey of Present Knowledge,* pages 104-105, 106-107, 112, London, 1932.
— Pacini, A. J., *Wheat Germ Oil—Vitamin E,* pages 10, 23, The American Physician, Inc., New York, 1935.
— Stepp, W., Kuhnau, J. and Schroeder, H., *The Vitamins and Their Clinical Application,* Ferdinand Enke, Stuttgart, Germany, 1936.

15. Pacini, A. J., *Wheat Germ Oil—Vitamin E,* page 10, The American Physician, Inc., New York, 1935.
— Ringsted, A., *A Preliminary Note on the Appearance of Paresis in Adult Rats Suffering from Chronic Avitaminosis E.,* Biochemical Journal, 29:788, 1933.
— Sure, B., *The Vitamins in Health and Disease,* page 123, The Williams and Wilkins Co., Baltimore, 1933.
— Verzar, F., *The Action of Vitamin E,* Magyar Orvosi, Arch., 32:273-292, 1931.
— Verzar, F. and Kokas, E. von, *The Action of Vitamin E Deficiency on the Hair Growth of Rats,* Pflugers Arch. Ges. Physiol., 227, 4:511-516, 1931.

16. Medical Research Council, *Vitamins: A Survey of Present Knowledge,* page 108, London, 1932.
— Pacini, A. J., *Wheat Germ Oil—Vitamin E,* page 10, The American Physician, Inc., New York, 1935.
— Stepp, W., Kuhnau, J. and Schroeder, H., *The Vitamins and Their Clinical Application,* Ferdinand Enke, Stuttgart, Germany, 1936.

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Posted for noncommercial historical preservation and educational use only by seleneriverpress.com

BIBLIOGRAPHY FOR VITAMIN F

1. Boyd, Eldon M. and Connell, W. Ford, *Essential Unsaturated Fatty Acids in the Relief of the Common Cold,* Canadian Medical Association Journal, 37:38, July, 1937.

2. Evans, H. M. and Burr, G. O., *New Dietary Deficiency with Highly Purified Diets; the Biological Effect of Fat in the Diet,* Proceedings of the Society of Experimental Biology and Medicine, 35:390-397, 1927.

3. Hinsberg, K. and Holland, G., *The Iodine Absorption Value of the Blood Fats in Normal and Pathological Conditions,* Klinische Wochenschrift, 12:1601-1602, 1933.

4. Burr, G. O. and Beber, A. F., *Metabolism Studies with Rats Suffering from Fat Deficiency,* Proceedings of the Society of Experimental Biology and Medicine, 31:911-912, 1934.

— Haven, F. L., *Effect of Dietary Fats on Growth and Composition of Tumors,* Proceedings of the Society of Experimental Biology and Medicine, 32:743-747, 1935.

5. Pacini, August J. and Avis, H. Wentworth, *Vitamin F in Cosmetics, Soap, Perfumery and Cosmetics,* September, 1936.

6. Mathews, Albert P., *Physiological Chemistry,* page 609, William Wood & Co., Baltimore, 1925.

7. Burr, G. O. and Burr, M. M., *A New Deficiency Disease Produced by the Rigid Exclusion of Fat from the Diet,* Journal of Biological Chemistry, 82:345-367, 1929.

— Burr, G. O. and Burr, M. M., *On the Nature and Role of the Fatty Acids Essential in Nutrition,* Journal of Biological Chemistry, 86:587-621, 1930.

— Cornbleet, T., *Use of Maize Oil (Unsaturated Fatty Acids in the Treatment of Eczema),* Archives of Dermatology and Syphilology, 31:224-226, 1931.

— Graham, C. E. and Griffith, A. H., *Observations on the Nutritive Value of Certain Fats,* Proceedings of the Society of Experimental Biology and Medicine, 28:756-761, 1931.

— Hansen, A. E., *Serum Lipid Changes and Therapeutic Effects of Various Oils in Infantile Eczema,* Proceedings of the Society of Experimental Biology and Medicine, 31:160-161, 1933.

— Hansen, A. E., *Study of Iodine Number of Serum Fatty Acids in Infantile Eczema,* Proceedings of the Society of Experimental Biology and Medicine, 30:1198-1199, 1933.

— Pacini, August J., *Are Allergies a Vitamin Deficiency Symptom,* Health Culture, 42, 3:18-19, 60-62, March, 1936.

— Pacini, August J., *Vitamin F (Unsaturates),* American Perfumer, December, 1936.

— Roche, A. and Roche, J., *Cutaneous Eruptions Attributed to Deficiency of Lipid in the Rat,* Comptes Rendus de la Societe Biologique, 109: 463-464, 1932.
— Shepherd, M. I., *Survey of Vitamin F in Cosmetics,* pages 3-5, Pharmaceutical Specialties Co., Chicago, 1936.
— Shepherd, M. I., *Vitamin F in Skin Creams,* Drug & Cosmetic Industry, March, 1936.
— Shepherd, M. I. and Linn, D. R., *Evaluation of Vitamin F,* Drug & Cosmetic Industry, page 629, May, 1936.
— Sinclair, R. G., *Some Observations on the Growth of Rats on Fat-Free and Fat-Containing Diets,* Proceedings of the Society of Experimental Biology and Medicine, 27:1059-1062, 1930.
— Tanze, U., *The Effects of Fatty Acids on Nutrition,* Scientific Papers from the Institute for Physical and Chemical Research, Tokyo, 20:13-28, 1932.
— Tanze, U., *The Effects of Fatty Acids on Nutrition,* Scientific Papers from the Institute for Physical and Chemical Research, Tokyo, 22:1-14, 1933.
— Weinstein, M. L. and Glennon, K., *Vitamin F Ointments,* Illinois Medical Journal, June, 1937.

8. Shepherd, M. I., *Survey of Vitamin F in Cosmetics,* Pharmaceutical Specialties Co., page 5, 1937.

9. Burr, G. O. and Burr, M. M., *A New Dietary Disease Produced by the Rigid Exclusion of Fat from the Diet,* Journal of Biological Chemistry, 82:345-367, 1929.
— Burr, G. O. and Burr, M. M., *On the Nature and Role of the Fatty Acids Essential in Nutrition,* Journal of Biological Chemistry, 86:587-621, 1930.
— Burr, G. O., Burr, M. M. and Miller, E. S., *Journal of Biological Chemistry,* 97:1, 1932.
— Evans, H. M. and Lepkovsky, S. C., *Journal of Biological Chemistry,* 96:143-157, 1932.
— Funk, C., Casper, S. and Casper, H., *Proceedings of the Society of Experimental Biology and Medicine,* 28:816, 1931.
— Graham, C. E. and Griffith, W. H., *Proceedings of the Society of Experimental Biology and Medicine,* 28:756-761, 1931.
— Hawk, P. B. and Gergeim, O., *Practical Physiological Chemistry,* P. Blakiston's Son and Company, Philadelphia, 1931.
— Hume, E. M. and Smith, H. H., *Journal of Biochemistry,* 25:300, 1931.
— Shepherd, M. I., *Vitamin F in Skin Creams,* Drug & Cosmetic Industry, March, 1936.
— Sinclair, R. G., *Proceedings of the Society of Experimental Biology and Medicine,* 27:1059, 1930.
— Weinstein, M. L. and Glennon, Kathryn, *Vitamin F Ointments,* Illinois Medical Journal, June, 1937.

10. Burr, G. O. and Brown, W. R., *On the Fatty Acids Essential in Nutrition,* Proceedings of the Society of Experimental Biology and Medicine, 30:1349-1352, 1933.
— Burr, G. O. and Burr, M. M., *A New Deficiency Disease Produced by*

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the Rigid Exclusion of Fat from the Diet, Journal of Biological Chemistry, 82:345-367, 1929.
— Burr, G. O. and Burr, M. M., *On the Nature and Role of the Fatty Acids Essential in Nutrition,* Journal of Biological Chemistry, 86:587-621, 1930.
— Pacini, August J., *Vitamin F (Unsaturates),* American Perfumer, December, 1936.
— Shepherd, M. I., *Vitamin F in Skin Creams,* Drug & Cosmetic Industry, March, 1936.
— Shepherd, M. I., and Linn, D. R., *Evaluation of Vitamin F,* Drug & Cosmetic Industry, page 629, May, 1936.

11. Pacini, August J., *Are Allergies a Vitamin Deficiency Symptom,* Health Culture, 42, 3:18-19, 60-62, March, 1936.

12. Graham, C. E. and Griffith, A. H., *Observation on the Nutritive Value of Certain Fats,* Proceedings of the Society of Experimental Biology and Medicine, 28:756-761, 1931.

13. Evans, H. M., Lepkovsky, S. and Murphy, E. A., *Vitamin Need of the Body for Certain Unsaturated Fatty Acids: A Digest of Three Communications,* Journal of Biological Chemistry, 106:431, 441, 445, 1934.

14. Platonov, G., *The Influence of Unsaturated Fatty Acids on the Virulence of Tubercle Bacilli,* American Review of Tuberculosis, 21:362-369, 1930.

15. Burr, G. O. and Brown, W. R., *On the Fatty Acids Essential in Nutrition,* Proceedings of the Society of Experimental Biology and Medicine, 30:1349-1352, 1933.
— Burr, G. O. and Burr, M. M., *A New Deficiency Disease Produced by the Rigid Exclusion of Fat from the Diet,* Journal of Biological Chemistry, 82:345-367, 1929.
— Evans, H. M. and Burr, G. O., *New Dietary Deficiency with Highly Purified Diets,* Proceedings of the Society of Experimental Biology and Medicine, 25:41-48, 1927.
— Shepherd, M. I., *Vitamin F in Skin Creams,* Drug & Cosmetic Industry, March, 1936.
— Sinclair, R. G., *Evidence of the Synthesis of Essential Unsaturated Fatty Acids by the Rat,* Journal of Biological Chemistry, 114:94, 1936.
— Tanze, U., *The Effects of Fatty Acids on Nutrition,* Scientific Papers from the Institute for Physical and Chemical Research, Toyko, 20:13-28, 1932.
— Tanze, U., *The Effects of Fatty Acids on Nutrition,* Scientific Papers from the Institute for Physical and Chemical Research, Toyko, 22:1-14, 1933.
— Weinstein, M. L. and Glennon, K., *Vitamin F Ointments,* Illinois Medical Journal, June, 1937.

16. Shepherd, M. I. and Linn, D. R., *Evaluation of Vitamin F,* Drug & Cosmetic Industry, page 629, May, 1936.
— Weinstein, M. L. and Glennon, K., *Vitamin F Ointments,* Illinois Medical Journal, June, 1937.

Posted for noncommercial historical preservation and educational use only by seleneriverpress.com

17. Burr, G. O. and Burr, M. M., *On the Nature and Role of the Fatty Acids Essential in Nutrition,* Journal of Biological Chemistry, 86:587-621, 1930.

— Evans, H. M. and Burr, G. O., *New Dietary Deficiency with Highly Purified Diets,* Proceedings of the Society of Experimental Biology and Medicine, 25:41-48, 1927.

— Evans, H. M. and Burr, G. O., *New Dietary Deficiency with Highly Purified Diets: The Biological Effect of Fat in the Diet,* Proceedings of the Society of Experimental Biology and Medicine, 25:390-397, 1927.

— Evans, H. M., Lepkovsky, S. and Murphy, E. A., *Vital Need of the Body for Certain Unsaturated Fatty Acids,* A digest of three communications, Journal of Biological Chemistry, 106-431, 441, 445, 1934.

— Shepherd, M. I., *Vitamin F in Skin Creams,* Drug & Cosmetic Industry, March, 1936.

— Weinstein, M. L. and Glennon, K., *Vitamin F Ointments,* Illinois Medical Journal, June, 1937.

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BIBLIOGRAPHY FOR VITAMIN G

1. Eddy, W. H. and Dalldorf, G., *The Avitaminoses*, page 121, The Williams and Wilkins Co., Baltimore, 1937.
— Harris, L. J., *Vitamins in Theory and Practice*, page 76, Cambridge University Press, London, 1935.
— Mathews, Albert P., *Principles of Biochemistry*, page 425, William Wood & Co., Baltimore, 1936.
— Sherman, H. C. and Ellis, L. N., *Necessary Versus Optimal Intake of Vitamin G (B_2)*, Journal of Biochemistry, 104:91-97, 1934.
— Sherman, H. C. and Smith, S. L., *The Vitamins*, Second Edition, Monograph Series, No. 6, page 146, The Chemical Catalog Co., Inc., New York, 1931.
— Wiggers, Carl J., *Physiology in Health and Disease*, page 962, Lea & Febiger Co., Philadelphia, 1934.

2. Mathews, Albert P., *Principles of Biochemistry*, page 429, William Wood & Co., Baltimore, 1936.
— Stepp, W., Kuhnau, J. and Schroeder, H., *The Vitamins and Their Clinical Application*, Ferdinand Enke, Stuttgart, Germany, 1936.

3. Sherman, H. C. and Smith, S. L., *The Vitamins*, Second Edition, Monograph Series, No. 6, page 146, The Chemical Catalog Co., Inc., New York, 1931.
— Wiggers, Carl J., *Physiology in Health and Disease*, page 962, Lea & Febiger Co., Philadelphia, 1934.

4. Stepp, W., Kuhnau, J. and Schroeder, H., *The Vitamins and Their Clinical Application*, Ferdinand Enke, Stuttgart, Germany, 1936.

5. Adams, Philip D., *The Oxygen Uptake and Composition of the Skin of Rats in Vitamin G Deficiency*, Journal of Biological Chemistry, 116, 2:641-651, December, 1936.
— Harris, L. J., *Vitamins in Theory and Practice*, pages 76-77, Cambridge University Press, 1935.
— Macleod, J. J. R., *Physiology in Modern Medicine*, Seventh Edition, page 746, C. V. Mosby Co., St. Louis, 1935.
— Medical Research Council, *Vitamins: A Survey of Present Knowledge*, page 151, London, 1932.
— Sherman, H. C. and Smith, S. L., *The Vitamins*, Second Edition, Monograph Series, No. 6, pages 142-143, 146, The Chemical Catalog Co., Inc., New York, 1931.
— Sure, B., *The Vitamins in Health and Disease*, page 136, The Williams and Wilkins Co., Baltimore, 1933.
— Wiggers, Carl J., *Physiology in Health and Disease*, page 962, Lea & Febiger Co., Philadelphia, 1934.

6. Sherman, H. C. and Smith, S. L., *The Vitamins*, Second Edition, Monograph Series, No. 6, page 142, The Chemical Catalog Co., Inc., New York, 1931.

— Sure, B., *The Vitamins in Health and Disease,* pages 143-144, The Williams and Wilkins Co., Baltimore, 1933.

7. Barborka, C. J., *Diet and Preventive Dentistry,* Journal of the American Dental Association, 23, 6:977-985, June, 1936.
— Harris, L. J., *Vitamins in Theory and Practice,* page 71, 74, Cambridge University Press, London, 1935.
— McCollum, E. V. and Simmonds, N., *The Newer Knowledge of Nutrition,* Fourth Edition, Chapter XXIII, pages 374-392, The Macmillan Co., New York, 1929.
— Medical Research Council, *Vitamins: A Survey of Present Knowledge,* pages 150-151, London, 1932.
— Schuler, R., *Chemistry and Psysiology of Vitamin B,* Drug & Cosmetic Industry, 39, 2:179-181, 186, August, 1936.
— Stepp, W., Kuhnau, J. and Schroeder, H., *The Vitamins and Their Clinical Application,* Ferdinand Enke, Stuttgart, Germany, 1936.
— Wolbach, Journal of the American Medical Association, 108:7-120, January 2, 1937.

8. Eddy, W. H. and Dalldorf, G., *The Avitaminoses,* page 134, The Williams and Wilkins Co., Baltimore, 1937.
— Mathews, Albert P., *Principles of Biochemistry,* page 430, William Wood & Co., Baltimore, 1936.
— Medical Research Council, *Vitamins: A Survey of Present Knowledge,* page 253, London, 1932.
— Remp, D. G. and Bing, F. C., *Inanition as a Factor in Vitamin G Deficiency,* Journal of Nutrition, 8:457-462, 1934.
— Sure, B., *The Vitamins in Health and Disease,* page 144, The Williams and Wilkins Co., Baltimore, 1933.
— Wiggers, Carl J., *Physiology in Health and Disease,* page 317, Lea & Febiger Co., Philadelphia, 1934.

9. Adams, Philip D., *The Oxygen Uptake and Composition of the Skin of Rats in Vitamin G Deficiency,* Journal of Biological Chemistry, 116, 2:641-651, December, 1936.
— Berglund, Medes, Huber, Longcope and Richards, *The Kidney in Health and Disease,* page 256, Lea & Febiger, Philadelphia, 1935.
— Eddy, W. H. and Dalldorf, G., *The Avitaminoses,* pages 131, 137-138, 140, 144, The Williams and Wilkins Co., Baltimore, 1937.
— Harris, L. J., *Vitamins in Theory and Practice,* page 75, Cambridge University Press, 1935.
— Macleod, J. J. R., *Physiology in Modern Medicine,* Seventh Edition, page 746, C. V. Mosby Co., St. Louis, 1935.
— McCollum, E. V. and Simmonds, N., *The Newer Knowledge of Nutrition,* Fourth Edition, page 374, The Macmillan Co., New York, 1929.
— Medical Research Council, *Vitamins: A Survey of Present Knowledge,* pages 150-151, London, 1932.
— Schuler, R., *Drug & Cosmetic Industry,* 39, 2:179-181, 186, August, 1936.
— Sherman, H. C. and Smith, S. L., *The Vitamins,* Second Edition, Monograph Series, No. 6, pages 142-143, The Chemical Catalog Co., Inc., New York, 1931.
— Stepp, W., Kuhnau, J. and Schroeder, H., *The Vitamins and Their Clinical Application,* Ferdinand Enke, Stuttgart, Germany, 1936.

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— Sure, B., *The Vitamins in Health and Disease,* pages 126, 137, The Williams and Wilkins Co., Baltimore, 1933.
— Wolbach, *Journal of the American Medical Association,* 108:7-120, January 2, 1937.

10. Eddy, W. H. and Dalldorf, G., *The Avitaminoses,* pages 134, 136-137, The Williams and Wilkins Co., Baltimore, 1937.
— Macleod, J. J. R., *Physiology in Modern Medicine,* Seventh Edition, page 746, C. V. Mosby Co., St. Louis, 1935.
— McCollum, E. V. and Simmonds, N., *The Newer Knowledge of Nutrition,* Fourth Edition, page 374, The Macmillan Co., New York, 1929.
— Medical Research Council, *Vitamins: A Survey of Present Knowledge,* pages 150-151, London, 1932.
— Schuler, R., *Drug & Cosmetic Industry,* 39:179-181, 186, August, 1936.
— Sherman, H. C. and Smith, S. L., *The Vitamins,* Second Edition, Monograph Series, No. 6, pages 142-143, The Chemical Catalog Co., Inc., New York, 1931.
— Stepp, W., Kuhnau, J. and Schroeder, H., *The Vitamins and Their Clinical Application,* Ferdinand Enke, Stuttgart, Germany, 1936.

11. Eddy, W. H. and Dalldorf, G., *The Avitaminoses,* page 144, The Williams and Wilkins Co., Baltimore, 1937.
— Lepkovsky, S. and Krause, M. E., *The Tripartite Nature of Vitamin G,* Proceedings of the American Institute of Nutrition, Abstracted in Journal of Nutrition, 13, 6, Suppl., page 12, June 10, 1937.
— Sherman, H. C. and Smith, S. L., *The Vitamins,* Second Edition, Monograph Series, No. 6, pages 121, 142-143, The Chemical Catalog Co., Inc., New York, 1931.
— Sure, B., *The Vitamins in Health and Disease,* pages 136-137, The Williams and Wilkins Co., Baltimore, 1933.

12. Fitzmorris, C. S., *Cincinnati Journal of Medicine,* 16:585, 1936.
— Mathews, Albert P., *Principles of Biochemistry,* pages 430-432, William Wood & Co., Baltimore, 1936.
— Rhoads and Miller, *Journal of the American Medical Association,* 103: 387, 1934.

13. Adams, Philip D., *The Oxygen Uptake and Composition of the Skin of Rats in Vitamin G Deficiency,* Journal of Biological Chemistry, 116, 2:641-651, December, 1936.

14. Eddy, W. H. and Dalldorf, G., *The Avitaminoses,* pages 131-132, 134, 136-137, The Williams and Wilkins Co., Baltimore, 1937.
— Macleod, J. J. R., *Physiology in Modern Medicine,* Seventh Edition, page 746, C. V. Mosby Co., St. Louis, 1935.
— Mathews, Albert P., *Principles of Biochemistry,* page 430, William Wood & Co., Baltimore, 1936.
— McCollum, E. V. and Simmonds, N., *The Newer Knowledge of Nutrition,* Fourth Edition, page 374, The Macmillan Co., New York, 1929.
— Medical Research Council, *Vitamins: A Survey of Present Knowledge,* pages 150-151, London, 1932.
— Schuler, R., *Drug & Cosmetic Industry,* 39, 2:179-181, 186, August, 1936.

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— Sherman, H. C. and Smith, S. L., *The Vitamins*, Second Edition, Monograph Series, No. 6, pages 121, 142-143, The Chemical Catalog Co., New York, 1931.
— Stepp, W., Kuhnau, J. and Schroeder, H., *The Vitamins and Their Clinical Application*, Ferdinand Enke, Stuttgart, Germany, 1936.
— Sure, B., *The Vitamins in Health and Disease*, pages 126-127, 137, The Williams and Wilkins Co., Baltimore, 1933.

15. Sherman, H. C. and Smith, S. L., *The Vitamins*, Second Edition, Monograph Series, No. 6, page 143, The Chemical Catalog Co., Inc., New York, 1931.

16. Berglund, Medes, Huber, Longcope and Richards, *The Kidney in Health and Disease, pages* 149-150, 256, Lea & Febiger, Philadelphia, 1935.
— Medical Research Council, *Vitamins: A Survey of Present Knowledge*, page 151, London, 1932.
— Sherman, H. C. and Smith, S. L., *The Vitamins*, Second Edition, Monograph Series, No. 6, page 143, The Chemical Catalog Co., Inc., New York, 1931.

17. Eddy, W. H. and Dalldorf, G., *The Avitaminoses*, page 132, The Williams and Wilkins Co., Baltimore, 1937.
— Medical Research Council, *Vitamins: A Survey of Present Knowledge*, page 151, London, 1932.
— Stepp, W., Kuhnau, J. and Schroeder, H., *The Vitamins and Their Clinical Application*, Ferdinand Enke, Stuttgart, Germany, 1936.

18. Macleod, J. J. R., *Physiology in Modern Medicine*, Seventh Edition, page 746, C. V. Mosby Co., St. Louis, 1935.
— Medical Research Council, *Vitamins: A Survey of Present Knowledge*, page 151, London, 1932.
ical Application, Ferdinand Enke, Stuttgart, Germany, 1936.
— Sure, B., *The Vitamins in Health and Disease*, page 136, The Williams and Wilkins Co., Baltimore, 1933.

19. Clapp, C. A., *Cataract: Its Etiology and Treatment*, pages 76-77, Lea & Febiger, Philadelphia, 1934.
— Eddy, W. H. and Dalldorf, G., *The Avitaminoses*, page 147, The Williams and Wilkins Co., Baltimore, 1937.
— Medical Research Council, *Vitamins: A Survey of Present Knowledge*, page 151, London, 1932.
— Oncken, Mildred, *Physiological Effects of Vitamin Deficiencies as Summarized Briefly from Recent and Authenticated Research Experiments*, Illinois Medical Journal, December, 1934.
— Sure, B., *The Vitamins in Health and Disease*, pages 136, 143-144, The Williams and Wilkins Co., Baltimore, 1933.

20. Medical Research Council, *Vitamins: A Survey of Present Knowledge*, pages 150-151, London, 1932.
— McClendon, J. F., *A Manual of Biochemistry*, page 6, John Wiley & Sons, Inc., New York, 1934.
— Stepp, W., Kuhnau, J. and Schroeder, H., *The Vitamins and Their Clinical Application*, Ferdinand Enke, Stuttgart, Germany, 1936.
— Wolbach, Journal of the American Medical Association, 108:7-120, January 2, 1937.

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21. Eddy, W. H. and Dalldorf, G., *The Avitaminoses*, pages 133-134, The Williams and Wilkins Co., Baltimore, 1937.
— Mathews, Albert P., *Principles of Biochemistry*, page 427, William Wood & Co., Baltimore, 1936.
— McCollum, E. V. and Simmonds, N., *The Newer Knowledge of Nutrition*, Fourth Edition, page 374, The Macmillan Co., New York, 1929.
— Medical Research Council, *Vitamins: A Survey of Present Knowledge*, pages 150-151, London, 1932.
— Schuler, R., *Drug & Cosmetic Industry*, 39, 2:179-181, 186, August, 1936.
— Sure, B., *The Vitamins in Health and Disease*, page 128, The Williams and Wilkins Co., Baltimore, 1933.

22. Sherman, H. C. and Smith, S. L., *The Vitamins*, Second Edition, Monograph Series, No. 6, pages 142-143, The Chemical Catalog Co., Inc., New York, 1931.

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