



# VITAMINS AND HORMONES

ADVANCES IN RESEARCH AND APPLICATIONS

w/ 606697

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## Editors' Preface

The success of volume I of Vitamins and Hormones, in spite of the difficulties imposed by war conditions, has shown the need that exists for critical and intelligent reviews of this field. The scattering of the literature through a wide variety of journals, the inevitable variation in the quality of the work, and the variety of interests represented, ranging through physics and chemistry to pathology and clinical medicine, make the task of the reviewer a difficult one and the value of the review correspondingly greater.

The Editors have felt that the authors should be free to exercise their judgment as to omission and selection of material, keeping in mind the aim of presenting a balanced picture of the development and current status of each subject. This is particularly true of fields of work which include numbers of inconclusive experiments. The two articles in the present volume relating to cancer provide an example of different approaches to this problem; in one the authors have aimed at discussing whatever work has been done, at the same time making clear the uncertain nature of some of it, while in the other only the best established results have been considered at all. Each author has difficulties of his own special kind to face, and the Editors wish to express their appreciation of the immense amount of work and thought which has gone into the preparation of all of the articles.

The policy of including complete subject and author indexes has been continued in the present volume, and it is believed that these indexes will add materially to the reference value of these yearly volumes. The Editors will welcome suggestions for improvement.

To some readers a volume like the present may appear to be essentially a series of complete but disconnected articles rather than an integrated whole. This must to a degree be true of any group of scientific reviews. In so far as it may be due to any real lack of correlation between ideas and results in different fields of endeavor, the bringing together of these reviews under one cover should be a stimulus toward closer interdependence of workers in distinct but related subjects. If such an integration is promoted, these volumes will have made a useful contribution to progress in the field of Vitamins and Hormones.

KENNETH V. THIMANN  
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## CONTENTS

CONTRIBUTORS TO VOLUME II. . . . .	v
EDITORS' PREFACE. . . . .	vii

### The Role of Vitamins in the Anabolism of Fats

BY E. W. MCHENRY AND MADELEINE L. CORNETT, *Department of Nutrition, University of Toronto, Toronto, Canada*

I. Introduction . . . . .	1
II. Classical Demonstrations of Fat Formation . . . . .	1
III. The Synthesis of Fat from Carbohydrate . . . . .	3
IV. The Synthesis of Fat from Protein . . . . .	7
V. The Formation of Phospholipids . . . . .	11
VI. The Synthesis of Cholesterol . . . . .	12
VII. Possible Mechanism of Fatty Acid Synthesis and the Relation of Vitamins to Enzyme Systems . . . . .	14
VIII. Thiamin-sparing Action of Fats . . . . .	17
IX. Essential Fatty Acids . . . . .	19
X. Summary. . . . .	23
References . . . . .	24

### The Chemistry of Biotin

BY DONALD B. MELVILLE, *Department of Biochemistry, Cornell University Medical College, New York, N. Y.*

Introduction . . . . .	29
I. Historical . . . . .	30
II. Methods of Determination . . . . .	31
III. Occurrence. . . . .	32
IV. Biochemical Significance. . . . .	33
1. Plants and Microorganisms . . . . .	33
2. Animal Nutrition . . . . .	33
a. Avidin. . . . .	34
b. Biotin in Rat Nutrition . . . . .	34
c. Biotin in Avian Nutrition. . . . .	35
d. Biotin in Human Nutrition . . . . .	35
e. Biotin and Neoplasms . . . . .	36
f. Biotin and Fat Metabolism . . . . .	36
g. Specificity of Biotin . . . . .	36
V. Isolation . . . . .	37
VI. Chemistry . . . . .	40
1. The Presence of a Carboxyl Group in Biotin . . . . .	42
2. The Presence of a Urea Ring in Biotin. . . . .	42
3. The Nature of the Sulfur of Biotin . . . . .	44
4. The Presence of a Valeric Acid Side Chain in Biotin. . . . .	48
5. The Size of the Urea Ring in Biotin. . . . .	51
6. Desthiobiotin . . . . .	55
7. The Formation of Thiophene-valeric Acid from Biotin . . . . .	59
References . . . . .	63
Addendum . . . . .	66

## The Nutritional Requirements of Primates Other than Man

BY PAUL L. DAY, *Department of Physiological Chemistry, School of Medicine,  
University of Arkansas, Little Rock, Arkansas*

I. Introduction . . . . .	71
II. Vitamin A Deficiency . . . . .	72
III. Rickets, Osteomalacia, Calcium Deficiency, and Hypervitaminosis D in Monkeys . . . . .	75
IV. Scurvy—Ascorbic Acid Requirement of the Monkey . . . . .	79
V. Beriberi in the Monkey . . . . .	86
VI. Experimental Attempts to Produce Pellagra in Monkeys . . . . .	88
VII. Nutritional Cytopenia in the Monkey—Vitamin M . . . . .	91
VIII. Primate Culture and Practical Dietetics . . . . .	100
IX. Common Diseases of Captive Primates . . . . .	101
X. Summary . . . . .	101
References . . . . .	102

## Physiological Action of Vitamin E and Its Homologues

BY KARL E. MASON, *School of Medicine and Dentistry, University of Rochester,  
Rochester, N. Y.*

I. Introduction . . . . .	107
II. The Nature of Vitamin E . . . . .	109
1. Chemistry of the Tocopherols . . . . .	109
2. Chemical and Physical Tests . . . . .	112
3. Biological Assay . . . . .	113
4. Distribution in Plants . . . . .	115
5. Distribution in Animals . . . . .	115
6. Biological Activity . . . . .	118
a. The Tocopherols and their Esters . . . . .	118
b. Other Compounds . . . . .	120
III. Structural and Functional Disturbances Due to Lack of Vitamin E . . . . .	121
1. Differences in Species . . . . .	121
2. Sterility in the Male . . . . .	124
3. Sterility in the Female . . . . .	125
a. Mortality of the Fetus . . . . .	125
b. Endocrine Relationships . . . . .	126
c. Veterinary and Clinical Implications . . . . .	128
4. Nutritional Muscular Dystrophy . . . . .	129
a. Nature of the Lesions . . . . .	129
b. Relation to the Nervous System . . . . .	131
c. Metabolic Disturbances . . . . .	132
5. Changes in Smooth Muscle . . . . .	135
6. Dysfunction of the Vascular System . . . . .	137
a. Embryonic Mortality in Chicks . . . . .	137
b. Exudative Diathesis . . . . .	137
c. Nutritional Encephalomalacia . . . . .	138
d. Dietary Factors Influencing Symptomatology . . . . .	139
7. Growth Inhibition . . . . .	141
IV. Minimal Requirements . . . . .	142
V. Interrelationships with Other Vitamins . . . . .	144
VI. Theories of Physiological Functions . . . . .	145
References . . . . .	148



### The Chemistry and Physiology of Vitamin A

By I. M. HEILBRON AND W. E. JONES, *Imperial College of Science and Technology, London, England*, AND A. L. BACHARACH, *Glaxo Research Laboratories, Greenford, Middlesex, England*

I. Historical . . . . .	155
II. Color Reactions and Spectrographic Analysis . . . . .	157
III. Pro-vitamin A . . . . .	159
1. Growth-promoting Activity of Vegetable Products . . . . .	159
2. The Biological Activity of the Carotenoids . . . . .	160
3. The Relationship between Carotene and Vitamin A . . . . .	162
4. The Constitution of Carotene . . . . .	163
IV. Isolation of pure Vitamin A . . . . .	167
V. Constitution of Vitamin A . . . . .	172
1. Degradation . . . . .	172
2. Synthesis of Perhydrovitamin A . . . . .	175
3. Possible Isomers of Vitamin A . . . . .	177
VI. Synthetic Experiments . . . . .	178
VII. Homologues of Vitamin A . . . . .	184
1. Degradation of $\beta$ -Carotene . . . . .	184
2. Oxidation of Vitamin A with Aluminum tert. Butoxide . . . . .	186
3. Vitamin A <sub>2</sub> . . . . .	187
VIII. The Measurement and Distribution of Vitamin A . . . . .	189
1. Difficulties of Biological Assay . . . . .	189
2. International Unit and Standard Preparation . . . . .	189
3. Criteria of Response to Vitamin A . . . . .	189
4. Error of Biological Assay . . . . .	191
5. Biological Activity, Ultra-violet Absorption and "Blue Value" . . . . .	192
6. Vitamin A and Carotene Contents of Dairy and Other Products . . . . .	194
7. Vitamin A Contents of Foods and Tissues . . . . .	195
IX. The Physiological Action of Vitamin A . . . . .	198
1. Vitamin A Deficiency . . . . .	198
2. Vitamin A and Infection . . . . .	199
3. Vitamin A and Vision . . . . .	200
4. Vitamin A and Lesions of Bone, Nerve, Skin, and Teeth . . . . .	202
5. Vitamin A Requirements . . . . .	203
References . . . . .	205

### Para-Aminobenzoic Acid—Experimental and Clinical Studies

By S. ANSBACHER, *American Home Products Corp., I. V. C. Research Laboratory, New York, N. Y.*

A. Introduction . . . . .	215
B. Experimental and Clinical Results . . . . .	216
I. Pigmentation Processes . . . . .	216
1. Sunburn and Suntan . . . . .	216
2. Gray Hair . . . . .	217
a. Terminology . . . . .	217
b. Theory . . . . .	217
c. Factors . . . . .	218
II. Dietary Studies . . . . .	221
1. Sulfonamide Rations . . . . .	221
2. Chick Nutrition . . . . .	222
3. Lactation . . . . .	223

III. Clinical Studies . . . . .	223
1. Achromotrichia . . . . .	223
2. Other conditions . . . . .	225
IV. Toxicity . . . . .	226
V. Detoxication . . . . .	227
VI. Hormones . . . . .	228
VII. Enzymes . . . . .	229
1. Rôle in Systems . . . . .	229
2. Rôle as Co-enzyme . . . . .	233
VIII. Microorganisms . . . . .	233
1. Sulfonamide Antagonism . . . . .	233
2. Clinical Incompatibility . . . . .	234
3. Bactericidal and Fungistatic Properties . . . . .	235
4. Physicochemical Data . . . . .	236
5. Growth-Promoting Activity . . . . .	238
IX. Determination . . . . .	240
1. Qualitative Methods . . . . .	240
2. Quantitative Methods . . . . .	240
a. Chemical Analyses . . . . .	240
b. Microbiological Assays . . . . .	241
X. Natural Occurrence . . . . .	242
1. Distribution . . . . .	242
2. Sulfonamide-Fastness . . . . .	244
C. Conclusion: Physiological Importance . . . . .	245
References . . . . .	247

### A Critique of the Etiology of Dental Caries

BY GERALD J. COX, *National Research Council, Washington, D. C.*

I. Introduction . . . . .	255
II. On Recording the Data of Dental Caries . . . . .	256
1. General Considerations . . . . .	256
2. A Working Hypothesis of Etiology . . . . .	256
3. Caries Indices . . . . .	257
4. A Proposal for the Recording of Dental Caries . . . . .	261
III. Experimental Dental Caries in Rats . . . . .	263
1. Studies of Etiological Significance . . . . .	263
2. Some Results of Studies of Caries in Rats and Their Significance . . . . .	267
IV. Microorganisms and Dental Caries . . . . .	268
1. Origin of the Chemico-Parasitic Theory with Especial Reference to Structure of Enamel and the Initiation of Caries . . . . .	268
2. Specific Organisms . . . . .	274
3. Plaques . . . . .	276
V. The Caries-Inhibiting Action of Saliva . . . . .	279
VI. Enamel Structure and Dental Caries . . . . .	281
1. Studies Concerned with Enamel Structure . . . . .	281
2. Some Nutritional Studies . . . . .	283
VII. Fluorine and Dental Caries . . . . .	285
1. Summary of Discovery of Fluorine in Various Tissues and in Water . . . . .	285
2. Mottled Enamel and Caries . . . . .	286
3. Direct Evidence of Anti-Caries Action of Fluorine . . . . .	288
a. Analytical . . . . .	288
b. Experimental . . . . .	289

c. Field Studies . . . . .	289
4. Posteruptively Applied Fluorides . . . . .	293
5. The Toxicity of Fluorides in Relation to Possible Use in the Prevention of Dental Caries . . . . .	294
6. Practical Application of Fluorides through Water Supplies . . . . .	295
7. The Opposition to Fluoridization of Water Supplies . . . . .	296
VIII. General Conclusions . . . . .	298
References . . . . .	299

### Vitamins and Cancer

By DEAN BURK AND RICHARD J. WINZLER, *National Cancer Institute, U. S. Public Health Service, Bethesda, Maryland*

I. Introduction . . . . .	306
II. The Relation of Individual Vitamins to Malignant Growth. . . . .	309
1. Vitamin A . . . . .	309
a. The Vitamin A Content of Tumors . . . . .	309
b. Vitamin A and Gastric Cancer. . . . .	310
c. The Effect of Carcinogens upon the Vitamin A Content of Liver . . . . .	310
d. Vitamin A and Tumor Incidence and Growth . . . . .	311
2. B Complex Vitamins . . . . .	312
a. Biotin . . . . .	312
b. Riboflavin . . . . .	315
c. Thiamine . . . . .	317
d. Pantothenic acid. . . . .	318
e. Niacin . . . . .	319
f. Pyridoxin . . . . .	320
g. Folic acid . . . . .	321
h. Inositol . . . . .	321
i. Choline . . . . .	321
j. <i>p</i> -Aminobenzoic acid . . . . .	321
k. B vitamin uniformities . . . . .	322
3. Vitamin C. . . . .	322
a. Ascorbic Acid Content of Tumors . . . . .	322
b. Ascorbic Acid and Tumor Growth . . . . .	323
c. Other Relationships between Ascorbic Acid and Malignant Growth. . . . .	324
4. Vitamin D. . . . .	324
5. Vitamin E. . . . .	325
6. Vitamin K. . . . .	327
III. Abnormal Metabolism of Vitamins in Cancer . . . . .	327
IV. The Relation of Vitamins to Lesions and Cancer of the Intestinal Tract . . . . .	329
V. Tumors Induced by <i>p</i> -Dimethylaminoazobenzene . . . . .	331
1. Effect of Dietary Vitamins on Tumor Production . . . . .	331
2. Changes in the Vitamin and Enzyme Content of Liver during Hepatoma Formation . . . . .	334
3. Changes in Metabolism with Tumor Formation . . . . .	337
4. The Metabolism of <i>p</i> -Dimethylaminoazobenzene in the Rat. . . . .	338
5. The Action of <i>p</i> -Dimethylaminoazobenzene and its Derivatives on Enzyme Systems . . . . .	339
6. General Remarks on Diet and <i>p</i> -Dimethylaminoazobenzene Induced Hepatomas . . . . .	339
VI. The Vitamin Concept and Future Research . . . . .	341
References . . . . .	346

## Effect of Androgens and Estrogens on Birds

By A. S. PARKES AND C. W. EMMENS, *Institute for Medical Research, London, England*

Introduction . . . . .	361
A. Effect of Androgenic Substances	
I. Description of substances . . . . .	362
II. Effect on sex differentiation of the embryo . . . . .	365
III. Effect on females . . . . .	366
1. Secondary sexual characters. . . . .	366
2. Ovary and oviduct . . . . .	368
IV. Effect on intact males. . . . .	368
V. Effect on capons. . . . .	370
1. Secondary sexual characters. . . . .	370
2. Accessory organs . . . . .	376
VI. Assay and relative activity of androgens on birds . . . . .	376
1. Assay . . . . .	376
2. Relative activity . . . . .	379
3. Prolongation of effect . . . . .	381
B. Effect of Estrogenic Substances	
I. Description of substances . . . . .	385
II. Effect on sex differentiation of the embryo . . . . .	388
III. Effect on females . . . . .	390
1. Secondary sexual characters. . . . .	390
2. Oviduct and crop-gland . . . . .	392
IV. Effect on intact males. . . . .	392
1. Plumage . . . . .	392
2. Testis and comb . . . . .	393
V. Effect on capons. . . . .	395
1. Head furnishings . . . . .	395
2. Plumage . . . . .	395
VI. Effect on response to exogenous androgens . . . . .	402
References . . . . .	404

## Hormones in Cancer

By E. C. DODDS, *Courtauld Institute of Biochemistry, Middlesex Hospital, London, England*

Introduction . . . . .	353
I. Sex Hormones as Carcinogens . . . . .	353
II. Estrogens and Malignant Disease of the Prostate . . . . .	354
III. Gonadotrophic Substances and Tumors of the Testes . . . . .	357
IV. Hormones and Mammary Tumors . . . . .	358
References . . . . .	359

## X-Ray Crystallography and Sterol Structure

By DOROTHY CROWFOOT, *Oxford University, Oxford, England*

I. Introduction . . . . .	409
II. The Crystal Structure of Cholesteryl Iodide . . . . .	414
III. The Investigation of the Choleic Acids . . . . .	422

IV. The Crystal Structure of Cholesteryl Chloride and Bromide . . . . .	427
V. A Classification of Sterol Crystal Structures . . . . .	431
VI. The Sex Hormones . . . . .	436
VII. The Heart Poisons . . . . .	441
VIII. The Sterols . . . . .	447
IX. Conclusion . . . . .	458
REFERENCES . . . . .	459
AUTHOR INDEX . . . . .	463
SUBJECT INDEX . . . . .	483

# The Role of Vitamins in the Anabolism of Fats

By E. W. MCHENRY AND MADELEINE L. CORNETT

## CONTENTS

	Page
I. Introduction . . . . .	1
II. Classical Demonstrations of Fat Formation. . . . .	1
III. The Synthesis of Fat from Carbohydrate . . . . .	3
IV. The Synthesis of Fat from Protein . . . . .	7
V. The Formation of Phospholipids. . . . .	11
VI. The Synthesis of Cholesterol . . . . .	12
VII. Possible Mechanism of Fatty Acid Synthesis and the Relation of Vitamins to Enzyme Systems. . . . .	14
VIII. Thiamin-sparing Action of Fats . . . . .	17
IX. Essential Fatty Acids . . . . .	19
X. Summary . . . . .	23
References . . . . .	24

## I. INTRODUCTION

In the interpretation of the title of this review the authors have used Lusk's definition of anabolism (1): the construction of higher substances from lower ones. On this basis, the review deals with the possible effects of various vitamins upon the formation of complex lipids from much simpler molecules derived by metabolic processes from carbohydrates and proteins.

A number of recent reviews have dealt with the synthesis of lipids and with the effects of vitamins upon the synthesis and metabolism of lipids. Particularly valuable have been the excellent reviews by Longenecker (2), by Best and Lucas (3), by Bollman (4), and by Mitchell (5).

## II. CLASSICAL DEMONSTRATIONS OF FAT FORMATION

During the past century the process of lipogenesis has been demonstrated repeatedly. Although Boussingault and Persoz had described fat formation in geese (6), Lawes and Gilbert (7) are responsible for the first evidence clearly indicative of such a process in animals. Analyses of carbohydrate, fat, and protein of the food consumed by pigs, as well as of the resultant composition of the carcasses, served to demonstrate that extensive formation of lipid material from carbohydrate and protein had taken place. These observations confirmed the opinion earlier expressed by Liebig (8) that fat could be synthesized in the animal body.

In 1886, Rubner (9) described lipogenesis in dogs and subsequently Rosenfeld (10) and also Morgulis and Pratt (11) contributed observations

on fat synthesis. The gaseous exchange experiments carried out by the latter, drew attention to the elevated respiratory quotient associated with active fat formation.

The synthesis of lipid material has also been shown to occur in bacterial and yeast cultures, in seeds, and in certain lower animals. In 1908, Weinland (12) described fat formation by macerated larvae incubated in a peptone medium. Beebe and Buxton (13) reached similar conclusions as a result of studies on *Bacillus pyocyaneus*; the pellicle formed by cultures of the organism after an incubation period of three weeks yielded a large amount of ether-extractable material.

More recent researches have indicated the extent to which this important metabolic process may function. In 1925, Wierzuchowski and Ling (14) corroborated the observation of Rapport and associates (15) on fat formation from carbohydrate by "well-nourished" swine. It was pointed out that lipid material was synthesized to the extent of 1% of the body weight daily. The contributions of Anderson and Mendel (16) on rats and of Ellis, *et al.* (17, 18) on hog fattening are in harmony with the earlier observations. Benedict and Lee (19), in a detailed study of fat formation in forced-fed geese, have emphasized the high degree to which lipogenesis may predominate in the metabolic processes of animals possessing a disposition to fat formation. Schoenheimer, *et al.* (20, 21) have demonstrated the rapidity with which lipogenesis occurs, and both Longenecker (22), and Hoagland and Snider (23) provided conclusive evidence of lipid formation from amino acids.

Although it had often been suggested that fat synthesis is essentially, if not exclusively, a hepatic function, only rather recently has satisfactory experimental support for this view become available. Bernhard and Schoenheimer (21) drew attention to the extreme rapidity of turnover of liver fatty acids, and Winter, *et al.* (24) described the failure of fat synthesis in Eck fistula dogs. Similar conclusions may be drawn from experiments of Barrett, Best, and Ridout (25), McHenry (26), and Stetten and Schoenheimer (27).

It is of interest that Hildesheim and Leathes (28) reported the formation of fat in minced dog, rabbit, and pig livers *in vitro*. However, their results were not considered conclusive since added carbohydrate did not stimulate lipid accumulation.

In investigations prior to 1910 and, indeed, in many subsequent to this date, no attention was paid to the vitamin content of the experimental diets. More recent investigations have indicated the essential relations of some vitamins to fat synthesis and have explained why certain foods proved to be lipogenic in the earlier work.

## III. THE SYNTHESIS OF FAT FROM CARBOHYDRATE

In 1936, Whipple and Church (29) extended observations made previously by Sure and associates (30, 31, 32), by Graham and Griffith (33), and by Mitchell (34) that vitamin B<sub>1</sub> had a specific effect upon body weight, as determined by using isocaloric feeding. In addition to repeating the earlier observations upon body weight, Whipple and Church analyzed the animal bodies and secured information regarding the reasons for the increase in weight. They found that, of the difference in weight between pair fed rats, 51% was due to deposition of fat and the balance to water. Since the animals had been maintained on a fat-free diet, and since the only difference in treatment of the two groups was the supply of thiamin to one group, Whipple and Church concluded that thiamin plays a rôle in the synthesis of fat in the animal body. In the following year, they reported (35) a marked difference in respiratory quotient between two isocalorically fed groups of rats, one of which received thiamin; the latter had a quotient well above unity, thus strengthening the hypothesis that thiamin brings about fat formation.

The observations regarding fat formation and deposition were confirmed by McHenry in 1937 (26), who also suggested that the effect of thiamin on fat synthesis could be harmonized with observations on the effect of the vitamin upon pyruvate utilization (36). In 1938, McHenry and Gavin began a series of reports on the relation of B vitamins to fat synthesis and metabolism. Thiamin was also found to cause synthesis in pigeons (37). Riboflavin and rice polish concentrate, used as a source of the B complex, given with thiamin, augmented the amount of synthesized fat (38). Pyridoxin, supplied with thiamin and riboflavin, likewise had a supplementary effect (39). In studying the effects of other members of the complex, an extract of beef liver was used as a source of unknown factors; this markedly augmented the amount of fat and caused fatty livers containing increased amounts of cholesterol (40). These fatty livers were not prevented by choline but were prevented by lipocaiç (41). Later it was shown that biotin had a similar effect to that of the liver fraction (42) and that inositol acted like lipocaiç in preventing the fatty livers caused by biotin in rats (43).

Included in the data arising from work with biotin, McHenry and Gavin gave results (42) which showed a specific effect of thiamin upon fat synthesis but to which they failed to call attention. The amounts of fat produced by various combinations of known B vitamins were cited. Riboflavin, pyridoxin, and pantothenic acid had augmentory effects upon fat synthesis. Examination of the data shows that biotin, while causing fatty livers, actually did not increase the percentage of body fat (as compared with the amount of body fat produced by all of the isolated B vita-



mins except biotin). The data show that rats given biotin were heavier and contained a larger total weight of fat but that the percentage of body fat was smaller. It is also clear from the data that no synthesis of fat occurred when thiamin was omitted from the supplements, even though five other B vitamins were supplied. The results obviously indicated that thiamin is essential for the synthesis of fat from carbohydrate and that other members of the B complex can augment the amount of synthesis.

Longenecker, *et al.* (44) studied the composition of the fats synthesized by the action of thiamin. Rats were depleted for three weeks on a diet free of B vitamins and of fat. At the end of this period one half of the number of animals were killed and tissue analyses made; the remaining rats were continued on the basal diet plus thiamin for twelve days, when they were killed and used for analysis. During the depleting period, body stores of fat were utilized and apparently no synthesis occurred; there was a marked increase in the iodine number of both liver and body fats. Thiamin administration caused a large increase in the amount of fat and a marked drop in iodine number; liver and body fats of supplemented animals contained a high proportion of  $C_{16}$  acids, a finding which Longenecker had previously shown (45) to be characteristic of synthesized fat. In a later study the composition of liver and body fat as effected by other B vitamins, by liver fraction (as a source of biotin), and by lipocaine was investigated (46). Fatty acids synthesized when thiamin, riboflavin, pyridoxin, and choline were given were largely  $C_{16}$  and  $C_{18}$  acids, the  $C_{16}$  acids being 54% of the total. Further supplementing the diet with the liver fraction caused a greater increase of  $C_{18}$  acids than of  $C_{16}$  acids and also augmented the quantity of unsaturated acids. This change in the fatty acid composition, and particularly the increase in unsaturated acids is of interest in connection with the question of essential fatty acids; in most of the studies on the latter subject, yeast has been used as a source of the B vitamins. It may well be that a concentration of the vitamins, different from that supplied by yeast, might cause a synthesis of essential fatty acids.

The hypothesis that thiamin has a specific effect upon fat synthesis has been criticized by Quackenbush, Steenbock, and Platz (47). Data from two types of experiments were cited in support of the criticism. In the first case, three groups of rats were used, all of which had been depleted on a diet containing autoclaved yeast, the first group was killed and analyzed at the end of the depleting period, the second group received thiamin and the basal diet *ad libitum*, the third group were given the same amount of thiamin as used in the second group but the intake of the basal diet was so restricted that body weights were held stationary. At