

Handbook of

# VITAMINS & HORMONES



ROMAN J. KUTSKY



# **HANDBOOK OF VITAMINS AND HORMONES**

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# Preface

The properties and modes of action of both the vitamins and the hormones, and their interrelationships to each other as metabolic controlling agents, are easily accessible in this handbook. The book was written to alleviate the continued frustration experienced by many people, including myself, when attempting to obtain unitary, basic information on vitamins and hormones. Although many of the data are separately available, they are so scattered in many compendia, original research papers, and reviews that a small research project on each vitamin and hormone is required before most of the data can be placed in proper context and profitably used. This feeling of dissatisfaction was brought to a head when I recently presented graduate courses in Endocrinology and on Vitamins and Hormones, thus providing the stimulus for this book. Much of the material, and the general format of this volume were generated from lecture notes for the course on Vitamins and Hormones.

It is hoped that this book will be of use to researchers and students in the various fields of life sciences, as well as to physicians, pharmacologists, nurses, and dietitians. Moreover, this book has sufficient content of semitechnical language to make it useful to the educated layman who might need ready information to guide him through the vitamin fads of the day, including rational meal and cooking selections, and to aid in understanding the hormone-related articles in various newspapers and magazines.

I wish to emphasize the fact that conflicting data exist in the various literature sources. The values finally selected, in cases of doubt, were those that could be confirmed by reference to other publications and/or to original literature, where possible. Comments and more recent data are solicited from the readers, especially on individual values and on the format and content of this

handbook, as it is my hope to continually improve the usefulness of this volume in future editions.

Many have aided and encouraged me in the preparation of this book. I am grateful to numerous investigators in the fields of nutrition and endocrinology and to my scientific colleagues. In particular I wish to acknowledge the assistance of Dr. Mohamed Aboul-Ela on the sections on plant biosynthesis of vitamins and the aid of Dr. Phyllis Kutsky, my wife, for helpful comments and criticisms and for expediting the final manuscript. My thanks also to Mrs. Bobbie Trietsch for her proficient typing of the manuscript.

I wish to thank the National Academy of Sciences for permission to reproduce the table of RECOMMENDED DAILY DIETARY ALLOWANCES, Seventh Revised Edition, 1968.

# Abbreviations

A.A.	amino acid	CF	. . . . . citrovorum factor
Absn.	absorption	Chl.	. . . . . chloroform
Acet.	acetone	CHO	. . . . . carbohydrate
ACH	acetyl choline	Chromatog.	. . . . . chromatograph
ACTH	adrenocorticotrop(h)ic hormone	CMC, CM cell	. . . . . carboxymethyl cellulose
ADH	antidiuretic hormone (vasopressin)	CNS	. . . . . central nervous system
Ala.	alanine	CoA	. . . . . coenzyme A
Aldos.	aldosterone	Conc.	. . . . . concentrated
Alc.	(ethyl) alcohol	Conv.	. . . . . converted
Alk.	alkaline	CoQ	. . . . . Coenzyme Q
AMP	adenosine monophosphate	Cort.	. . . . . cortisol
cAMP	cyclic adenosine mono- phosphate	CRH	. . . . . corticotrop(h)in-releasing hormone
Approx.	approximately	Cys.	. . . . . cysteine
Aq.	aqueous	DDT	. . . dichloro-diphenyl-trichloro- ethane (insecticide)
Arg.	arginine	DEAE	. . . . . diethylaminoethyl (cellulose)
Asn.	asparagine	Defic.	. . . . . deficiency
Asp.	aspartic acid	Dil.	. . . . . dilute
ATP	adenosine triphosphate	DOPA	. . . dihydroxyphenylalanine
Benz.	benzene	DPN	. . . diphosphopyridine nucleotide
Bio.	biotin	DNA	. . . deoxyribonucleic acid
BMR	basal metabolic rate		

Enz.	enzyme	Leu.	leucine
Ep., Epi.	epinephrine	LH	luteinizing hormone
Equiv.	equivalent	LLD	<i>L. lactis Dorner</i>
Esp.	especially	LRH	LH-releasing hormone
Est.	estradiol	Lys.	lysine
Eth.	ether	Max.	maximum
Ext.	extract	me.	methyl
F.A.	folic acid	Met.	methionine
FAD	.flavin adenine dinucleotide	Metab.	metabolism
FMN	.flavin mononucleotide	MIH	MSH-inhibiting hormone
FRH	FSH-releasing hormone	Monocl.	monoclinic
FSH	.follicle-stimulating hormone	MP	melting point
Fluoresc.	fluorescent	MRH	MSH-releasing hormone
GH	growth hormone (STH)	MSH	melanocyte-stimulating hormone
G.I.	gastro-intestinal	MW	molecular weight
Gln.	glutamine	NAD(P)	nicotinamide adenine di-nucleotide (phosphate)
Glu.	glutamic acid	NADPH	.reduced NADP
Gluc(ag).	glucagon	Nia.	.niacin
Gly.	glycine	NIH	National Institutes of Health
GPU	.guinea pig unit	Nor., Norepi.	norepinephrine
GRH	growth (somatotrop(h)in) releasing hormone	NRC	National Research Council
HCG	.human chorionic gonado-trophin	OAA	oxaloacetic acid
HGH	human growth hormone	Oxy.	.oxytocin
His.	histidine	P.A., Pant.	pantothenic acid
HMG	.human menopause gonadotro-phin (mixture of FSH and LH)	PBI	protein-bound iodine
HMP	hexose monophosphate	Pet.	.petroleum
Hyp. R.F., HRH	.hypothalamic-releas-ing factor (hormone)	PGA	.pteroyl glutamic acid, folic acid
Ile.	isoleucine	Phe	phenylalanine
In.	insulin	pl	isoelectric point
Insol.	.insoluble	PIH	prolactin-inhibiting hormone
IRC	ion exchange resin	PMSG	.pregnant mare serum gonadotrophin
Irrad.	irradiated	Ppt.	precipitate
I.U.	international unit	PRH	prolactin-releasing hormone
I.V.	intravenous	Pro.	.proline
		Prog.	progesterone

Prol.	.....	prolactin
PTH	.....	parathormone
RBC	.....	red blood cell
Relax.	.....	relaxin
RNA	.....	ribonucleic acid
mRNA	.....	messenger ribonucleic acid
Ser.	.....	serine
Serot.	.....	serotonin
Sl.	.....	slightly
Sol.	.....	soluble
Soln.	.....	solution
Std.	.....	standard
STH	.....	somatotrop(h)in (GH)
T3	.....	triiodothyronine
T4	....	tetraiodothyronine (thyroxine)
TCA	.....	tricarboxylic acid (cycle), Krebs (cycle)
TCT	.....	thyrocalcitonin
Test., Testos.	.....	testosterone
Thr.	.....	threonine
TPN	..	triphosphopyridine nucleotide (NADP)
TRH	.....	TSH-releasing hormone
Try.	.....	tryptophan
TSH	...	thyroid-stimulating hormone
Tyr.	.....	tyrosine
UDP	.....	uridine diphosphate
USP	....	<i>United States Pharmacopeia</i>
UV	.....	ultraviolet
Val.	.....	valine
Vaso.	.....	vasopressin
Vit.	.....	.vitamin



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# Introduction

With the new discoveries in molecular biology, biochemistry, physiology, and endocrinology, the emphasis in research in life sciences is turning from descriptive biochemistry and electron microscopy to the functional, dynamic aspects of the vital, metabolic processes. In particular, great interest has been generated in the actual controlling agents which accurately blend all the cellular enzyme systems and organelles to produce a living cell, and, from that, a living multicellular organism. It is precisely in this area of control mechanisms that the vitamins and hormones play such a key role, because they are controlling agents.

This book is written primarily from the standpoint of the vitamin and hormone requirements and contents of individuals of the *human* species. It should be understood that requirements and contents differ from species to species, in general becoming simpler as one goes down the evolutionary scale. For the purposes of this book, a *vitamin* is defined as a biologically active, organic compound, a controlling agent essential for an organism's (human's) normal health and growth (its absence causing a deficiency disease or disorder), not synthesized within the organism, available in the diet in small amounts, and carried in the circulatory system in small concentrations to act on target organs or tissues. A *hormone* is defined as a biologically active, organic compound, a controlling agent essential for normal health and growth (its absence causing a deficiency disease or disorder), synthesized within the organism (human being) in ductless glands which release the agent in very small concentrations into the circulatory system to act on the target organs or tissues.

The chief differences between a vitamin and a hormone seem to be the site of biosynthesis, the types of organic compounds present in vitamins as opposed to the hormones, and some of the modes of action. These differences between

vitamins and hormones in essential properties are small compared to their similarities and explain why both vitamins and hormones are combined into one book.

In the light of new evidence, it is becoming difficult to differentiate certain vitamins from some hormones. For example, both vitamin D and niacin are synthesized (but in an inadequate amount) in the human, thus conferring on them a hormonal quality. Similarly, the human requirement for the hormone thyroxine can be partially satisfied by a dietary intake of iodine, and some of the steroid hormones are active in a dietary form thus giving them a vitamin quality. Moreover, the fat-soluble vitamins (A, D, E, K) show many similarities in biosynthesis, structure, properties and function to the fat-soluble hormones (steroids). Finally, the same molecule can function as a hormone or as a vitamin depending on the species involved. For example, vitamin C functions as a vitamin in primates because they cannot synthesize it, but it functions as a hormone in rats because they can synthesize it.

We can see that the concept of vitamins and hormones, as defined here, could be extended to all organisms with circulatory systems and would therefore include all vertebrates, many invertebrates, and the higher plants, excepting mainly the lower plants and animals and unicellular organisms. If the definition of circulatory system were to include intracellular circulation, then all living organisms would be included. The concept of vitamin is therefore very much dependent on the species concerned as, if we accept the expanded definition of circulatory system, then the "vitamins" synthesized by unicellular organisms would actually be hormones. Vitamins seem to have arisen very early in the evolution of life as judged by their presence and requirement in some of the most primitive forms of life known today. Hormones, according to our original definition, however, denote a much later period of emergence, becoming prominent mainly with the evolution of the various animals. They, therefore, reflect a shorter evolutionary history. In view of their primitive nature, vitamins would be expected to have, in general, a simpler structure than hormones, and this is indeed the case, with a few exceptions.

As we compare modes of action of vitamins and hormones, we should compare their chemical structures. The vitamins consist of a fat-soluble series and a water-soluble series. The fat-soluble vitamins (A, D, E, K) consist of derivatives of partially cyclized isoprenoid polymers, somewhat similar to the intermediates in cholesterol (steroid) synthesis. These vitamins seem to act by virtue of their lipid solubility in various cell membranes to affect permeability or transport, and by virtue of their chemical groups as redox agents (A, E, K), as coenzymes or enzyme activators (D, K, A), or as enzyme inhibitors (E). The water-soluble vitamins ( $B_1$ ,  $B_2$ ,  $B_6$ ,  $B_{12}$ , niacin, pantothenic acid, folic acid, biotin, C) consist, in general, of derivatives or substituted derivatives of sugars (C), pyridine (niacin,  $B_6$ ), purines and pyrimidines (folic acid,  $B_2$ ,  $B_1$ ), amino

acid-organic acid complexes (folic acid, biotin, pantothenic acid) and a porphyrin-nucleotide complex ( $B_{12}$ ). These structurally diverse water-soluble vitamins act as enzyme activators and coenzymes ( $B_1$ ,  $B_2$ ,  $B_6$ ,  $B_{12}$ , pantothenic acid, folic acid, biotin, niacin), as redox agents on enzyme reactions (C,  $B_2$ ,  $B_{12}$ , folic acid, niacin) as nuclear agents (folic acid,  $B_{12}$ , C, biotin) and probably mitochondrial agents ( $B_2$ , C, niacin).

The hormones also include a fat-soluble, steroid series (estradiol, progesterone, aldosterone, testosterone, cortisol) which seems to act (1) by virtue of lipid solubility to stabilize and change permeability of the cell membranes, (2) to regulate enzyme activity and membrane polarization, (3) to regulate redox potential, and (4) to affect RNA transcription in the nucleus (aldosterone, estradiol, testosterone). The water-soluble hormones consist of a protein series (STH, TSH, FSH, LH, Prol.) which seems to act on the cell membrane to stimulate cyclic AMP production with consequent ATP production, and enzyme activation, and to activate certain genes in the nucleus. The peptide series of water-soluble hormones (insulin, glucagon, ACTH, MSH, oxytocin, ADH, PTH, T4, TCT, and relaxin) acts similarly to the proteins and also has an effect on the mitochondria by T4 and PTH. The amine, water-soluble hormone series (epinephrine, norepinephrine) seems to act chiefly by the cyclic AMP mechanism on the membrane, with consequent enzyme activation. The very extensive role of cAMP as an intracellular mediator of hormonal activity is most noteworthy.

It can be seen that the fat-soluble vitamins and hormones act similarly on membranes, on redox potentials, and as enzyme activators, the only difference being in a demonstrated action on the nucleus by the steroids. Comparison of the water-soluble series of hormones with that of the vitamins again shows a basic similarity in action, the vitamins acting as direct enzyme activators and coenzymes, and the hormones acting as indirect activators via cyclic AMP. Both act on the nucleus but differ in that only some of the water-soluble vitamins have redox properties. Again here, the differences between the two water-soluble series of vitamins and hormones lie chiefly in their differing structures and in some of their properties, such as redox regulation and presence of cyclic AMP intermediates.

The subject of vitamin requirements requires comment. There is now sufficient evidence to indicate that the concept of biochemical individuality has much merit. Thus the recommended allowances as stated in this book (NRC Data) should be considered only as average figures, and variations (increase or decrease) of twentyfold or more in individual human requirements may be found, depending on the genetic and physiological state of the individual. Germane to this are the topics of subclinical vitamin deficiencies and megavitamin therapy, i.e., large overdosages of one or more vitamins such as are now being used as treatment of colds and schizophrenia.

The existence of subclinical vitamin deficiencies is extremely difficult to prove without adequate statistical data, but, undoubtedly, if we accept the principle of biochemical individuality, they do exist. In like manner, the use of megavitamins may be helpful to those individuals whose systems for some reason destroy these vitamins rapidly or require these vitamins in large quantity due to their biochemical individuality. However, in view of the fact that accurate data are lacking, megavitamins should be treated and used as drugs with competent medical advice, being wary of possible unexpected individual toxicity.

A perusal of the miscellaneous section for each hormone or vitamin will indicate to the reader the enormous amount of interplay occurring among vitamins and hormones themselves and also with each other. This includes both antagonisms and synergisms occurring simultaneously among various vitamins and hormones. Undoubtedly there exists an optimal set of levels for each vitamin and hormone which, presumably, is that which has been found in "normal" human values. But maximum optimization of levels at "normal" human values has not been proven experimentally; perhaps the human system could run more efficiently at a different set of values. More research is needed to determine this. In any case, optimum amounts and ratios of all vitamins and hormones are important to get full benefits of these agents.

Lack of space and time has precluded extensive mention of the trace elements and mineral cofactors required for functioning of most coenzyme systems as well as some hormones, e.g., magnesium, iron, copper, iodine, selenium, cobalt, etc. These trace elements should be present in correct amounts and ratios in any balanced diet containing adequate vitamins.

In relation to requirements, the subject of undiscovered or unaccepted vitamins and hormones should be mentioned. This book has included only those vitamins and hormones with widespread acceptance. In addition to the 13 vitamins listed here, there are at least another 13 compounds with various acceptabilities as vitamins, plus possibly other vitamins still undiscovered. In relationship to individual requirements, this means that taken together with the facts of mutual interdependence of vitamins as mentioned above, it would still be advisable to rely for one's vitamin requirement chiefly on rich natural sources in the diet, since these would most likely contain the undiscovered vitamins. However, in view of the possible extreme losses of vitamin potency even in our richest dietary sources caused by our present methods of processing, storing, and cooking of food, it would be advisable to consider vitamin supplementation of certain vitamins, especially if one's diet has not been carefully planned.

As far as the hormones are concerned, at least another 23 compounds, in addition to the 23 listed here, are known with various degrees of acceptance as true hormones. No doubt many more remain to be discovered. This book has not listed the insect or plant hormones, because the human requirements and levels are being stressed.

# 2

# Presentation of Data

This book will serve as a ready reference to four major groups of readers, inasmuch as the data for each vitamin and hormone are presented in several separate sections, as follows: "General Information" and "Miscellaneous Information" for the general reader and all other groups; "Medical and Biological Role" mainly for the biologists, physicians, nurses, and pharmacologists; "Chemical Properties" and "Metabolic Properties" for the biochemists and physiologists; and "Nutritional Role" for dietitians and nutritionists. However, it is hoped that parts of all sections will be useful to all the groups. Insofar as possible, the format is similar for both hormones and vitamins for ease of reference. A list of abbreviations is given at the beginning of the book.

The specific vitamins and hormones chosen for coverage in this book are those that have the widest acceptance by the various workers in both fields. Only the most active of the steroid hormones in each category of mineralocorticoids, glucocorticoids, and sex hormones in the human is being covered (out of the 40 plus already discovered).

## Chapters on Vitamins and Hormones

### General Information Section

"Active analogs and related compounds" includes vitamers, isotols, etc.

"Antagonists" and "Synergists" may be the same chemical species but in different concentrations. Interaction at the target site is used as a criterion of antagonism or synergism.

"Sources for Species" (Essentiality) indicates degree of requirement for various species including man. Endogenous = made within organism. Exogenous sources include intestinal bacteria.

### Chemical Properties Section

"Reactions" refers to those carried out with standard laboratory conditions and reagents and not under extreme conditions, unless otherwise noted. i.e., heat  $\leq 100^{\circ}\text{C}$ , weak acids or alkalies, reactivity with water, atmospheric or mild oxidation agents, mild reducing agents, bright daylight.

Isolation method gives a typical procedure now in use.

### Medical and Biological (Nutritional) Section

This provides, in general, clinical information. Contents of vitamins are per 100 g. edible portion

Antigenicity is defined as the ability to act as an antigen creating an immune response when administered to an organism. Specificity is here defined as the degree of restriction of biological activity to a certain species.

### Metabolic Role Section

"Enzyme Reactions" lists enzyme systems affected by the vitamin or hormone, organ location, and effects on enzymes, where known.

"Mode of Action" subdivides functions on both a cellular basis (anabolic, catabolic, etc.) and an organismal basis. Anabolic denotes synthetic processes; catabolic denotes degradative reactions and includes most energy yielding reactions.

### Miscellaneous Information Section

"Relationships to other Vitamins, Hormones" attempts to indicate the mutual involvement of both vitamins and hormones in most actions of both groups either together or within the group.

"Unusual Features" includes various chemical, biological, and pharmacological features that could not be listed elsewhere.

"Possible Relationships" attempts to draw a parallel between the action of a vitamin or a hormone and its deficiency symptoms.

The tables following Chapter 38 list in tabular fashion some of the data already presented and some new data in an attempt to indicate fundamental similarities and dissimilarities in structure and function of both vitamins and hormones.

References are presented in numbered form at the end of the book, and are subdivided into three categories: General; Specific: Vitamins; and Specific: Hormones. An effort has been made to cite only the latest available handbooks, compendia, journal references, and texts.

# 3 Vitamin A

## GENERAL INFORMATION

**1. Synonyms:** Retinol, axerophthol, biosterol, vitamin A<sub>1</sub>, anti-xerophthalmic vitamin, anti-infective vitamin

### **2. History**

1912—Hopkins reported factor in milk needed for growth of rats

1913—Osborne and Mendel demonstrated milk factor is fat soluble; present in other fats also

1913-15—McCollum and Davis identified milk factor (fat-soluble A) in butter, egg yolk

1917—McCollum and Simmonds found xerophthalmia in rats due to lack of fat-soluble A

1920—Drummond renamed fat-soluble A, vit. A

1930—Moore determined carotene a precursor for vit. A

1930-37—Karrer *et al.* isolated and synthesized vit. A

1935—Wald reported visual purple in retina a complex of protein and vit. A

### **3. Physiological Forms**

Retinol (vit. A<sub>1</sub>) and esters

3-Dehydroretinol (vit. A<sub>2</sub>) and esters

Retinal (retinene, vit. A aldehyde), 3-dehydroretinal (retinene-2)

Retinoic acid

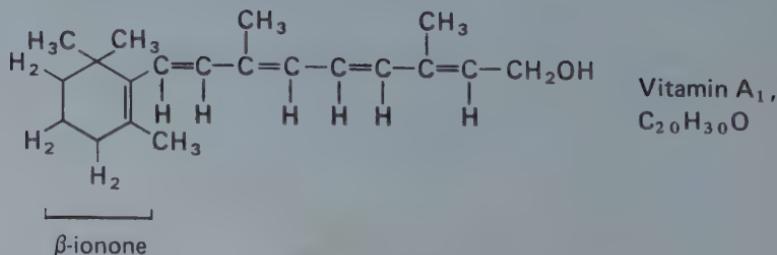
Neovitamin A

Neo-b-vit. A<sub>1</sub>

4. Active Analogs and Related Compounds:  $\alpha$ ,  $\beta$ ,  $\gamma$ -carotene, neo- $\beta$ -carotene B, cryptoxanthine, myroxanthine, torularhodin, aphanicin, echinenone
5. Inactive Analogs and Related Compounds: Kitol, xanthophyll, lycopene
6. Antagonists: Sodium benzoate, bromobenzene, citral, oxidized derivatives of vit. A, thyroxine (large concentrations), estrogens, vitamin E (membrane permeability)
7. Synergists: Vitamins B<sub>2</sub>, B<sub>12</sub>, C, E, thyroxine, testosterone, MSH, STH
8. Physiological Functions: Growth, production of visual purple, maintenance of skin and epithelial cells, resistance to infection, gluconeogenesis, mucopolysaccharide synthesis, bone development, maintenance of myelin and membranes, maintenance of color and peripheral vision, maintenance of adrenal cortex and steroid hormone synthesis
9. Deficiency Diseases, Disorders: Xerophthalmia, nyctalopia, hemeralopia, keratomalacia, hyperkeratosis
10. Sources for Species Requiring It
  - Required by many animal species
  - Exogenous sources—All vertebrates and some invertebrates convert plant dietary carotenoids in gut to vit. A<sub>1</sub>, which is absorbed
  - Endogenous sources—None reported

## CHEMISTRY

### 1. Structure



## 2. Reactions

Heat—Labile (isomerizes)	Oxidation—Labile (isomerizes)
Acid—Labile (isomerizes)	Reduction—Stable
Alkali—Stable	Light—Labile (isomerizes) (UV inactivates)
Water—Insol.	

## 3. Properties

Appearance—Yellow oil	Solubility
MW—286.4	$\text{H}_2\text{O}$ —Insol.
MP—62-64°C	Acet., Alc.—Sol.
Crystal Form—Prisms	Chl., Eth.—Sol.
Salts, Esters—Acetate palmitate	Absn. Max.—325-328 m $\mu$
Important Groups for activity	Chemical Nature—Unsaturated alc.
$\beta$ -ionone ring	$\alpha_D = 0$ (inactive)
<i>trans</i> -methyl	
Alcoholic hydroxyl	

## 4. Commercial Production

Chemical—Extraction of fish liver  
Synthetic—From citral or  $\beta$ -ionone

## 5. Isolation

Sources—Fish liver oils  
Method—Saponification in alcoholic KOH. Extract with ether, crystallize

## 6. Determination

Bioassay—Growth rate of rats  
Physicochemical—Spectrophotometric determination of blue color on reacting with antimony trichloride or trifluoracetic acid

## DISTRIBUTION AND SOURCES

### 1. Occurrence

Plants  
Fruit—Provitamin carotenoids—apricots, yellow melons, peaches, prunes  
Vegetables—Provitamin carotenoids—beet greens, broccoli greens, carrots, endive, kale, lettuce, mint, mustard, parsley, pumpkins, spinach, sweet potatoes, turnip greens, cress  
Nuts—Provitamin carotenoids—in small quantity in most nuts

**Animals:**

Vitamin A in all vertebrates, and carotenoids in certain invertebrates (crustacea) ( $A_2$  especially in fresh-water fish)

Location: Liver, heart, lungs, fat, adrenals, retina, kidney, milk, blood plasma, egg

Provitamin carotenoids found in many animals depending on diet

Hen's egg carotenoid mainly xanthophyll (inactive analog)

Microorganisms: Provitamin carotenoids in algae, fungi, bacteria. No intestinal synthesis of vit. A

**2. Dietary Sources: (Vit. A and Procarotenoids)**

High: 10,000–76,000 I.U./100 g

Liver (beef, pig, sheep, calf, chicken)

Liver oil (cod, halibut, salmon, shark, sperm whale)

Carrots, mint, kohlrabi, parsley, spinach, turnip greens, dandelion greens, palm oil

Medium: 1000-10,000 I.U./100 g

Butter, cheese (except cottage), egg yolk, margarine, dried milk, cream

White fish, eel

Kidneys (beef, pig, sheep), liver (pork)

Mangoes, apricots, yellow melons, peaches, cherries (sour), nectarines

Beet greens, broccoli, endive, kale, mustard, pumpkin, sweet potatoes, watercress, tomatoes, leek greens, chicory, chives, collards, fennel, butterhead and romaine lettuce, squash (acorn, butternut, hubbard), chard

Low: 100-1000 I.U./100 g

Milk

Herring, salmon, oyster, carp, clams, sardines

Grapes, bananas, berries (black-, goose-, rasp-, boysen-, logan-, blue-), sweet cherries, olives, oranges, avocados, prunes, kumquats, pineapples, plums, rhubarb, tangerines, red currants

Summer and zucchini squash, asparagus, beans (except kidney), brussel sprouts, cabbages, leeks, peas, artichokes, corn, cucumbers, lentils (dry), peppers, lettuce, celery, cowpeas, rutabagas, okra

Hazelnuts, peanuts, black walnuts, cashew, pecans, pistachios

**MEDICAL AND NUTRITIONAL ROLE**

**1. Units:** 1 I.U. = 0.344  $\mu$ g vit. A acetate = 0.3  $\mu$ g retinol

**2. Normal Blood Levels:** 100-300 I.U./100 ml serum

### 3. Recommended Allowances

Children—2000-3500 I.U./day

Adults—5000 I.U./day

Special—Pregnancy—6000 I.U./day, Lactation—8000 I.U./day

### 4. Administration

Injection—Parenteral

Topical—No data

Oral—Preferred route

### 5. Factors Affecting Availability

Decrease

Liver damage

Impaired intestinal conversion of carotenes

Impaired absorption (low bile)

Food preparation (cooking and frying—heat oxidation)

Presence of antagonists

Illness—increased destruction and excretion

Increase

Storage in body (liver)

Intestinal conversion of carotenes—T4, insulin increase

Absorption aids—bile, fat

Dietary protein—mobilizes Vit. A from storage in liver

### 6. Deficiency Symptoms

General

Retarded growth

Night blindness (nyctalopia)—degeneration of retina

Hyperkeratinization of epithelial tissues—

Degenerative changes in eye epithelium (xerophthalmia, hemeralopia)

Atrophy of odontoblasts

Lab animals

Poor bone and tooth development

Resorption of fetus, atrophy of germinal epithelium

Urolithiasis—urinary calculi

### 7. Effects of Overdose

100,000 units/day (man)—generally toxic

Irritability, nerve lesions

Fatigue, insomnia, painful bones and joints

Exophthalmia

Mucous cell formation in keratinized membranes

Abnormal bone growth  
Loss of hair, jaundice, itchy skin, anorexia  
Decreased clotting time  
Elevated serum alkaline phosphatase

## METABOLIC ROLE

### 1. Biosynthesis

Precursors

Animals—Carotenoid conversion  
(except rat, pig, sheep, carnivores, some invertebrates and human infants)—cannot convert  
 $\alpha$ ,  $\beta$ ,  $\gamma$ -carotenes, cryptoxanthin, myxoxanthin, torularhodin

Plants—Cholesterol pathways—acetate, etc., aphanicin, echinenone

Intermediates

Plants—Mevalonic acid, squalene

### 2. Production: Species and sites

Plants (carotenoids)

Higher plants—Green leaves, yellow vegetables and fruits  
Some algae, fungi, bacteria—carotenoids

Animals

Most vertebrates (except rat, pig, sheep)  
Conversion of carotenoids to vit. A in intestinal wall  
Some invertebrates also convert

### 3. Storage Sites: Liver, kidney (rat, cat)

### 4. Blood Carriers

$\alpha_1$  and  $\alpha_2$ -globulins,  $\beta$ -lipoproteins (carotenoids)  
Retinol esters via lymphatics (esp. palmitate)  
chylomicrons in lymphatics (retinol esters)

### 5. Half-life: Weeks or months

### 6. Target Tissues: Retina, skin, bone, liver, adrenals, germinal epithelium

## 7. Reactions

Coenzyme forms—Neo-b-vit. A<sub>1</sub>, retinoic acid

<i>Organ</i>	<i>Enzyme System</i>	<i>Effect</i>
Adrenal cortex	Hydroxylating—deoxycorticosterone → corticosterone	Activated
Liver	Sulfurylases—ATP + SO <sub>4</sub> = phospho-adenosinephosphosulfate	Activated
Intestine	Esterases—Vitamin A ester → vit. A + fatty acid	Activated
Intestine	Synthetases—Vit. A + Fatty acid → vit. A ester	Activated
Liver	Dehydrogenases—neo-b-vit. A <sub>1</sub> → retinene, retinal → retinoic acid	Activated
Retina	Isomerasers— <i>trans</i> -retinene → <i>cis</i> -retinene (inactive)	Activated
Liver	Hydrolases—Acid phosphatase, β-glucuronidase, cathepsin, etc., in lysosomes on hyper- or hypo-vitaminosis A	Released

## 8. Mode of Action

### Cellular

Anabolic—Synthesis of mucopolysaccharides via “active” sulfate.  
Synthesis of corticosterone

Catabolic—No data

Other—Precursor of retinene in retina—forms visual pigments. Maintains stability of lysosomes + cell membranes

### Organismal

Maintenance of visual sense organs

Maintains reproductive systems

Maintains glucocorticoid production in adrenals

Maintains mucous membranes

Regulates cartilage for bone development

## 9. Catabolism

Intermediates—Retinoic acid

Excretion products

Urine—Vitamin A (only in disease)  
fatty acid, small soluble molecules

Breath—CO<sub>2</sub>

## MISCELLANEOUS

### 1. Relationship to Other Vitamins

- Vitamin C—Plasma vit. C levels drop on depletion of vit. A, occurrence and action of vits. A and C coincide often
- Vitamin D—Occurs naturally with vit. A in animal liver oils. Toxic overdose effects reduced by vit. A
- Niacin—Involved with DPN + vit. A in activity of retinene reductase.
- Vitamin E—Decreases serum cholesterol in rabbit when given with vit. A  
Protects vit. A from oxidation
- Similarity of structure to vitamin A
- Antagonistic to vit. A in maintaining membrane permeability
- Pantothenic acid—Promotes synthesis of vit. A in plants

### 2. Relationship to Hormones

- Thyroxine—Stimulates intestinal conversion of carotene to vit. A  
Increases vit. A storage in liver
- Antagonizes decreased basal metabolism caused by vit. A  
Increases use of vit. A
- Insulin—Stimulates intestinal conversion of carotene to vit. A
- STH—A synergist in growth
- Cortisol, Aldosterone, Testosterone, Progesterone—Decreased on vit. A depletion (chemical adrenalectomy). Production of deoxycorticosterone and other steroids stimulated by vit. A
- Estradiol—Antagonistic to vit. A peripherally
- MSH—Decreases dark adaptation time—synergistic to vit. A

### 3. Unusual Features

- Decreases serum cholesterol in large quantity administration (chicks)
- Dietary protein required to mobilize liver reserves of vit. A
- Decreased in tumors
- Coenzyme Q<sub>10</sub> accumulates in A-deficient rat liver
- Ubichromenol-50 accumulation in A-deficient rat liver
- Retinoic acid functions as vit. A except for visual and reproductive functions
- Anti-infection properties and anti-allergic properties
- Decreases basal metabolism
- Detoxification of poisons in the liver aided by vit. A
- Involved in triose → glucose conversions

**4. Possible Relationships of Deficiency Symptoms to Metabolic Action**

Growth Retardation—Effects on steroid synthesis, bone growth, and membrane structure, and development of epithelial tissues

Keratinization—Effects on membranes and mucopolysaccharide biosynthesis

Bone development—Formation of chondroitin sulfate in cartilage

Reproductive failure—Effects on membranes and steroid hormones

Visual defects—Absence of retinene precursors

# 4 Vitamin D

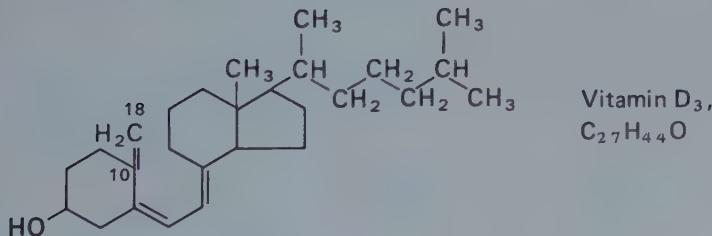
## GENERAL INFORMATION

1. **Synonyms:** Antirachitic vitamin, vitamin D<sub>3</sub>, rachitamin, rachitasterol, cholecalciferol, activated 7-dehydrocholesterol
2. **History**
  - 1918—Mellanby produced experimental rickets in dogs
  - 1919—Huldschinsky ameliorated rachitic symptoms in children with ultraviolet irradiation
  - 1922—Hess showed liver oils contain same antirachitic factor as sunlight
  - 1922—McCollum increased calcium deposition in rachitic rats with cod liver oil factor
  - 1924—Steenbook and Hess demonstrated irradiated foods have anti-rachitic properties
  - 1925—McCollum named antirachitic factor vit. D.
  - 1931—Angus isolated crystalline vit. D (calciferol)
  - 1936—Windaus isolated vit. D<sub>3</sub> (activated 7-dehydrocholesterol)
3. **Physiological Forms:** Vitamin D<sub>2</sub> (calciferol, ergocalciferol), vit. D<sub>3</sub> (cholecalciferol), phosphate esters of D<sub>2</sub>, D<sub>3</sub>, 25-hydroxycholecalciferol, 1,25-dihydroxycholecalciferol, 5,25-dihydroxycholecalciferol
4. **Active Analogs and Related Compounds:** Irrad. [22-dihydroergosterol (vit. D<sub>4</sub>) 2-dehydrostigmasterol (vit. D<sub>6</sub>), 7-dehydrositosterol (vit. D<sub>5</sub>)]. Dihydrotachysterol

- 5. Inactive Analogs and Related Compounds:** Lumisterol, tachysterol, ergosterol, 7-dehydrocholesterol
- 6. Antagonists:** Toxisterol, phytin, phlorizin, cortisone, cortisol, thyrocalcitonin, PTH
- 7. Synergists:** Niacin, PTH, STH
- 8. Physiological Functions:** Normal growth (via bone growth), Ca and P absorption from intestine, antirachitic, increases tubular P reabsorption, increases citrate blood levels, maintains and activates alkaline phosphatase in bone, and maintains serum calcium and phosphorus levels
- 9. Deficiency Diseases, Disorders:** Rickets, osteomalacia, hypoparathyroidism
- 10. Sources for Species Requiring It:** Required by vertebrates  
 Exogenous sources—Infant vertebrates and deficient adult vertebrates  
 Endogenous sources—Vertebrates (synthesized in skin under UV irrad.)

## CHEMISTRY

### 1. Structure



### 2. Reactions

Heat—Stable  
 Acid—Stable  
 Alkali—Stable  
 Water—Insol.

Oxidation—Unstable  
 Reduction—Stable  
 Light—Unstable

**3. Properties**

Appearance—White powder  
 MW—384.65  
 MP—84-85°C  
 Form—Fine needles  
 Salts, Esters  
 Palmitate, 3,5-dinitrobenzoate  
 Important Groups for Activity  
 $C_{10}-C_{18}$  Methylene  
 Alcoholic—OH

Solubility  
 $H_2O$ —Insol.  
 Acet., Alc.—Sol.  
 Benz., Chl., Eth.—Sol.  
 Absn. Max.—265 mμ  
 Chemical Nature—Sterol, alc.  
 $\alpha_D^{20} = +102.5^\circ$  (alc.)

**4. Commercial Production**

Irradiation of ergosterol, 7-dehydrocholesterol  
 Extraction of fish liver oils

**5. Isolation**

Sources—Liver oil, irradiated yeast

Method—Saponify oil, remove vit. A and sterols by partitioning solvents,  
 and adsorption chromatography, remove inactive sterols with  
 digitonin, crystallize as 3,5-dinitrobenzoate ester, saponify, recrys-  
 tallize

**6. Determination**

Bioassay—Antirachitic test on rats

Physicochemical—Reaction with antimony trichloride

**DISTRIBUTION AND SOURCES****1. Occurrence**

Plants

Fruit—None

Vegetables—Grain and vegetable oils (provitamins)

Nuts—None

Animals: Tuna, halibut, cod liver oils

Egg yolk, milk (irrad.), bones, intestine, blood, brain, skin, spleen, fish  
 liver

Shrimp, mollusks

Microorganisms: Yeast, algae, bacteria (provitamins)

## 2. Dietary Sources

High:  $1000-25 \times 10^6$  I.U./100 g

Liver oils (bonito, tuna, lingcod, sea bass, swordfish, halibut, herring, cod, sablefish, soupfin shark)

Medium: 100-1000 I.U./100 g

Egg yolk, margarine, lard, herring, salmon, mackerel, pilchards, sardines, shrimp, tuna, kippers

Low: 10-100 I.U./100 g

Grain and vegetable oils

Cod roe, halibut

Butter, cream, eggs, cheeses, milk (vit. D or irrad.)

Liver (calf, pork, lamb, beef)

Veal, horse meat, beef

## MEDICAL AND NUTRITIONAL ROLE

1. Units: 1 U.S.P. = 1 I.U. = 0.025  $\mu$ g vit. D<sub>3</sub>

2. Normal Blood Levels: 2.75  $\mu$ g/100 ml (serum); 66-165 I.U./100 ml (serum)

3. Recommended Allowances

Children—400 I.U./day

Adults—None in equatorial zones; 400 I.U./day in temperate zones (available in normal diet)

Special—Pregnancy, 400 I.U./day; lactation, 400 I.U./day; senility, night workers, miners, northern people

4. Administration

Injection—Subcutaneous, intraperitoneal, intramuscular (D<sub>3</sub> esters)

Topical—Absorbed through skin

Oral—Preferred route

5. Factors Affecting Availability

Decrease

Liver damage

Presence of antagonists

Presence of phytin in gut

Low bile salts in gut

- High pH in gut
- Destruction by intestinal flora
- Excretion in feces
- Increase
  - Storage in liver, skin
  - Absorption aids—bile salts
  - Long acting feature (slow destruction)
  - Decrease in pH of lower intestine
  - Irradiation by UV

## 6. Deficiency Symptoms

- In young or experimental animals, including man
  - Retarded growth—Rickets
  - Malformation of long bones—Rickets
  - Skeletal malformation
  - Demineralization of bone
  - Decreased blood calcium and phosphorus
  - Increased serum alkaline phosphatase

## 7. Effects of Overdose (Man)—Generally toxic

- 4000 (or more) I.U./day
  - Anorexia, nausea, thirst, diarrhea
  - Polyuria, muscular weakness, joint pains
  - Increased serum calcium—calcification of soft tissues (arteries, muscle)
  - Resorption of bone
  - Arterial lesions and kidney injury (rats)

## METABOLIC ROLE

### 1. Biosynthesis

- Precursors—Cholesterol (skin—UV) animals; ergosterol (algae, yeast-UV)  
plants
- Intermediates—Pre-ergocalciferol, tachysterol, 7-dehydrocholesterol

### 2. Production: Species and Site

- Plants—Leaves, seeds, shoots (provitamins)
- Fungi—Various
- Bacteria—Various, but no intestinal synthesis
- Animals—Skin

### 3. Storage Sites: Animals—Liver, skin

**4. Blood Carriers:** Lipoproteins ( $\alpha + \beta$ )

**5. Half-life:** Long acting (days, weeks)

**6. Target Tissues:** Kidney, bone, intestine, liver

## 7. Reactions

Reactive form—25-Hydroxycholecalciferol and metabolites

Coenzyme forms—Phosphorylated vit. D

Organ	Enzyme System	Effect
Intestine	Phytase	Activated
Serum	Alk. phosphatase—Organic phosphate (serum) $\rightarrow$ inorganic phosphate	Activated
Liver	Phosphorylase—Glycogen $\rightarrow$ glucose-1-phosphate	Activated

## 8. Mode of Action

Cellular

Anabolic—Increases protein synthesis in intestinal cells

Catabolic

Depresses protein synthesis except in intestinal cells

Other

Decreases citrate oxidation

Increases release of calcium by mitochondria

Activates active transport of calcium by intestinal cells

Repair of mitochondrial membrane

Regulates phosphorus metabolism

Organismal

Promotes normal bone calcification

Increases formation of osteoclasts and capillaries in cartilage—  
Increases cartilage degeneration in normal bone calcification

Regulates phosphorus and calcium metabolism—increases calcium absorption by intestine—Maintains normal serum calcium and phosphorus levels

Mobilizes phosphorus from soft tissues

Mobilizes calcium from bone in hypocalcemia (with PTH)

Converts organic phosphates to inorganic phosphates

Catabolic

**9. Catabolism**

- Intermediates—Similar to cholesterol conversion products: bile acids and steroid hormones
- Excretion products
  - No vit. D in urine (human)
  - Animals—Excess vit. D into feces
  - Humans—70% of ingested vit. D in feces as fecal sterols

**MISCELLANEOUS****1. Relationship to Other Vitamins**

- Vitamin A—
  - Reduces toxic effects of vit. D
  - Occurs naturally with vit. D in many fish oils
- Vitamin B<sub>1</sub>—Increases tolerance of vit. D

**2. Relationship to Hormones**

- Parathormone—activity intensified by vit. D; deficiency of vit. D stimulates parathyroid
- Cortisone—Antagonizes effect of vit. D on citrate metabolism
- STH—A synergist in growth

**3. Unusual Features**

- Has hormonal qualities due to internal synthesis
- Vitamin D<sub>2</sub> little activity for chickens—species differ in response.
- May play role in aging calcification phenomena, especially in skin
- Can mimic rickets with high calcium low phosphorus diet
- Can mimic osteomalacia with low calcium high phosphorus diet
- Absorbed through skin
- Activates transport of heavy metals by intestinal cells
- Ample available for adults from most diets and skin synthesis
- Long acting, stored
- Furred and feathered animals obtain vit. D in grooming and licking
- Fish thought to obtain vit. D from marine invertebrates
- Useful in lead poisoning treatment

**4. Possible Relationships of Deficiency Symptoms to Metabolic Action**

- Decreased growth—Retarded calcification and bone growth
- Increased alkaline phosphatase—Attempt by organism to increase inorganic phosphate
- Osteomalacia—Demineralization of bone, (e.g. in pregnancy)
- Skeletal malformation—Retarded calcification

# 5

# Vitamin E

## GENERAL INFORMATION

**1. Synonyms:**  $\alpha$ -Tocopherol, antisterility vitamin, 5,7,8-trimethyltocol, Epsilon, Ephynal, Tokopharm, factor X

**2. History**

1922—Evans and Bishop reported dietary factor "X" needed for normal rat reproduction

1922—Matill found dietary factor "X" in yeast or lettuce

1923—Evans *et al.* found factor "X" in alfalfa, wheat, oats, meat, butterfat

1924—Sure named factor "X" vit. E.

1936—Evans *et al.* demonstrated vit. E belongs to tocopherol family of compounds—isolated several active tocopherols—vit. E ( $\alpha$ -tocopherol) most active of tocopherols

1938—Fernholz determined structure of vit. E

1938—Karrer synthesized vit. E

1956—Green discovered eighth tocopherol

**3. Physiological Forms**

$d$ - $\alpha$ -tocopherol, tocopheronolactone, and their phosphate esters

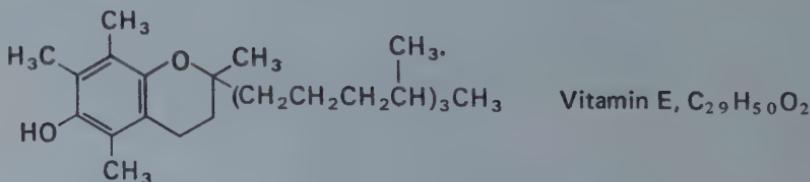
**4. Active Analogs and Related Compounds**

$dl$ - $\alpha$ -Tocopherol,  $l$ - $\alpha$ -tocopherol, esters (succinate, acetate, phosphate),  $\beta$ ,  $\zeta_1$ ,  $\zeta_2$ -tocopherols

5. Inactive Analogs and Related Compounds:  $\delta$ ,  $\epsilon$ ,  $\eta$ -tocopherols
6. Antagonists:  $\alpha$ -tocopherol quinone, oxidants, cod liver oil, thyroxine
7. Synergists: Vitamins A, B<sub>6</sub>, B<sub>12</sub>, C, K, folic acid, estradiol, testosterone, STH
8. Physiological Functions
  - Biological antioxidant
  - Normal growth maintenance
  - Protects unsaturated fatty acids and membrane structures
  - Aids intestinal absorption of unsaturated fatty acids
  - Maintains normal muscle metabolism
  - Maintains integrity of vascular system and central nervous system
  - Detoxifying agent
  - Maintenance of kidney tubules, lungs, genital structures, liver and RBC membranes
9. Deficiency Diseases and Disorders
  - Laboratory animals—Degeneration of reproductive tissues, muscular dystrophy, encephalomalacia, liver necrosis
  - Man—Skin collagenosis, red cell hemolysis, xanthomatosis, cirrhosis of gall bladder, steatorrhea, creatinuria
10. Sources for Species Requiring It
  - Required by most organisms
  - Exogenous sources—Man and higher vertebrates, protozoa, some microorganisms
  - Endogenous sources—Plants, some microorganisms

## CHEMISTRY

### 1. Structure



**2. Reactions**

Heat—Labile	Oxidation—Labile
Acid—Stable	Reduction—Stable
Alkali—Labile	Light—Labile (esp. UV)
Water—Insol.	

**3. Properties**

Appearance—Yellow oil	Solubility
MW—430.7	H <sub>2</sub> O—Insol.
MP—2.5-3.5°C	Acet., Alc.—Sol.
Crystal Form—No data	Benz., Chl., Eth.—Sol.
Salts, Esters—Succinate, acetate, phosphate	Absn. Max.—292 m $\mu$ (alc.)
Important Groups for activity	Chemical Nature: Aromatic quinoid, alc.
Hydroxyl (alcoholic)	$\alpha_D^{25} = +0.32^\circ$ (alc.)

**4. Commercial Production:** Molecular distillation from vegetable oils**5. Isolation**

Sources—Wheat germ oil, soybean oil, rice oil  
 Method  
   Saponify oil with methanolic KOH  
   Nonsaponifiable fraction has vit. E, dissolve in ether  
   Remove sterols with digitonin precipitation  
   Remove xanthophylls with methanol extraction  
   Convert tocopherols to allophanate esters with HCN  
   Crystallize allophanates, hydrolyze, extract vit. E with ether

**6. Determination**

Bioassay  
   Rats—Prevent fetal resorption and RBC hemolysis  
   Chick—Liver storage  
 Physicochemical—Colorimetric 2-dimensional paper chromatography

**DISTRIBUTION AND SOURCES****1. Occurrence**

Plants  
   Fruit—Apples, olives

**Vegetables—Legumes, lettuce, spinach, corn, soybean (oil), mustard, cauliflower, green peppers, turnip greens, kale, kohlrabi, sweet potatoes**

**Nuts and Seeds—Coconuts, peanuts, palm (oil), cottonseed**

**Grains—Cereals, oils (rice, wheat) oats, brown rice, wheat germ, barley, rye**

#### **Animals**

**Birds—Eggs**

**Mammals—Liver, fat, muscle, milk, pituitary, adrenals, testes**

#### **Microorganisms: Yeast**

## **2. Dietary Sources**

**High: 50-300 mg/100 g**

Oil (cottonseed, corn, soybean, safflower, wheat germ)

Margarine

**Medium: 5-50 mg/100 g**

Oils (coconut, peanut, olive)

Wheat germ, apple seeds, alfalfa, barley, dry soybeans, peanuts

Chocolate, rose hips, yeast

Cabbage, spinach, asparagus

**Low: 0.5-5 mg/100 g**

Brussel sprouts, carrots, parsnips, mustard, corn, brown rice, lettuce, cauliflower, peas, sweet potatoes, turnip greens, kale, kohlrabi, green peppers

Bacon, beef, lamb, pork, veal, beef liver

Eggs, butter, cheese

Whole wheat flour, dried navy beans, corn meal, oatmeal, coconut, rye, oats, wheat

Blackberries, pears, apples, olives

## **MEDICAL AND NUTRITIONAL ROLE**

### **1. Units:**

1 mg *d*- $\alpha$ -tocopherol = 1.49 I.U.

1 mg *dl*- $\alpha$ -tocopherol acetate = 1 I.U.

### **2. Normal Blood Levels (Man): 1.11 mg/100 ml (serum)**

### **3. Recommended Allowances**

Children—10-15 I.U./day

Adults—25 I.U./day (females); 30 I.U./day (males)

**Special—Related to unsaturated fatty acid intake; increased requirements in pregnancy and lactation, detoxification, aging, stress**

#### **4. Administration**

Injection—Used for large doses

Topical—Creams, ointments

Oral—Preferred route

#### **5. Factors Affecting Availability**

Decrease

Presence of antagonists

Mineral oil ingestion

Presence of vit. E oxidation products

Occurrence with other less active analogues

Excretion in feces

Impaired fat absorption

Chemical binding in foods

Increased destruction (stress)

Cooking losses—Heat and O<sub>2</sub> labile

Losses in frozen storage, steatorrhea, variability of natural sources

Increase

Storage in (adipose and muscle) tissue

Esterification increases stability

Use of unprocessed fresh food sources

Absorption aids—Bile salts

#### **6. Deficiency Symptoms**

General

RBC hemolysis

Creatinuria

Xanthomatosis and cirrhosis of gall bladder

Steatorrhea (young)

Cystic fibrosis of pancreas (young)

Poorly developed muscles

Muscular dystrophy (rats, dogs, monkeys, chickens)

Myocardial degeneration (dogs, rabbits)

Resorption of fetus, degeneration of germ epithelium, disturbance of estrus cycle (rats)

Hepatic necrosis (rats)

Encephalomalacia (chickens)

Vascular degeneration (chickens)

7. Effects of Overdose: Possible increase in blood pressure

## METABOLIC ROLE

1. Biosynthesis

Precursors—Mevalonic acid—Side chain (?); phenylalanine—ring (?)  
Intermediates—Tocotrienol

2. Production: Species and Sites

Plants—Nuts, seeds, cereal germ, green leaves, legumes  
Fungi—Yeast  
Bacteria—Various

3. Storage Sites

Muscle—Small amounts  
Adipose tissues—Small amounts  
Liver—Small amount

4. Blood Carriers: Lipoproteins, globulins,  $\beta$ -Lipoproteins, chylomicrons

5. Half-life: 60-70% of daily dose ingested is excreted in feces  
30-40% absorbed portion—less than 1 week proportional to dose.

6. Target Tissues: Adrenals, pituitary, kidneys, genital organs, muscles, liver, lungs, bone marrow

7. Reactions

Data available on enzyme reactions is questionable as to extent of DIRECT involvement in enzyme reactions by Vitamin E. Evidently, Vitamin E's main role in enzyme reactions is indirect by way of maintenance or reducing conditions, stabilizations of various membranes, or some other undiscovered functions.

## 8. Mode of Action

### Cellular

Anabolic—Maintains protein synthesis by prevention of formation of enzyme-toxic peroxides from unsaturated fatty acid

Catabolic—Participates in oxidation-reduction reactions via CoQ and respiratory enzyme systems

Other—Protects unsaturated fatty acids against oxidation; maintains structure of cellular, mitochondrial, microsomal, and lysosomal membranes

### Organismal

Anabolic—increases N retention

Maintains kidney tubules and genital organs

Maintains muscle cell membranes

## 9. Catabolism

Intermediates—tocopheryl-*p*-quinone

Excretion products

Breath—CO<sub>2</sub>

Urine—Water soluble degradation products, tocopheronic acid glucuronate, tocopheronolactone glucuronate

## MISCELLANEOUS

### 1. Relationship to Other Vitamins

Vitamin C—Reduces oxidized vit. E back to vit. E in rats

Decreased synthesis of vit. C in vit. E deficient animals

Vitamin A—Conserved by vit. E in chick; protected against oxidation by vit. E; synergizes with vit. E in promoting growth and disease resistance

Vitamin B<sub>12</sub> and Folic Acid

Act with vit. E in treatment of macrocytic anemia

Vit. E can substitute for or potentiate vit. B<sub>12</sub>

Vitamin K and CoQ

Very similar in structure to vit. E

Pantothenic acid—Promotes synthesis of vit. E in plants

## 2. Relationship to Hormones

FSH and LH—Production increased in vit. E deficiency

Testosterone—Testicular degeneration due to vit. E deficiency in rats  
causes decreased production of testosterone

High content of vit. E in testicular tissues, seminal fluid

Cortisone—Requirements for cortisone and vit. E increase during stress.  
High content of vit. E at sites of cortisone synthesis in adrenal cortex

STH—A synergist in growth

## 3. Unusual Features

May be involved in aging mechanisms by protecting unsaturated fatty acids and membranes against free radicals

Only d-isomers occur naturally

Vitamin E replaceable by selenium salts in therapy of rat and pig liver necrosis, and chick exudative diathesis

Vitamin E replaceable by CoQ and antioxidants for certain symptoms of vit. E deficiency but not for all, e.g., RBC hemolysis, resorption gestation not affected.

Species differences in response to vit. E treatment of similar symptoms,  
e.g. muscular dystrophy—rabbits positive, humans negative

Other tocopherols only slightly active compared to vit. E

Decreased in tumors

## 4. Possible Relationships of Deficiency Symptoms to Metabolic Action

Muscular dystrophy, creatinuria (rabbit, monkey)—Maintenance of muscle cell membranes

RBC hemolysis (man)—Maintenance of red cell membranes

Fetal resorption (rats)—Maintenance of uterine membranes and uterine nerve ganglia

Mycardial degeneration (dog, rabbit)—Maintenance of muscle cell membranes

- Steatorrhea (man)—Impaired lipid absorption by intestinal cells; maintenance of intestinal cell membranes
- Encephalomalacia (chick)—Maintenance of nerve and membrane structures

# 6

# Vitamin K

## GENERAL INFORMATION

1. **Synonyms:** Antihemorrhagic vitamin, prothrombin factor, Koagulations-vitamin

2. **History**

- 1929—Dam reported chicks on synthetic diet develop hemorrhagic conditions
- 1935—Dam named vit. K as the missing factor in synthetic diet
- 1935—Almquist and Stokstad demonstrated vit. K present in fish meal and alfalfa
- 1939—Dam and Karrer isolated vit. K from alfalfa
- 1939—Doisy isolated K<sub>1</sub> from alfalfa, K<sub>2</sub> from fish meal, and demonstrated difference
- 1939—MacCorquodale, Cheney, Fieser determined structure of vit. K<sub>1</sub>
- 1939—Almquist and Klose synthesized vit. K<sub>1</sub>
- 1941—Link *et al.* discovered dicoumarol

3. **Physiological Forms**

Plant—Vitamin K<sub>1</sub> (phylloquinone, phytonadione)

Animal—Vitamin K<sub>2(20)</sub>

Bacterial—Vitamin K<sub>2</sub> (farnoquinone) (K<sub>2(30)</sub>, K<sub>2(35)</sub>)

4. **Active Analogs and Related Compounds**

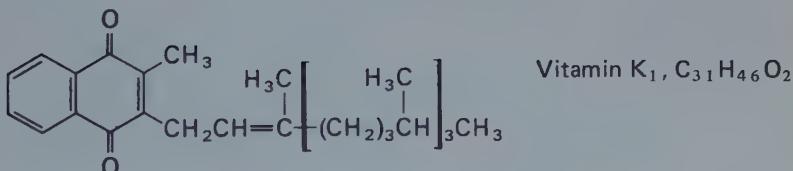
Menadiol diphosphate, menadione (vit. K<sub>3</sub>), menadione bisulfite

Phthiocol, synkayvite, menadiol (vit. K<sub>4</sub>), vits. K<sub>5</sub>, K<sub>6</sub>, K<sub>7</sub>

5. Inactive Analogs and Related Compounds: Reduced vit. K
6. Antagonists: Dicoumarol, sulfonamides, antibiotics,  $\alpha$ -tocopherol quinone, dihydroxystearic acid glycide, salicylates, iodinin, warfarin
7. Synergists: Vitamins E, A, C; STH
8. Physiological Functions: Prothrombin synthesis in liver, blood-clotting mechanisms, electron transport mechanisms, growth, photo-synthetic mechanisms
9. Deficiency Diseases, Disorders: Hypoprothrombinemia
10. Sources for Species Requiring It:
  - Many species require it
  - Exogenous sources: Vertebrates, some bacteria. (Intestinal bacteria provide in man)
  - Endogenous sources: Plants, bacteria, and all other organisms requiring it

## CHEMISTRY

### 1. Structure



### 2. Reactions

Heat—Stable	Oxidation—Stable
Acid—(Strong) labile	Reduction—Labile
Alkali—Labile	Light—Labile
Water—Insol.	

### 3. Properties

Appearance—Yellow oil	Important Groups for activity
MW—450.7	Menadiol nucleus
MP—20°C	Phytol side chain
Crystal Form—No data	<i>Trans</i> -methyl groups
Salts—Disodium phosphate	

Solubility	Absn. Max.—243, 249, 260,
H <sub>2</sub> O—Insol.	269, 325 m $\mu$ (hexane)
Acet., Alc.—Sol.	Chemical Nature: Quinone
Benz. Chl. Eth.—Sol.	$\alpha_D^{20} = -0.4^\circ\text{C}$ (benzene)

#### 4. Commercial Production: Column Chromatography of fish meal extracts

#### 5. Isolation

Sources—Fish meal, alfalfa

Method

Remove chlorophyll from pet. ether extract by column chromatography on ZnCO<sub>3</sub>

Reduce to hydroquinone using sodium hydrosulfite

Extract with pet. ether, alkali, ether

Oxidize hydroquinone to quinone

#### 6. Determination

Bioassay—Vitamin K deficient chick assay

Physicochemical—Polarographic methods; spectrophotometry of pure solutions; prothrombin time determination

### DISTRIBUTION AND SOURCES

#### 1. Occurrence

Plants:

Fruit—Orange (peel), tomato

Vegetables—Spinach, cabbage, brussel sprouts, alfalfa, cauliflower, soybean (oil)

Nuts and seeds—Hemp seed

Animals: Pork liver, eggs, milk, fish meal

Microorganisms: Intestinal bacteria, *M. phlei*

#### 2. Dietary Sources

High: 100-300  $\mu\text{g}/100\text{ g}$

Cabbage, cauliflower, soybeans, spinach

Pork, Beef liver, beef kidney

Medium: 10-100  $\mu\text{g}/100\text{ g}$

Potatoes, strawberries, tomatoes, alfalfa, wheat (whole, germ, bran), pine needles, egg yolk

Low: 0-10  $\mu\text{g}/100\text{ g}$

Corn, carrots, peas, parsley, mushrooms, milk

## MEDICAL AND NUTRITIONAL ROLE

**1. Units:** 0.0008 mg menadione = 20 dam units = 1 ansbacher unit

**2. Normal Blood Levels (Man):** Not reported

**3. Recommended Allowances**

Children—Supplied by intestinal bacteria normally

Adults—Supplied by intestinal bacteria normally

Special

Increases with external temperature

Newborn infants with neonatal hemorrhage

Mothers in labor

Overdosage with anticoagulants

**4. Administration**

Injection—Intravenous, intramuscular

Topical—No data

Oral—Occasionally

**5. Factors Affecting Availability**

Decrease

Biliary obstruction

Liver damage—cirrhosis, toxins

Poor food preparation conditions

Presence of antagonists

Impaired lipid absorption in gut

Ingestion of mineral oil

Sterilization of gut with antibiotics and sulfa drugs

Excretion in feces

Increase

Storage in liver

Absorption aids—bile salts

**6. Deficiency Symptoms**

Hypoprothrombinemia—General

Increased bleeding and hemorrhage—General

Increased clotting time—General

Neonatal hemorrhage—General

Internal hemorrhage (chick)

## 7. Effects of Overdose

Usually nontoxic, occasionally toxic  
 Possible thrombosis, vomiting, porphyrinuria—man  
 Albuminuria—dog  
 Increased clotting time—rabbit  
 Cytopenia, hemoglobinemia—mouse  
 Kernicterus (menadione)

## METABOLIC ROLE

### 1. Biosynthesis

Precursors—Polyacetic acid (ring); acetate (side chain)  
 Intermediates—Dehydroquinic acid (ring); farnesol (side chain)

### 2. Production: Species and sites

Plants—green leaves  
 Bacteria—intestinal (main source)

### 3. Storage Sites: Liver (small)

### 4. Blood Carriers: Lipoproteins

### 5. Half-life: Depletion causes deficiency within 10 days in rat

### 6. Target tissues: Liver, vascular system

### 7. Reactions

Coenzyme form—Vitamin K<sub>2(20)</sub>, CoQ(?)

<i>Organ</i>	<i>Enzyme System</i>	<i>Effect</i>
Electron transport		
Bacteria	Malate reductase	Activated
Bacteria	DPNH dehydrogenase	Activated
Liver	Vit. K reductase	Reduction of vit. K
Liver	Oxidative phosphorylation	Completes system
Liver	Respiratory chain	Completes system

## 8. Mode of Action

Cellular

Anabolic

Prothrombin synthesis (liver)

$\beta$ -Globulin synthesis (liver)

Photosynthesis-Hill reaction

Catabolic—Decreases phosphate incorporation into liver RNA

Other—Mitochondrial electron transport systems component

Organismal

Maintenance of prothrombin and clotting factors VII, IX, X

Control internal hemorrhage

Anabolic—Increase nitrogen retention

## 9. Catabolism

Intermediates—Lactones

Excretion products—As glucuronide and sulfate conjugates in urine, bile, feces

## MISCELLANEOUS

### 1. Relationship to Other Vitamins

Vitamin E—Synergistic to vit. K—Maintains reduced state similar in structure to vit. K<sub>1</sub> and probably interconvertible by way of CoQ and ubichromenols

Vitamins A and C—Fragility of RBC correlated with vits. A, C, K

### 2. Relationship to Hormones

STH—Synergist in growth

### 3. Unusual Features

Intestinal absorption of vit. K in chicks poor

Side chains of vit. K identical to those in ubiquinones (CoQ)

Completely supplied by intestinal flora in normal adults

Vitamin K lost on  $\gamma$ -irradiation of foods

### 4. Possible Relationships of Deficiency Symptoms to Metabolic Action

Hemorrhage—Decreased synthesis of prothrombin and other clotting factors by the liver

# 7

# Thiamine

## GENERAL INFORMATION

1. **Synonyms:** Vitamin B<sub>1</sub>, aneurin, antineuritic factor, antiberiberi factor, oryzamin
2. **History**
  - 1897—Eijkman ameliorated beriberi in humans by addition of rice polishings to diet
  - 1911—Funk isolated dietary growth factor from rice polishings which cured beriberi; coined term "vitamine"
  - 1915—McCollum and Davis proposed term "water-soluble B" for antiberiberi factor
  - 1920—Emmet and Luros demonstrated two growth factors in rice polishings, including antiberiberi factor destroyed by autoclaving
  - 1926—Jansen and Donath isolated crystalline antiberiberi factor from rice bran
  - 1927—Brit. Med. Res. Council proposed name of B<sub>1</sub> for antiberiberi factor
  - 1936—Williams synthesized B<sub>1</sub> and named it thiamine

### 3. Physiological Forms

- Thiamine pyrophosphate (cocarboxylase)—Animals
- Thiamine orthophosphate—Animals
- Free thiamine—Plants

**4. Active Analogs and Related Compounds**

Ethyl substituted for methyl on pyrimidine C-2

Thiamine disulfide, acylated thiamine

**5. Inactive Analogs and Related Compounds:** Reduced thiamine

**6. Antagonists:** Pyrithiamine, oxythiamine, 2-n-butyl homologue

**7. Synergists:** Vitamins B<sub>12</sub>, B<sub>2</sub>, B<sub>6</sub>, niacin, pantothenic acid, STH

**8. Physiological Functions:** Coenzyme in pyruvate metabolism; growth, appetite, digestion, nerve activity, gastrointestinal tonus, carbohydrate metabolism, energy production

**9. Deficiency Diseases, Disorders:** Beriberi, opisthotonus (in birds), polyneuritis, hyperesthesia, bradycardia, edema

**10. Sources for Species Requiring It**

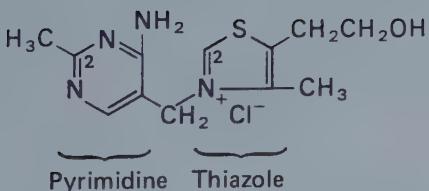
All species require it for life

Exogenous sources—All animals, some (algae, fungi, bacteria). Not much available from intestinal bacteria in man, although it is made there

Endogenous sources—Some (algae, fungi, bacteria), all higher plants. Sheep and cattle get sufficiency from intestinal bacteria

## CHEMISTRY

**1. Structure**



Thiamine hydrochloride,  
C<sub>12</sub>H<sub>17</sub>N<sub>4</sub>OSCl·HCl

**2. Reactions**

Heat—Labile

Acid—Stable

Alkali—Unstable

Water—Acid (HCl)

Oxidation—Forms thiochrome  
(fluoresc.)

Reduction—Unstable

Light—UV decomposes

**3. Properties**

Appearance—White crystals	Solubility
MW—337.3 (as HCl)	$H_2O$ —1 g/ml $H_2O$
MP—244°C	Alc.—sol.
Crystal Form— Monocl. plates	Acet. Benz., Chl., Eth.—Insol
Salts—Mononitrate, noble metals	Absn. Max.—235, 267 $\mu\mu$
Important Groups for activity —OH of $-CH_2CH_2OH$	Chemical Nature—Base, alc., substituted pyrimidine
C-2 of pyrimidine	Misc.—Charact. odor
C-2 of thiazole	$pK_a = 4.8, 9.2$
	$\alpha_D = 0$ (inactive)

**4. Commercial Production: Synthesis**

Pyrimidine + thiazole nuclei synthesized separately and then condensed  
 Build on pyrimidine with acetamidine

**5. Isolation**

Sources—Rice bran, wheat germ, yeast

Method—Aqueous extraction, adsorption on Fuller's earth; elute with quinine sulfate, precipitate as phosphotungstate, decompose precipitate and reprecipitate with  $AuCl_3$ , extract with water, precipitate from EtOH as hydrochloride

**6. Determination:**

Bioassay—Yeast fermentation; polyneuritic rat—rate of cure; bacterial metabolism

Physicochemical—Thiochrome fluorescence; polarographic; chromatographic; absorption at 235-267  $\mu\mu$  in neutral solution; at 247 in acid solution

**DISTRIBUTION AND SOURCES****1. Occurrence****Plants**

Fruit—All. Low (except gooseberries, plums, which are medium)

Vegetables—All. Low (except beans, green leafy types, cauliflower, corn, peas, potatoes—medium)

Nuts—All. Medium (except coconut, which is low)

Grains—All. Medium (except outer grain kernels, bran, polishings, wheat germ, which are high)

Animals: All—Medium (except pork, which is high, and some fish, which are low)

Microorganisms: Yeast (killed)—high. Intestinal bacteria not available  
Misc.—Mushrooms—medium

## 2. Dietary Sources

High: 1000-10,000  $\mu\text{g}/100 \text{ g}$

Wheat germ, rice bran, soybean flour

Yeast

Ham

Medium: 100-1000  $\mu\text{g}/100 \text{ g}$

Gooseberries, plums, prunes (dry), raisins (dry), asparagus, beans (kidney, lima, snap, soy, wax), beet greens, broccoli, brussel sprouts, cauliflower, chicory, endive, corn, dandelion greens, kale, kohlrabi, leeks, lentils (dry), parsley, peas, potatoes, watercress, barley, oats, rice (brown), almonds, brazil, cashews, chestnuts, hazelnuts, peanuts, pecans, walnuts

Beef, calf, chicken, pork, lamb, turkey meat and organs, mushrooms

Eggs, milk, carp, clams, cod, lobster, mackerel, oysters, salmon

Low: 10-100  $\mu\text{g}/100 \text{ g}$

Apples, apricots, avocados, bananas, berries (black-, blue-, cran-, rasp-, straw-), melons (cantaloupe, water, honeydew), cherries, currants, dates (dry), figs, grapes, grapefruit, lemons, oranges, peaches, pears, pineapples, prunes, tangerines

Artichokes, beets, cabbage, carrots, celery, cucumbers, eggplant, lettuce, onions, parsnips, peppers, pumpkins, radishes, rhubarb, spinach, sweet potatoes, turnips, coconut, cheeses, flounder

Haddock, halibut, herring, pike, sardines, scallops, shrimp, trout, tuna

## MEDICAL AND NUTRITIONAL ROLE

1. Units: 1 USP unit = 3  $\mu\text{g}$  thiamine HCl = 1 I.U.

2. Normal Blood Levels (Man): 1.3  $\mu\text{g}/100$  free base in serum. 3-11  $\mu\text{g}/100$  cocarboxylase in blood cells

3. Recommended Allowances

Children—0.6-1.1 mg/day

Adults—1.0 mg/day, female; 1.4 mg/day, male

Special—Increased requirements in pregnancy and lactation. Depends on body weight, calorie intake, intestinal synthesis and absorption, fat content of diet (increased pyruvate)

**4. Administration**

Injection—Intravenous, intraperitoneal

Topical—No data

Oral—Preferred route

**5. Factors Affecting Availability**

Decrease

Cooking—heat labile, water soluble

Enzymes in food; thiaminase for vitamin breakdown

Destruction by  $\text{CaCO}_3$ ,  $\text{K}_2\text{HPO}_4$ ,  $\text{MnSO}_4$

Nitrites, sulfites destroy

Diuresis, gastrointestinal diseases

Live yeast, alkali

Increase

Cellulose in diet increases intestinal synthesis

Small storage capacity in heart, liver, kidney

Bacterial synthesis in intestine (normally none)

**6. Deficiency Symptoms**

General (Man); beriberi

Anesthesia, hyperesthesia

Retarded growth, neuron degeneration

Fatigue, weight loss, anorexia, G.I. complaints, weakness, loss of reflexes, and vibratory sense

Circulatory and cardiac involvement

Mental disturbances—depression, irritability, memory loss

Muscular atrophy in extremities

Increased blood pyruvate and lactate

Lab animals

Decreased fat stores, decreased body temperature

Neurological disturbance—polyneuritis, decrease in tone

Bradycardia, cardiac enlargement, edema

Opisthotonus (chickens, pigeons, turkey)

**7. Effects of Overdose**

Humans—Limited toxicity, starting at approx. 125-350 mg/kg dosage.

Edema, nervousness, sweating, tachycardia, tremors, herpes, allergy, fatty liver, vascular hypotension

Rats—Sterility,  $\text{B}_6$  Deficiency

## METABOLIC ROLE

### 1. Biosynthesis

Precursors—Thiazole, pyrimidine pyrophosphate  
Intermediates—Thiamine phosphate

### 2. Production Sites

Plants—Grain and cereal germ  
Bacteria—Intestinal

### 3. Storage Sites: Heart, liver, kidney, brain (all small amounts)

### 4. Blood Carriers: Blood cells—As cocarboxylase. Serum—free B<sub>1</sub>

### 5. Half-life: 1 mg/day destroyed in tissues

### 6. Target Tissues: Heart, liver, kidney, peripheral nerves, brain

### 7. Reactions

Coenzyme Forms—cocarboxylase (thiamine pyrophosphate, disphosphothiamine). Needs Mg<sup>++</sup> ion

<i>Organ</i>	<i>Enzyme System</i>	<i>Effect</i>
Liver, plants	Transketolase	Activated
Serum	Choline esterase	Inhibited
Liver, yeast	Thiaminokinase—thiamine → cocarboxylase	Activated
Plants	Decarboxylases: Nonoxidative decarboxylation of pyruvate to OAA	Activated
Liver (mammals)	Oxidative decarboxylation of pyruvate with lipoic acid	Activated
Liver (mammals)	Phosphorolytic cleavage of α-keto acids	Activated
Liver (mammals)	Formation of acetoin	Activated
Liver (mammals)	Oxidative decarboxylation of α-ketoglutarate to succinate	Activated

### 8. Mode of Action

#### Cellular

Anabolic—Condensations, synthesis of acetylcholine

Catabolic—α-Keto acid decarboxylation (Krebs cycle coenzyme—ATP generation), oxidations, dismutations

Other—Transketolation, formation of NADPH, and ribose via HMP shunt, acyl transfer agent—"active" acetaldehyde

**Organismal**

- Maintenance of nerve tissues
- Maintenance of heart muscle
- Decrease blood pyruvate and lactate
- Maintain supply of ATP
- Normal growth maintenance

**9. Catabolism:** Intermediates—Pyrimidine. Excretion products—Pyrimidine and thiamine**MISCELLANEOUS****1. Relationship to Other Vitamins**

- Vitamin B<sub>12</sub>—Synergistic to B<sub>1</sub>
- Pantothenic Acid, Niacin, Riboflavin—Energy from oxidation of carbohydrates depends on synergism with thiamine (oxidative decarboxylation)
- Vitamin C—Decreases requirement for B<sub>1</sub>
- Vitamin B<sub>6</sub>—Overdose of B<sub>1</sub> causes B<sub>6</sub> deficiency in rats
- Vitamin D—Tolerance increased by vit. B<sub>1</sub>
- Riboflavin, Pyridoxine—Synergize with thiamine to produce niacin

**2. Relationship to Hormones**

- Acetylcholine—Synthesis requires vit. B<sub>1</sub>
- Thyroxine—Metabolic rate increase in hyperthyroidism increases B<sub>1</sub> requirement
- Insulin—In diabetes B<sub>1</sub> content of blood and liver reduced
- STH—Synergist in growth

**3. Unusual features**

- Hormonal function in plants—controls root growth
- Phosphorylation in liver, dephosphorylation in kidney
- Vitamin B enzymes easily poisoned by heavy metals, mustard gas, acetyl iodide
- Plant and animal cocarboxylases identical
- Has a diuretic effect, is constipative
- Can be allergenic on injection
- Blood contains most cocarboxylase in leukocytes
- Thiamine sparing action by alcohol, fat, protein
- Not available from intestinal bacteria

**4. Possible Relationships of Deficiency to Metabolic Action**

Flooding of system with pyruvate

Weight loss

G.I. complaints

Fatigue

Anorexia

Decreased synthesis of acetylcholine

Polyneuritis

Mental disturbances

Circulatory and cardiac involvement

# 8

# Riboflavin

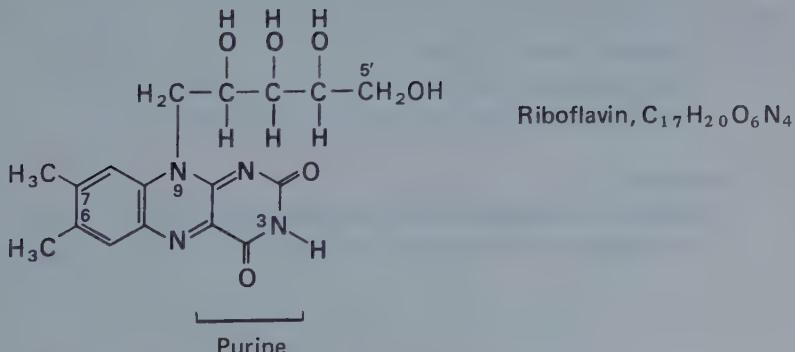
## GENERAL INFORMATION

- 1. Synonyms:** Vitamin B<sub>2</sub>, vit. G, lactoflavin, hepatoflavin, ovoflavin, verdoflavin, 6,7-dimethyl-9-(d-1'-ribityl)isoalloxazine
- 2. History**
  - 1917—Emmet and McKim showed dietary growth factor for rats in rice polishings
  - 1920—Emmett suggested presence of several dietary growth factors in yeast concentrate, including heat-stable component and B<sub>1</sub>
  - 1927—Brit. Med. Res. Council proposed name of B<sub>2</sub> for heat-stable component
  - 1932—Warburg and Christian isolated yellow enzyme (containing riboflavin (FMN)) from bottom yeast
  - 1933—Kuhn isolated pure B<sub>2</sub> (riboflavin) from milk; recognized growth promoting activity
  - 1935—Kuhn *et al.*; Karrer *et al.*—Achieved structure and synthesis of vit. B<sub>2</sub>; named it riboflavin
  - 1954—Christie *et al.* determined structure and synthesized FAD
- 3. Physiological Forms:** Riboflavin mononucleotide (FMN). Riboflavin dinucleotide (FAD)
- 4. Active Analogs and Related Compounds:** 7-Methyl-9-methyl, and 6-ethyl-7-methyl compounds, arabinoflavin

5. Inactive Analogs and Related Compounds: 3,6,7-T trimethyl-9-(d-1'-ribityl)isoalloxazine
6. Antagonists: Isoriboflavin, lumiflavin, araboeflavin, hydroxyethyl analogue, formyl methyl analogue, galactoflavin, flavin mono-SO<sub>4</sub>
7. Synergists: Vitamins A, B<sub>1</sub>, B<sub>6</sub>, B<sub>12</sub>, niacin, pantothenic acid, folic acid, biotin, T4, insulin, STH
8. Physiological Functions
  - Coenzyme in respiratory enzyme systems
  - Constituent of flavoproteins, redox systems, respiratory enzymes
  - Growth and development of fetus
  - Maintenance of mucosal, epithelial, and eye tissues
9. Deficiency Diseases, Disorders: Glossitis, cheilosis, seborrheic dermatitis, corneal vascularization, anemia
10. Sources for Species Requiring It
  - All organisms require it
  - Endogenous sources—Higher plants, algae, some bacteria, some fungi
  - Exogenous sources—All animals, some fungi and bacteria (intestinal bacteria make it, but most is unavailable to man)

## CHEMISTRY

### 1. Structure



## 2. Reactions

Heat—Blackens at 240°C  
 Acid—Stable  
 Alkali—Labile → lumiflavin  
 Water—Soluble, acidic

Oxidation—Decomposes  
 Reduction—Easily → leucoriboflavin  
 Light—Photolyses to lumiflavin  
 Intense green fluorescence  
 $565 \text{ m}\mu$

## 3. Properties

Appearance—Orange-yellow powder  
 MW—376.4  
 MP—282°C  
 Crystal Form—Needles  
 Salts—Borate,  $\text{PO}_4$ , acetate  
 Important Groups  
 9-N, 5'-OH  
 6,7-methyl  
 3-N

Solubility  
 $\text{H}_2\text{O}$ —Sol. 0.01 g/100 ml  
 Acet., Alc.—Insol.  
 Benz., Chl., Eth.—Insol.  
 Absn. Max.—220, 267, 336,  
 $446 \text{ m}\mu$   
 Misc.— $\text{pI} = 6$   
 $[\alpha]_D^{20} = -114^\circ$  (0.1 N NaOH)  
 Chemical Nature  
 Reducing agent; nucleotide  
 Substituted purine

## 4. Commercial Production

Fermentation bacteria or yeast  
 Chemical synthesis from alloxan, ribose, and *o*-xylene

## 5. Isolation

Sources—Free—urine, whey, retina. Combined—as FMN or FAD—tissues or egg whites

### Method

Aq. extract of tissue treated with ether  
 Fractional pptn. with picric acid  
 Ppt. out proteins with ammon sulfate  
 Adsorb on Fuller's earth  
 Elute with 0.1 N NaOH  
 Crystallize from aq. pet. ether-acetone mixture

## 6. Determination

Bioassay—Rats—growth rate. Microbiological—*L. caseii*, *L. mesenteroides*  
 Physicochemical—Fluorimetry, paper electrophoresis, polarography

## DISTRIBUTION AND SOURCES

### 1. Occurrence

#### Plants

Fruit—All. Low

Vegetables—All. High in tomato leaves. Medium in green leafy types, corn, cauliflower, beans. Low in others

Nuts—All. Medium except coconut (low)

Flowers—Saffron (high)

Animals—All (liver > kidneys > heart > other tissues). High in organs, medium in other tissues. Crustaceans—High

Microorganisms: All, esp. yeast, anaerobic bacteria (high)

### 2. Dietary Sources

High: 1000-10,000  $\mu\text{g}/100 \text{ g}$

Beef (kidneys, liver), calf (kidney, liver)

Chicken (liver)

Pork (heart, kidneys, liver), sheep (liver, kidneys)

Yeast (killed)

Medium: 100-1000  $\mu\text{g}/100 \text{ g}$

Avocados, currants

Asparagus, beans (kidney, lima, snap, wax), beet greens, broccoli, brussel sprouts, cauliflower, chicory, endive, corn, dandelion greens, kale, kohlrabi, lentils (dry), parsley, parsnips, peas, soybeans (dry), spinach, turnip greens, watercress, almonds (dry), cashews, peanuts, pecans, walnuts, rice bran, wheat germ, oats, cheeses, cream, eggs, milk

Bacon, beef, chicken, duck, goose, pork, lamb, turkey, veal, fish

Low: 10-100  $\mu\text{g}/100 \text{ g}$

Apples, apricots, bananas, blackberries, blueberries, cranberries, raspberries, strawberries, cherries, grapes, grapefruit, melons, oranges, peaches, dates (dry), figs, pears, pineapples, plums, raisins (dry), tangerines, artichokes, beets, cabbages, carrots, celery, cucumbers, eggplant, lettuce, onions, peppers, potatoes, pumpkins, radishes, sweet potatoes, tomatoes, turnips, coconuts, barley, rice

## MEDICAL AND NUTRITIONAL ROLE

### 1. Units: By weight, $\mu\text{g}$ or mg

### 2. Normal Blood Levels: 6.6 $\mu\text{g}/100 \text{ ml}$

**3. Recommended Allowances**

Children—0.6-1.2 mg/day \*

Adults—1.5 mg/day female\*; 1.7 mg/day male\*

**4. Administration**

Injection—I.V.

Topical—No data

Oral—Preferred route

**5. Factors Affecting Availability**

Decrease

Cooking (sl. sol. in H<sub>2</sub>O)

Plant foods—Lower availability, bound forms

Decreased phosphorylation in intestines prevents absorption

Exposure of foods to sunlight

Enzymes for breakdown

Gastrointestinal disease

Diuresis

Increase

Storage in heart, liver and kidneys

Very actively producing intestinal bacteria (small amount)

**6. Deficiency Symptoms**

General

Orogenital syndrome

Stomatitis

Glossitis

Cheilosis

Seborrheic dermatitis

Ocular—Photophobia, indistinct vision, corneal vascularity increased

Rats

Poor growth, ocular abnormality

Dermatitis (eczema—nostrils, eyes)

Myelin degeneration, testicular atrophy

Thymus involution

Dogs

Weight loss, fatty liver, muscle weakness

Opacity of corneal epithelium

\* Related to caloric intake and protein levels. Increased in pregnancy, lactation. Additional sources in intestinal bacteria (small).

Chicken

Egg production and hatchability decline, nerve degeneration

Monkey

Anemia, leukopenia

## 7. Effects of Overdose

Essentially nontoxic in man

Anuria—rat

Azotemia—rat

Kidney insufficiency—rat

Paresthesia—man

Itching—man

## METABOLIC ROLE

### 1. Biosynthesis

Precursors—Purines, pyrimidines, ribose

Intermediates—6,7-Dimethyl-8-ribityllumazine

### 2. Production Site

Plants—Leaves, germinating seeds, root nodules

Bacteria—Intestinal

### 3. Storage Sites: Heart, liver, kidneys (small amount)

### 4. Blood carriers: As nucleotides

### 5. Half-life: 12% of intake excreted in 24 hr

### 6. Target Tissues: Heart, liver, kidneys, others in lesser amount

### 7. Reactions

Coenzyme forms

Redox couple: oxidized  $\rightleftharpoons$  reduced form

FMN, FAD (binding to apoenzyme via cations ( $\text{Fe}^{++}$ ,  $\text{Cu}^{++}$ ,  $\text{Mo}^{++}$ ) to  $\text{PO}_4$  of coenzyme)

<i>Organ</i>	<i>Enzyme System</i>	<i>Effect</i>
Liver	(1) FMN—Warburg yellow enzyme, cytochrome C reductase, l-amino acid oxidase, succinic dehydrogenase	Activated
Liver	(2) FAD—Xanthine oxidase, d-amino acid oxidase, glycine oxidase, diaphorase, fumaric dehydrogenase, glucose oxidases, histaminases, aldehyde oxidase	Activated
Intestine	(3) Flavokinase—Phosphorylation of riboflavin	Activated

## 8. Mode of Action

### Cellular

Anabolic—No data

Catabolic—Carbohydrate metabolism

Other—Essential complexed part of flavoproteins

Mitochondrial electron transport system

Oxidation-reduction enzyme systems

Accepts 2H on isoalloxazine ring

Part of respiratory enzyme system

### Organismal

Ectodermal maintenance—skin and cornea

Growth and development of fetus

Maintenance of nervous system (myelin sheath)

Resistance to disease

## 9. Catabolism

Intermediates—No data

Excretion products

Urine—Free vitamin—Diurnal variations. Normally ~1/3 of dietary amounts excreted

Feces—Uroflavin—Diurnal variations

## MISCELLANEOUS

### 1. Relationship to Other Vitamins

Vitamin A, Niacin—Present with riboflavin in visual structures (retina) involved in visual process

Niacin—Riboflavin enzymes utilize DPN, and DPNH

Thiamine—Deficiency of B<sub>1</sub> leads to increased storage of riboflavin.

Involved with riboflavin in thyroxine and insulin utilization in CHO metabolism

Other B vitamins—Synergistic with riboflavin

## 2. Relationship to Hormones

ACTH—Riboflavin involved in release of ACTH from pituitary  
Thyroxine, Insulin—Effective only if riboflavin and thiamine are present  
Thyroxine—Incorporation of iodide by sheep thyroid stimulated by FMN  
Adrenal hormones—Aid in phosphorylation of riboflavin in intestines  
Estradiol—Inactivation in liver decreased in riboflavin deficiency (rat)  
STH—Synergist in growth

## 3. Unusual Features

High levels in liver inhibit tumor formation by azo compounds in animals  
Free radicals formed by light or dehydrogenation: flavine  $\rightleftharpoons$  semi-quinone  $\rightleftharpoons$  dihydroflavin  
Free vitamin only in retina, urine, milk and semen  
Substitution of adenine by other purines, pyrimidines destroys activity of FAD  
Phosphorylation of vitamin in intestines allows absorption as FMN  
Blood levels decrease during life in humans  
Brain content remains constant  
Available in plants as FMN and FAD  
Concentrated in bull semen

## 4. Possible Relationships of Deficiency Symptoms to Metabolic Action

Ectodermal manifestations related to other B-vitamin deficiencies

Cheilosis  
Glossitis  
Stomatitis  
Seborrheic dermatitis  
Corneal vascularity  
Orogenital syndrome

Synergistic functions of vit. A and riboflavin in visual structures—Photophobia

# 9 Vitamin B<sub>6</sub>

## GENERAL INFORMATION

### 1. Synonyms: Pyridoxine, adermine, pyridoxol

### 2. History

- 1934—György cured a dermatitis in rats not due to B<sub>1</sub> or B<sub>2</sub> with yeast extract factor
- 1938—Lepkovsky isolated similar factor from rice bran extract
- 1938—Keresztesy and Stevens isolated and crystallized pure B<sub>6</sub> from rice polishings
- 1938—Kohn, Wendt, and Westphal synthesized pyridoxine, gave pyridoxine its name
- 1939—Stiller, Keresztesy, and Stevens established structure of pyridoxine
- 1945—Snell discovered pyridoxal and pyridoxamine
- 1953—Snyderman *et al.* first recognized and established B<sub>6</sub> requirement in humans

### 3. Physiological Forms

- Interconvertible *in vivo* (pyridoxine ⇌ pyridoxal ⇌ pyridoxamine)
- Animals—Pyridoxal-5-phosphate (codecarboxylase); pyridoxamine phosphate
- Plants—Pyridoxol-5-phosphate, pyridoxal-5-P, pyridoxamine-P

### 4. Active Analogs and Related Compounds: Pyridoxal, pyridoxamine

**5. Inactive Analogs and Related Compounds:** Nor-vitamin B<sub>6</sub>, 4-pyridoxic acid, 5-pyridoxic acid

**6. Antagonists:** 4-deoxypyridoxine, 4-methoxypyridoxine, toxopyrimidine, penicillamine, semicarbazide, isoniazid

**7. Synergists:** Vitamins B<sub>1</sub>, B<sub>2</sub>, C, E, niacin, biotin, folic acid, STH, glucagon, epinephrine, norepinephrine

### 8. Physiological Functions

Protein, CHO, and lipid metabolism

Coenzyme in many phases of amino acid metabolism; especially in gluconeogenesis, production of neural hormones, bile acids, unsaturated fatty acids, and porphyrins

Erythrocyte formation, growth

### 9. Deficiency Diseases, Disorders

Monkey—Arteriosclerosis

Rats—Acrodynia

Man—Lymphopenia, convulsions, dermatitis, irritability, nervous disorders

### 10. Sources for Species Requiring It

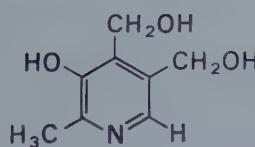
All animals require B<sub>6</sub>

Exogenous sources—Animals, some bacteria (intestinal bacteria make it, but not much is available to man)

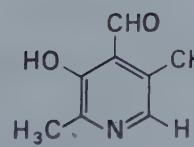
Endogenous sources—Plants, fungi, intestinal bacteria

## CHEMISTRY

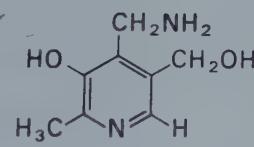
### 1. Structures



Pyridoxine, C<sub>8</sub>H<sub>11</sub>NO<sub>3</sub>



Pyridoxal



Pyridoxamine

**2. Reactions**

Heat—Stable  
Acid—Stable  
Alkali—Stable  
Water—Basic

Oxidation—Unstable  
Reduction—Unstable  
Light—Labile (stable in acid)

**3. Properties**

Appearance—White powder  
MW—169 pyridoxine  
MP—160° pyridoxine  
Crystal Form—Platelets  
Salts—Hydrochloride,  $\text{Ca}^{++}$   
Important Groups for activity  
— $\text{CH}_2\text{OH}$   
—N=

Solubility  
 $\text{H}_2\text{O}$ —0.2 g/ml  
Acet., Alc.—Sol.  
Benz., Chl., Eth.—Insol.  
Absn. Max.—256, 327 m $\mu$   
pH 7.0  
Chemical Nature  
hydroxylated weak nitrogen base,  
substituted pyridine  
 $\text{pKa} = 5.0, 8.9$   
 $\alpha D = 0$  (inactive)

**4. Commercial Production**

Commercially available as pyridoxine hydrochloride  
Synthesized by method of Harris and Folkers. Ethoxy acetylacetone  
condensed with cyanoacetamide  
Easiest route for synthesis is probably from oxazoles

**5. Isolation**

Sources—Rice polishings or bran and yeast  
Methods  
Adsorption on Fuller's earth or charcoal  
Elute with  $\text{Ba}(\text{OH})_2$   
Precipitate impurities with heavy metals  
Precipitation with phosphotungstic acid

**6. Determination**

Bioassay—Animal  
Rat acrodynia test  
Rat growth and chicken growth assays  
Tryptophane loading test  
Blood cell  
Bioassay—Microbial—Microbioassay  
Physicochemical—Photofluorometric procedure detects 4-pyridoxic acid—  
(major metabolite) in urine. Chromatographic procedure to detect  
4-pyridoxic acid

## DISTRIBUTION AND SOURCES

### 1. Occurrence

#### Plants

Fruit—All low, except bananas, avocados, grapes, pears (medium)

Vegetables—All low or medium

Nuts—All high

Misc.—Cereals—medium, except brown rice, wheat germ (high); and blackstrap molasses (high)

Animals: All medium, except herring, salmon, liver (high)

Microorganisms: All high or medium—yeast, intestinal bacteria (high); some other bacteria

### 2. Dietary Sources

High: 1000-10,000 µg/100 g

Liver (beef, calf, pork), herring, salmon

Walnuts, peanuts, wheat germ, brown rice

Yeast, blackstrap molasses

Medium: 100-1000 µg/100 g

Bananas, avocados, grapes, pears

Barley, cabbage, carrots, corn, oats, peas, potatoes, rye, kale, tomatoes, turnips, yams, brussel sprouts, cauliflower, spinach, soybeans, wheat

Beef, lamb, pork, veal (heart, brains, kidney); cod, flounder, halibut, mackerel, whale, sardines, tuna

Butter, eggs

Low: 10-100 µg/100 g

Apples, cantaloupes, grapefruit, lemons, oranges, peaches, raisins, strawberries, watermelons, cherries, currants (red)

Asparagus, beans, beet greens, lettuce, onions

Cheese, milk

## MEDICAL AND NUTRITIONAL ROLE

### 1. Units: By weight, mg

### 2. Normal Blood Levels: 11.2 ug/100 ml

### 3. Recommended Allowances

Children—0.5-1.2 mg/day \*

Adults—2.0 mg/day \*

Special—Pregnancy and lactation, 2.5 mg/day

\* Depends on protein content of food and inborn errors of metabolism; irradiation increases need.

**4. Administration**

- Injection—Intravenous, subcutaneous
- Topical—No data
- Oral—Preferred route

**5. Factors Affecting Availability**

Decrease

- Administration of isoniazid
- 30-45% loss in cooking, water sol.

Diuresis, G.I. diseases

Irradiation

Increase

- Intestinal bacterial production (very small amount)
- Storage in liver

**6. Deficiency Symptoms**

General

- Cutaneous lesions
- Anemia
- Neuronal dysfunction including convulsions
- Increased excretion of xanthurenic acid

Lab Animals

- Blood urea and urea excretion enhanced
- $\gamma$ -globulin and hemoglobin decreased
- Urinary oxalate increased
- Insulin insufficiency
- Acrodynia
- Demyelinization of peripheral nerves
- Tonic-clonic convulsion
- Adrenal—enlarged zona fasciculata
- Poor reproduction

**7. Effects of Overdose**

- Limited toxicity man (only at 3 g/kg dosage)
- Convulsions at 4 g/kg (rat)

**METABOLIC ROLE****1. Biosynthesis**

- Precursors—Possibly glycine, serine or glycolaldehyde
- Intermediates—Unknown

**2. Production: Species and Site**

Plants—Fungi, cereal germ, seeds

Bacteria—Intestinal

Animals—None

**3. Storage Site: Muscle phosphorylase (skeletal muscle) (small amount)****4. Blood Carriers: Blood protein complexes****5. Half-life: 57% of ingested dose excreted per day****6. Target Tissues: Nervous tissue, liver, lymph nodes, muscle tissue****7. Reactions**

Coenzyme forms—Codecarboxylase (pyridoxal-5-phosphate); pyridoxamine phosphate; Cu, Fe, Al chelates of coenzymes probably are active forms

<i>Organ</i>	<i>Enzyme System</i>	<i>Effect</i>
Liver	1. Transaminases (glutamic, aspartic)	Activated
Liver	2. Amino acid decarboxylases (histidine)	Activated
Liver	3. Tryptophan metabolism (kynureninase)	Activated
Liver	4. Tyrosine and phenylalanine metabolism	Activated
Muscle	5. Phosphorylases (constituent of)	Completed
Liver	6. Dehydrases (porphyrin synthesis, serine)	Activated
Liver	7. Racemases (alanine racemase)	Activated
Liver	8. Oxidases (diamine)	Activated
Liver	9. Desulfhydrases (cysteine)	Activated
Liver	10. Serine transhydroxymethylase	Activated

**8. Mode of Action****Cellular**

Anabolic—Unsaturated fatty acid biosynthesis

Catabolic—Nonoxidative metabolic changes, decarboxylations, transaminations, glycogen phosphorylation

Other—amino acid absorption and transport

**Organismal**

Growth, maintenance of adrenal cortex

Production of niacin, norepinephrine, serotonin, histamine, acetylcholine,  $\gamma$ -aminobutyric acid

Production of bile acids (taurine synthesis)

Erythrocyte formation, gluconeogenesis and glycogenolysis reactions

## 9. Catabolism

Intermediates—All converted to pyridoxal

Excretion products

Urine—4-pyridoxic acid (3-4 mg/day); pyridoxal (0.2-0.3 mg/day)

Feces—0.5-0.8 mg/day

## MISCELLANEOUS

### 1. Relationship to Other Vitamins

Pantothenic acid—B<sub>6</sub> defic. results in lowered concentration of co-enzyme A

B<sub>12</sub>—B<sub>6</sub> defic. results in reduced absorption and storage of B<sub>12</sub>

Vitamin E—B<sub>6</sub> synergizes with E to control metabolism of unsaturated fats

Vitamin C—Excretion of C increased in B<sub>6</sub> deficiency, conversion of vit. C to oxalates increased, i.e., oxaluria. Helps alleviate some symptoms of B<sub>6</sub> deficiency. Synergizes with B<sub>6</sub> in tyrosine metabolism

Niacin—B<sub>6</sub> coenzyme for niacin synthesis from tryptophan, also synergistic

Vitamin B<sub>1</sub>—Overdose of B<sub>1</sub> causes B<sub>6</sub> deficiency in rats, synergistic

Vitamin B<sub>2</sub>—Synergistic in action with B<sub>6</sub>

Biotin—Synergistic with B<sub>6</sub>, B<sub>2</sub> and niacin in skin maintenance

### 2. Relationship to Hormones

Thyroxine—decreases the activity of various pyridoxalphosphate dependent enzyme systems

Insulin—Insufficiency of insulin in B<sub>6</sub> deficiency in animals

Norepinephrine, Acetylcholine, serotonin, epinephrine—B<sub>6</sub> involved in synthesis of these hormones

ACTH—Adrenal cortex zona fasciculata enlarged (hypertrophied) on B<sub>6</sub> deficiency

B<sub>6</sub> possibly involved in synthesis and function of these hormones (STH a synergist in growth)

STH

Estradiol-17 $\beta$

Testosterone

FSH

LH

Cortisol  
Aldosterone  
Epinephrine  
Glucagon

### 3. Unusual Features

- Involved in dental caries, oxaluria
- Linoleic acid relieves dermatitis symptoms of B<sub>6</sub> deficiency
- Presence of B<sub>6</sub> in phosphorylase a and b in large amounts implicates glucagon, epinephrine, and norepinephrine in function of B<sub>6</sub>
- Great diversity of deficiency symptoms depending on species
- Heavy metal ion involved in binding to enzyme
- Involvement in stress, electrolyte balance, energy production, and water metabolism by unknown pathways

### 4. Possible Relationships of Deficiency Symptoms to Metabolic Action

- Cutaneous lesions—Synergism of B<sub>6</sub> with niacin and B<sub>2</sub> for skin maintenance
- Convulsions—Synergism of B<sub>6</sub> with B<sub>1</sub> involved in nervous tissue maintenance
- Xanthurenic acid excretion—Kynureninase requires B<sub>6</sub> as coenzyme
- Anemia—Synergism of B<sub>6</sub> with B<sub>12</sub> for anti-anemic action, maintenance of erythrocyte production

# 10

# Vitamin B<sub>12</sub>

## GENERAL INFORMATION

**1. Synonyms:** Cobalamin, cyanocobalamin

**2. History**

1926—Minot and Murphy controlled pernicious anemia using liver

1944—Castle demonstrated intrinsic factor needed to control pernicious anemia with liver

1948—Rickes *et al.* isolated and crystallized factor in liver controlling pernicious anemia

1948—Smith and Parker crystallized and designated liver factor as vit. B<sub>12</sub>

1948—West demonstrated clinical activity of vit. B<sub>12</sub>

1955—Hodgkin *et al.* determined structure of vit. B<sub>12</sub>

**3. Physiological Forms:** Hydroxocobalamin (vit. B<sub>12a</sub>). Aquocobalamin (vit. B<sub>12b</sub>)

**4. Active Analogs and Related Compounds**

Nitrocobalamin (vit. B<sub>12c</sub>), chlorocobalamin, thiocyanatocobalamin

**5. Inactive Analogs and Related Compounds (in Man)**

ψ-Vitamin B, factors B, C, D, E, F, G, H, I

**6. Antagonists:** Methylamide, ethylamide, anilide, lactone derivatives, pteridine, nicotinamide

**7. Synergists:** Vitamins A, E, C, B<sub>1</sub>, folic acid, biotin, pantothenic acid,

**8. Physiological Functions**

Coenzyme in nucleic acid, protein and lipid synthesis

Maintain growth, nucleic acid synthesis, protein synthesis, lipid synthesis, and methylations

Maintain epithelial cells and nervous system (myelin sheath), erythropoiesis (with folic acid) and leukopoiesis

**9. Deficiency Diseases, Disorders:** Retarded growth, pernicious anemia, megaloblastic anemia, macrocytic, hyperchromic anemia, glossitis, spinal cord degeneration, sprue

**10. Sources for Species Requiring It**

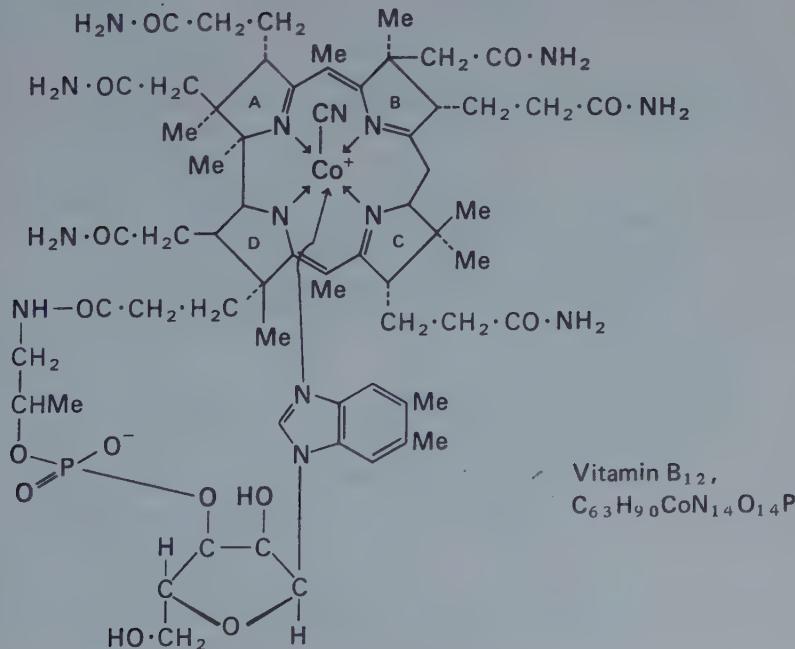
Required by most vertebrates, some protozoa, bacteria, algae

Exogenous sources—Vertebrates, some bacteria, protozoa, algae (not available from intestinal bacteria in man)

Endogenous sources—Bacteria, actinomycetes

## CHEMISTRY

**1. Structure**



**2. Reactions**

Heat—Unstable  
Acid—Unstable  
Alkali—Unstable  
Water—Neutral

Oxidation—Unstable  
Reduction—Unstable  
Light—Unstable

**3. Properties**

Appearance—red powder  
MW—1357  
MP—Blackens at 190°C  
Crystal Form—Orthorhombic needles  
Salts—Perchloric acid  
Important Groups for activity  
    5,6-Dimethylbenzimidazole  
     $\alpha$ -Ribothiazole

Solubility  
H<sub>2</sub>O—1.25 g/100 ml  
Alc.—sol.  
Acet., Benz., Chl., Eth.—Insol.  
Absn. Max.—278, 361,  
    550 m $\mu$  (H<sub>2</sub>O)  
[ $\alpha$ ]<sub>D</sub><sup>23</sup> = -59° (aq. soln.)  
Chemical Nature  
    Polyacidic base  
    Benzimidazole nucleotide  
    Porphyrin-like corrin  
    Reducing agent

**4. Commercial Production**

Fermentation of *S. griseus* or *S. aureofaciens*  
By-product of antibiotic production

**5. Isolation**

Sources—Liver, fish solubles  
Method  
    Extract with aqueous alcohol  
    Adsorb B<sub>12</sub> on charcoal, elute with 65% alcohol  
    Column chromatography on silica or alumina  
    Wash with acetone, elute with alcohol  
    Crystallize

**6. Determination**

Bioassay  
    Microbial—*L. leichmanii*, *O. malhamensis*, *E. gracilis*  
    Animal—Chick and rat—curative dose  
Physicochemical—Spectrophotometry, polarography, isotope dilution

## DISTRIBUTION AND SOURCES

### 1. Occurrence

Plants: Vegetables—Very low—soybeans, green beans, beets, carrots, peas

Nuts, seeds—Very low—oats, wheat

Animals: All animals, especially in organs—Liver, kidney, heart, spleen, brain, stomach, intestine

Eggs, milk

Microorganisms: *S. aureofaciens*, *B. megatherium*, protozoa, soil bacteria, intestinal bacteria

Miscellaneous: Sea water, sewage sludge

### 2. Dietary Sources

High: 50 µg-500 µg/100 g

Kidney (lamb, beef)

Liver (lamb, beef, calf, pork)

Brain (beef)

Medium: 5-50 µg/100 g

Kidney (rabbit)

Liver (rabbit, chicken)

Heart (beef, rabbit, chicken)

Egg yolk

Clams, sardines, salmon, crabs, oysters, herring

Low: 0.5-5 µg/100 g

Cod, flounder, haddock, halibut, lobster, scallop, shrimp, swordfish, tuna, whale

Beef, pork lamb, chicken

Cheeses, milk, eggs

## MEDICAL AND NUTRITIONAL ROLE

1. Units: 1 USP = 1 µg vit. B<sub>12</sub> = 11,000 LLD units (*L. lactis Dorner* units)

2. Normal Blood Levels (Man): 0.08 µg/100 ml (0.03 µg/100 ml, serum)

### 3. Recommended Allowances

Children—2-5 µg/day

Adults—5-6 µg/day

Special—Pregnancy, 8 µg/day; lactation, 6 µg/day; intestinal malabsorption or disease; anorexia; old age; neuropathies; malnutrition; alcoholism

#### 4. Administration

Injection—Parenteral, intramuscular

Topical—No data

Oral—Not very effective unless intrinsic factor (enzyme) present

#### 5. Factors Affecting Availability

Decrease

Cooking losses—Heat labile

Cobalt deficiency (ruminants)

Intestinal malabsorption or parasites

Lack of intrinsic factor

Intestinal disease, aging

Vegetarian diet

Excretion in feces

Gastrectomy

Increase

Administration of sorbitol

Synthesis by intestinal bacteria (not normally)

Reduced temperature

Food in stomach

#### 6. Deficiency Symptoms

Poor growth

Increased hemolysis of RBC's

Megaloblastic marrow

Macrocytic, hyperchromic anemia

Glossitis

Degenerative changes in spinal cord, nervous symptoms

Decreased blood and tissue lipids

Disturbed carbohydrate metabolism—excretion of methylmalonic acid

Leukopenia

Gastrointestinal tract changes

Loss of hatchability } Chickens

Poor feathering }

Reproductive failure } Rats

Porphyrin whiskers }

Dermatitis }

Impaired reproduction } Pigs

#### 7. Effects of Overdose, Excess

Polycythemia reported

General lack of toxicity

## METABOLIC ROLE

### 1. Biosynthesis

#### Precursors

- Glycine—corrin nucleus
- $\delta$ -Aminolevulinic acid—corrin nucleus
- Methionine—corrin nucleus

#### Intermediates

- Porphobilinogen
- $\alpha$ -d-Ribosides of benzimidazole
- 5,6-Dimethylbenzimidazole
- $\alpha$ -Ribazole

2. Production: Species—Bacteria (some); actinomycetes (some)

3. Storage: Liver (30-60%), lungs, kidneys, spleen

4. Blood Carriers:  $\alpha_1$ -Globulins (52%),  $\alpha_2$ -globulins (21%), Albumins (16%),  $\beta$ -globulins (7%),  $\gamma$ -globulins (6%)

5. Half-life: > 1 year

6. Target Tissues: Central nervous system, kidneys, myocardium, muscle, skin, bone

### 7. Reactions

#### Coenzyme forms

- Adenyl cobamide coenzyme (adenyl nucleoside)
- 5,6-Dimethylbenzimidazolylcobamide coenzyme
- Benzimidazolylcobamide coenzyme

Organ	Enzyme System	Effect
MUTASES		
Liver	Glutamate mutase (glut—aspartic)	Activated
Liver	Methylmalonyl CoA mutase (methyl malonic—succinic)	Activated
DEHYDRASES		
Liver	Diol dehydrase (glycerol-1,3-propanediol)	Activated
Liver	Glycerol dehydrase (glycerol- $\beta$ -OH-propionaldehyde)	Activated
Liver	Ethanolamine deaminase (ethanolamine-ammonia, acetaldehyde)	Activated

**TRANSMETHYLASES**

Liver            B<sub>1,2</sub> enzyme (homocysteine—methionine) with folate            Activated

Liver            Thymidine synthesis enzymes (purine biosynthesis)            Activated

**REDUCTASES**

Liver            Methane formation enzymes            Activated

Liver            Ribonucleotide reductase (ribonucleotide—deoxyribonucleotide)            Activated

Liver            Lysine fermentation enzymes            Activated

Liver            Acetate synthesis enzymes            Activated

**8. Mode of Action**

## Cellular

## Anabolic

DNA synthesis (nucleolar methylations, ribotide conversion)

RNA synthesis (purine synthesis, nucleolar methylation)

Protein synthesis (DNA synthesis, methionine synthesis)

Synthesis of lipids

Porphyrin synthesis

Anabolic action—mitosis and growth

Choline synthesis

## Catabolic

Carbohydrate metabolism (propionic acid)

Lipid metabolism (glycerol, ethanolamine)

## Other

Maintenance of membranes, esp. myelin sheath

Maintenance of —SH groups in reduced form

## Organismal

Maintains epithelial and mucosal cells

Maintains normal bone marrow

Maintains normal G.I. tract

Maintains normal CNS

Maintains erythropoiesis and leukopoiesis

Maintains body lipids, lipotropic

Maintains normal growth

Improves nitrogen retention

**9. Catabolism**

Intermediates—No body destruction

Excretion products

Urine—0.131 µg/day (free)

Feces—34% of ingested dose

Bile—Some reabsorption (enterohepatic recirculation)

## MISCELLANEOUS

### 1. Relationship to Other Vitamins

Folic acid—Active with B<sub>12</sub> in nucleic acid and methionine synthesis; combined action with vit. B<sub>12</sub>; deficiency of F.A. increases B<sub>12</sub> absn.

Vitamin A—Uptake and utilization of carotenes increased with B<sub>12</sub> in diet; maintenance of mucosal and epithelial cells

Vitamin B<sub>6</sub>—Deficiency reduces B<sub>12</sub> absorption in gut

Biotin—Active with B<sub>12</sub> in methylmalonyl CoA metabolism

Niacin—B<sub>12</sub> deficiency causes decrease in liver NAD

Pantothenic acid—B<sub>12</sub> participates in methylmalonyl CoA conversion; has sparing action of B<sub>12</sub> and vice versa

Riboflavin—Possible synthesis from 5,6-dimethylbenzimidazole moiety of B<sub>12</sub>

Vitamins E, C—Can substitute for vit. B<sub>12</sub> in certain conditions and synergize it; synergize vit. B<sub>12</sub> in treatment of macrocytic anemia

Vitamin B<sub>1</sub>—Synergistic to B<sub>12</sub>

### 2. Relationship to Hormones

T4-Deficiency of T4 impairs B<sub>12</sub> absorption

Antithyroid antibodies in serum of B<sub>12</sub> deficient patients

Increased T4 produces loss of B<sub>12</sub>

Parathormone—Pernicious anemia found coexisting with hypoparathyroidism (Ca metabolism)

STH—B<sub>12</sub> needed for mitosis and growth (with folic acid)

### 3. Unusual Features

Cyanide group an artifact of preparation

The only vitamin synthesized in sizable amounts only by microorganisms (possibly in tumors)

Only vitamin with metal ion

Works with glutathione

Glutathione content decreased on B<sub>12</sub> deficiency

Mitosis retarded in B<sub>12</sub> deficiency

Requires intrinsic factor (enzyme) for oral activity

Increases tumor size (Rous sarcoma)

Diamagnetic properties

No acidic or basic groups revealed on titration (no pKa).

**4. Possible Relationships of Deficiency Symptoms to Metabolic Action**

- Degenerative changes in spinal cord—decreased RNA synthesis
- Megaloblastic marrow—decreased DNA synthesis (with folate)
- Glossitis—decreased cell division of tongue cells
- Macrocytic hyperchromic anemia—decreased DNA synthesis of precursor cells
- Decreased blood and tissue lipids—possibly due to presence of plasma hemolytic factor in  $B_{12}$  deficiency
- Disturbed CHO metabolism—activation of methylmalonic acid mutase by  $B_{12}$
- Leukopenia—decreased DNA synthesis in stem cells
- GI tract changes—decreased cell division of gastric mucosal cells
- Increased hemolysis—presence of plasma hemolytic factor in  $B_{12}$  deficiency

# 11 Ascorbic Acid

## GENERAL INFORMATION

- 1. Synonyms:** Vitamin C, antiscorbutic vitamin, cevitamic acid, hexuronic acid
- 2. History**
  - 1757—Lind described scurvy
  - 1907—Holst and Frolich produced experimental scurvy
  - 1928—Zilva described antiscorbutic agents in lemon juice
  - 1928—Szent-Györgyi isolated hexuronic acid from lemon juice
  - 1932—Waugh and King identified hexuronic acid as antiscorbutic agent
  - 1933—Haworth established configuration of hexuronic acid
  - 1933—Reichstein synthesized hexuronic acid
  - 1933—Haworth and Szent-Györgyi changed name of hexuronic acid to ascorbic acid
- 3. Physiological Forms:** L-Ascorbic acid, dehydroascorbic acid
- 4. Active Analogs and Related Compounds:** L-Glucoascorbic acid, d-arabofuranosyl-ascorbic acid, L-rhamnoascorbic acid, 6-desoxy-L-ascorbic acid
- 5. Inactive Analogs and Related Compounds:** d-Ascorbic acid
- 6. Antagonists:** d-Glucoascorbic acid, deoxycorticosterone

**7. Synergists:** Vitamins A, E, B<sub>12</sub>, B<sub>6</sub>, K, pantothenic acid, testosterone, STH, folic acid

**8. Physiological Functions**

- Absorption of iron
- Cold tolerance, maintenance of adrenal cortex
- Antioxidant
- Metabolism of tryptophan, phenylalanine, tyrosine
- Growth
- Wound healing
- Synthesis of polysaccharides and collagen
- Formation of cartilage, dentine, bone, teeth
- Maintenance of capillaries

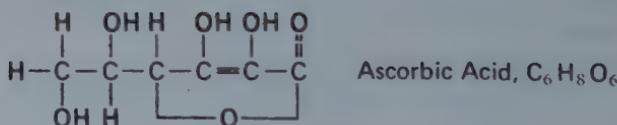
**9. Deficiency Diseases and Disorders:** Scurvy, megaloblastic anemia of infancy

**10. Sources for Species Requiring It:**

- Most species require it (most make it)
- Exogenous sources—Primates, Guinea pig, Indian fruit bat, red vented bulbul, trypanosomes, yeast
- Endogenous sources—Remainder of vertebrates, invertebrates, plants, and some molds and bacteria

## CHEMISTRY

**1. Structure**



**2. Reactions**

- Heat—Labile
- Acid—Stable
- Alkali—Labile
- Water—Acid (pH 3) labile

- Oxidation—Labile
- Reduction—Stable (reducing agent)
- Light—Labile

**3. Properties**

- Appearance—White powder

MW—176.12	Solubility
MP—190–192°C (decomp.)	H <sub>2</sub> O—0.3 g/ml
Crystal Form—plates, needles	Acet., Alc.—Slightly sol.
Salts—Ca, Na, metals	Benz., Chl., Eth.—Insol.
Important Groups for activity	Absn. Max.—245 m $\mu$ (acid)
Lactone ring	265 m $\mu$ (neutral)
Enolic hydroxyls	Redox Potential—E <sub>0</sub> <sup>1</sup> = +0.166 volt (pH 4)
	Chemical Nature—Hexose acid
	$\alpha_D^{25} = 20.5^\circ$ (H <sub>2</sub> O)
	Misc.—pK <sub>a1</sub> = 4.17
	pK <sub>a2</sub> = 11.57

#### 4. Commercial Production

Microbiological—*Acetobacter suboxidans* oxidative fermentation of calcium d-gluconate.  
Chemical—Oxidation of L-sorbose

#### 5. Isolation

Sources—Adrenal cortex, citrus juices  
Method—Ppt, from citrus juice as Pb-complex; crystallize from alcohol-petroleum ether

#### 6. Determination

Bioassay—Guinea pig growth or tooth structure; serum alkaline phosphatase  
Physicochemical—Titration against standard oxidizing dye solution, colorimetry of excess dye.

### DISTRIBUTION AND SOURCES

#### 1. Occurrence

Plants (High):

Fruit—Strawberry, citrus, pineapple, guava, black currant, West Indian cherry  
Vegetables—Cabbage, turnip greens, tomatoes, broccoli, kale, horseradish, parsley, corn  
Nuts—English walnuts (green)  
Miscellaneous—Rose hips, molds

Animals: All-Retina > pituitary > corpus luteum > adrenal cortex > thymus > liver > brain > testes > ovaries > spleen > thyroid >

pancreas > saliv. glands > lungs > kidney > intestine > heart muscle > WBC > RBC > plasma

#### Microorganisms

No intestinal synthesis except in rat

Produced by certain molds

Required by bacteria, yeasts, and molds for multiplication

## 2. Dietary Sources

High: 100-300 Mg/100 g

Broccoli, brussel sprouts, collards, horseradish, kale, parsley, peppers (sweet), turnip greens

Black currant, guava, rose hips

Medium: 50-100 mg/100 g

Beet greens, cabbages, cauliflower, chives, kohlrabi, mustard, watercress, spinach

Lemons, oranges, papayas, strawberries

Low: 25-50 mg/100 g

Asparagus, lima beans, beet greens, chard, cowpeas, mint, okra, spring onions, peas, potatoes, radishes, rutabagas, turnips, dandelion greens, fennel, soybeans, summer squash

Gooseberries, passion fruit, grapefruit, limes, loganberries, mangoes, cantaloupes, honeydews, red currants, white currants, tangerines, raspberries, tomatoes, kumquats

## MEDICAL AND NUTRITIONAL ROLE

1. Units: 1 I.U. = 1 U.S.P. unit = 0.05 mg l-ascorbic acid

2. Normal Blood Levels: 0.5-1 mg% (plasma), 25 mg% (white blood cells); vary with diet

3. Recommended Allowances

Children—40 mg/day

Adults—60 mg/day (males), 55 mg/day (females)

Special—Pregnancy (60 mg/day), lactation (60 mg/day); increased with infection, stress, trauma, allergies, old age, increased protein consumption

4. Administration

Injection—Intramuscular, intravenous

Topical—No data

Oral—Preferred route

## 5. Factors Affecting Availability

Decrease

- Damage to adrenal cortex, presence of antagonists
- Food preparation (oxidation, storage, leaching, cooking)

Increase

- Storage in body (adrenal cortex)
- Antioxidants, synergists in diet

## 6. Deficiency Symptoms

General

- Hyperkeratotic papules on buttocks and calves
- Perifollicular hemorrhage, edema
- Wound healing failure
- Teeth and gum defects
- Weakness, listlessness, rough skin, aching joints
- Scorbutic bone formation

Lab animals

- Anemia, loss of weight
- Abnormal collagen, no intercellular cement

## 7. Effects of Overdose

- None noted—Essentially nontoxic in man, except as noted below
- Possible kidney stones, in gouty individuals
- Inhibitory in excess doses on cellular level (mitosis inhibited)
- Possible damage to  $\beta$ -cells of pancreas and decreased insulin production by dehydroascorbic acid

## METABOLIC ROLE

### 1. Biosynthesis

- Precursors—d-Mannose, d-fructose, glycerol, sucrose, d-glucose, or d-galactose
- Intermediates—UDP glucose, d-glucuronic acid, gulonic acid, L-gulono-lactone, ( $Mn^{++}$  cofactor)

### 2. Production—Species and Sites

- All animals (except primates, guinea pig, fruit bat, bulbul)—kidney and liver (rat—intest. bacteria supply)
- Plants (green leaves, fruit skin)
- Cell sites—Microsomes, mitochondria, golgi

### 3. Storage Sites: Adrenal cortex (small amount)

4. **Blood Carriers:** Free in blood, especially in white blood cells
5. **Half-life:** 16 days (man), few days (guinea pig)
6. **Target Tissues:** Adrenal cortex, pituitary, ovary, connective tissue, bone, liver, teeth, gums

### 7. Reactions

Coenzyme form: Redox couple—I-ascorbic  $\rightleftharpoons$  dehydroascorbic acid

<i>Organ</i>	<i>Enzyme Systems</i>	<i>Effect</i>
<b>HYDROXYLATING</b>		
Connective tissue	Proline $\rightarrow$ hydroxyproline (collagen synth.)	Activated
Liver	Tryptophan $\rightarrow$ 5-hydroxytryptophan (tryptophan metab.)	Activated
Adrenal cortex	Deoxycorticosterone $\rightarrow$ hydroxycorticosteroids (steroid hormone synth.)	Activated
<b>OXIDATION-REDUCTION</b>		
Liver	DPNH—cytochrome b <sub>5</sub> (electron transport)	Activated
Liver	Tyrosine—homogentisic acid (tyrosine metabolism)	Activated
Liver	Glutathione (reduction reaction)	Activated
Liver	Ascorbic acid oxidase (oxidation reactions)	Activated
Liver	Plasma iron—ferritin (reduction)	Activated
Liver	Amidases, proteases, glycosidases, peroxidases, esterases	Activated
Liver	Arginase, papain, liver esterase, catalase, cathepsin	Activated
Liver	Urease, b-amylase	Inhibited

### 8. Mode of Action

Cellular

Anabolic

Collagen synthesis—Proline hydroxylation

Steroid synthesis—Accelerates acetate incorp. into cholest.

Serotonin, melanin synthesis

Polysaccharide synthesis—Chondroitin sulfate incorp.

Catabolic—Antimitotic agent

**Other**

- Cellular antioxidant—Maintains membranes
- Respiration—Cellular reductions and oxidations
- Maintenance of electron transport chain in mitochondria
- Maintains low redox level for vit. E and sulfhydryl enzymes
- Maintenance of peroxidase system (detoxification)
- Stimulates phagocytosis

**Organismal**

- Absorption of iron, ferritin production.
- Maintenance of adrenals and ovaries (hormone biosynthesis)
- Maintenance of connective tissues
- Maintenance of steroid endocrine glands
- Maintains stress and wound healing reactions
- Maintenance of cartilage, bone, and teeth
- Maintenance of capillaries, control hemorrhage
- Respiration—maintains oxygen turnover

**9. Catabolism**

Intermediates—Diketogulonic acid, oxalic acid

**Excretion products**

- Urine—12-14% excreted as L-ascorbic acid
  - 12-18% excreted as diketogulonic acid
  - 24-63% excreted as oxalic acid
- Also in feces, sweat, respiratory CO<sub>2</sub>.

**MISCELLANEOUS****1. Relationship to Other Vitamins**

Vitamin A—Depletion causes drop in plasma vit. C levels; protected by vit. C against oxidation

Vitamin B<sub>12</sub>—Replaced by vit. C in lactic acid bacteria; can be replaced or potentiated by vit. C

Folic acid—Vitamin C decreases symptoms of folic acid deficiency; formation promoted by vit. C, stimulates formation of citrovorum factor (folinic acid)

Pyridoxine—Pyridoxine-PO<sub>4</sub> and vit. C related to tyrosine metabolism

Vitamin E—Decreased synthesis and excretion of vit. C in vit. E deficient animals; protected by vit. C against oxidation

Pantothenic acid—Compensated partly by vit. C in deficiency of pantothenic acid

## 2. Relationship to Hormones

- Serotonin—Produced from tryptophan under influence of vit. C
- Thyroxine—Cold survival capacity due to vit. C (mediated via thyroxine)
- Epinephrine, Norepinephrine—Produced from tyrosine under influence of vit. C; vit. C protects against oxidation
- Deoxycorticosterone—Depresses action of vit. C on growth of skeletal tissues
- Aldosterone, estradiol- $17\beta$ , testosterone, cortisol—Vit. C stimulates conversion of deoxycorticosterone in adrenal cortex (maybe needed for steroid synthesis)
- Cortisone—Alleviates scorbutic symptoms in joints
- STH, ACTH, FSH, LH—High concentrations of vit. C noted in pituitary tissues; STH a synergist in growth

## 3. Unusual Features

- Only d-form active
- Antistress factor and anti-infection factor
- Activates terminal oxidases in respiratory systems
- Sensitivity to oxidation by heavy metals (e.g., Cu) hemochromogens, and quinones
- Ease of reversible oxidation
- Increased excretion due to barbiturates and drugs
- Increased synthesis of vit. C due to chloretone in vit. C deficient animals
- Production of  $H_2O_2$  on aerobic oxidation
- Increases nitrogen assimilation by plants
- Protects tissues against ionizing radiation

## 4. Possible Relationships of Deficiency Symptoms to Metabolic Action

- Failure to produce intercellular cement—Decrease of mucopolysaccharide synthesis from glucuronic acid
- Hemorrhage—Weak intercellular fibers causing capillary fragility
- Poor tooth and gum structure—Decreased collagen, mucopolysaccharide synthesis; bacterial invasion
- Lethargy—Decreased supply of adrenocortical and adrenal hormones
- Edema—Decreased aldosterone synthesis and capillary fragility
- Weight loss—Possibly decreased growth hormone level

# 12

# Biotin

## GENERAL INFORMATION

1. **Synonyms:** Bios IIB, protective factor X, vit. H, egg white injury factor, CoR

### 2. History

1924—Miller fractionated yeast growth factor Bios into Bios, I, IIB, IIC

1933—Allison *et al.* isolated CoR (respiratory factor legume nodule bacteria)

1934—Lease and Parsons described egg white injury in chicks

1936—Kögl, Tonnis isolated growth stimulant from yeast, and egg yolk, and named it biotin

1940—György identified vit. H, CoR, and biotin as equivalent

1941—Williams *et al.* found egg white injury due to antivitamin, avidin (inactivates biotin)

1942—Du Vigneaud characterized and determined structure of biotin

1943—Harris synthesized biotin

### 3. Physiological Forms

*d* (or +) Biotin (*cis*-form) ( $\beta$ -isomer, *d*( $\beta$ -biotin)*cis*)

Of 8 possible stereoisomers (4 *cis*, 4 *trans*), only one active: *d*-biotin (*cis*  $\alpha$  and  $\beta$ -isomers based on orientation of isomeric side chains of *cis* and *trans* forms

**4. Active Analogs and Related Compounds**

- Desthiobiotin in some species
- dl*-Oxybiotin (microorganisms, rats, chicks)
- Biotinol (in rats)
- Biotin sulfoxide (in some)
- Biocytin (in some)

**5. Inactive Analogs and Related Compounds**

- dl*-Epibiotin (*cis*)
- dl*-Allobiotin (*trans*)
- dl*-Epiallobiotin (*trans*)
- l*-Biotin (*cis*)
- $\alpha$  and  $\beta$ -Isomers of these

**6. Antagonists**

- Desthiobiotin in some forms
- Ureylene phenyl
- Homobiotin
- Urelenecyclohexyl butyric and valeric acids
- Norbiotin
- Avidin
- Lysolecithin
- Biotin sulfone

**7. Synergists:** Vitamins B<sub>2</sub>, B<sub>6</sub>, B<sub>12</sub>, folic acid, pantothenic acid, STH, testosterone**8. Physiological Functions**

- As coenzyme for
- Carboxylation reactions
- Pyruvic oxidase
- Decarboxylation of OAA, succinate, aspartate, malate
- Biosynthesis of aspartate, citrulline, unsaturated fatty acids
- Growth
- Maintenance of skin, hair, sebaceous glands, nerves, bone marrow, sex glands

**9. Deficiency Diseases and Disorders (Man)**

- Nonspecific dermatitis
- Seborrheic dermatitis in infants, furunculosis

## 10. Sources for Species Requiring It

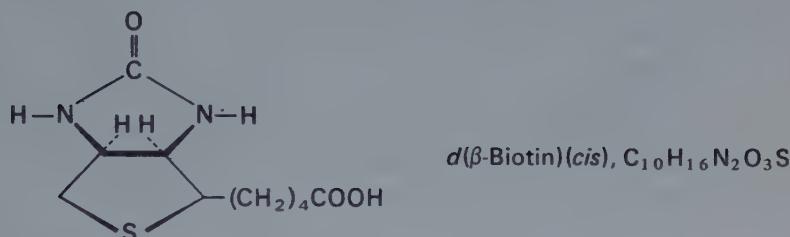
Most organisms require it

Exogenous sources—Most vertebrates, invertebrates, some bacteria and fungi (intestinal bacteria supply needs of man)

Endogenous sources—Higher plants, most fungi and bacteria

## CHEMISTRY

### 1. Structure



### 2. Reactions

Heat—Stable

Acid—Unstable

Alkali—Unstable

Water—Acidic

Oxidation—Unstable

Reduction—Forms desthiobiotin

Light—Stable

### 3. Properties

Appearance—White powder

MW—244.3

MP—230–32°C

Crystal Form

Orthorhombic (α)

Colorless needles (β)

Salts—Na

Important Groups

Solubility

H<sub>2</sub>O—0.03 g/100 ml

Alc.—Sol.

Acet., Benz. Chl. Eth.—Insol.

Absn. Max.—234 mμ

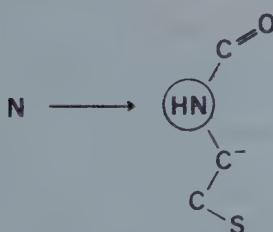
Chemical Nature

Diamino-, monocarboxylic acid

Substituted amino acid

Miscellaneous—pI = 3.5

$\alpha_D^{21} = +91^\circ$  (0.1 N NaOH)



**4. Commercial Production**

Use meso-diamino succinic acid derivative of fumaric acid for starting synthesis

**5. Isolation**

Sources—Egg yolk, liver, milk

Method—Extraction with acetone, precipitation with alc. and phosphotungstate, adsorb and elute from charcoal, ppt. with  $\text{HgCl}_2$ , dissolve, purify, crystallize

**6. Determination**

Bioassay

Microbiological—*L. arabinosus*

Rat and chick method—Growth response after biotin deficiency

Physicochemical: Polarography

**DISTRIBUTION AND SOURCES****1. Occurrence**

Plants

Fruit—All low

Vegetables—All low, except beans, peas, cauliflower

Nuts—All medium, also cereals

Animals: All low except in organs (esp. liver and kidneys are high)

Microorganisms: Afford best source of biotin, especially yeast, lower fungi and bacteria

**2. Dietary Sources**

High: 100-400  $\mu\text{g}/100 \text{ gm}$

Royal jelly, yeast, lamb liver, pork liver

Medium: 10-100  $\mu\text{g}/100 \text{ gm}$

Wheat, rice, corn, oats, barley

Eggs, beef liver, chicken, mushrooms

Cowpeas, chick-peas, lentils, soybeans, cauliflower, chocolate

Mackerel, salmon, sardines

Almonds, peanuts, pecans, walnuts, filberts, hazelnuts

Low: 0-10  $\mu\text{g}/100 \text{ gm}$

Cheese, milk

Apples, bananas, strawberries, cantaloupes, grapefruit, grapes, oranges, peaches, watermelon, avocados

Lima beans, beets, carrots, cabbages, corn, lettuce, onions, peas, sweet potatoes, tomatoes, spinach, beet greens  
Beef, lamb, veal, pork, tuna, halibut, oyster

## MEDICAL AND NUTRITIONAL ROLE

1. **Units:** By weight,  $\mu\text{g}$
2. **Normal Blood Levels:** (Man):  $0.95\text{-}1.66 \mu\text{g}/100 \text{ ml serum}$ ,  $0.75\text{-}1.73 \mu\text{g}/100 \text{ ml blood}$
3. **Recommended Allowances**  
Children—Unknown  
Adults— $150\text{-}300 \mu\text{g}/\text{day}$  estimated. May be available from intestinal bacteria and diet.
4. **Administration**  
Injection—parenteral, intramuscular  
Topical—No data  
Oral—Mainly used
5. **Factors Affecting Availability**  
Decrease  
Presence of avidin in food  
Cooking losses  
Antibiotics  
Sulfa drugs  
Binding in foods (yeast, animals)  
Increase: Synthesis by intestinal bacteria
6. **Deficiency Symptoms**  
General  
Desquamation of the skin  
Lassitude, somnolence, muscle pain  
Hyperesthesia  
Seborrheic dermatitis  
Alopecia, spastic gait, and kangaroo-like posture (rats and mice)  
Dermatitis and perosis (chicks and turkeys)  
Progressive paralysis,  $K^+$  deficiency (dogs)  
Alopecia, spasticity of hind legs (pigs)  
Thinning and depigmentation of hair (monkeys)

## 7. Effects of Overdose

None noted—1 g/kg not toxic  
Essentially nontoxic in man

## METABOLIC ROLE

### 1. Biosynthesis

Precursors—Pimelic acid, cysteine, carbamyl phosphate  
Intermediates—Desthiobiotin

### 2. Production: Species and Sites

Plants—Seedlings, leaves  
Fungi—Some  
Bacteria—Intestinal, some others

### 3. Storage Sites: Liver

### 4. Blood Carriers: Unknown

### 5. Half-life: Requires 3-4 weeks to produce human deficiency with avidin

### 6. Target Tissues: Skin, nervous tissue, male genitalia, bone marrow, liver, kidney

### 7. Reactions

Coenzyme forms: CO<sub>2</sub>-biotin-enz; d-biotin-lys-enz

<i>Organ</i>	<i>Enzyme System</i>	<i>Effect</i>
	CARBOXYLASES	
Liver	Propionyl-CoA carboxylase $\beta$ -methylcrotonyl-CoA carboxylase Acetyl-CoA carboxylase Phosphoenolpyruvate carboxykinase ATP-dependent pyruvic carboxylase	Activated
	TRANSCARBOXYLASES	
Liver	Oxalosuccinate-acetyl-CoA transcarboxylase Methylmalonyl-oxalacetic transcarboxylase	Activated
Liver	Malic enzyme	Activated
Liver	Ornithine transcarbamylase	Activated

## 8. Mode of Action

### Cellular

Anabolic—Purine, protein, and carbohydrate synthesis; synthesis of aspartic acid, oleic acid, fatty acids

Catabolic—Deamination of serine in animals; tryptophan metabolism

Other—CO<sub>2</sub> fixation; ureido carbon of enzyme-bound biotin is the "active carbon"; implicated in carbamylation reactions

Organismal—Growth; maintenance of sebaceous glands, nervous tissue, skin, blood cells, hair, male genitalia

## 9. Catabolism

Intermediates—Little known

Excretion product

Urine—29-52 µg/day biotin and biotin sulfoxide (?)

Feces—2.5 × amount in food intake (bacterial synthesis)

## MISCELLANEOUS

### 1. Relationship to Other Vitamins

Pantothenic acid—Indicated by depigmentation of hair in deficiency of biotin + pantothenic acid

Vitamin C—ascorbic acid biosynthesis requires biotin

Vitamins B<sub>2</sub>, B<sub>6</sub>, niacin, A, D—Synergistic with biotin in maintenance of skin

Niacin—Not synthesized from tryptophan in biotin deficiency

Folic acid—(With pantothenic acid and biotin) increased stress response in adrenalectomized rats

### 2. Relationship to Hormones

Testosterone—Rat male genital system retarded in biotin deficiency (symptoms develop earlier than in female)

Cortisol—Adrenocortical insufficiency noted in biotin deficient rats.

STH—Synergist in growth

### 3. Unusual Features

Binding and inactivation by avidin protein found in egg white

Fetal tissues and cancer tissues are higher in biotin than adult tissues

Biotin deficiency increases severity and duration of some diseases notably some protozoan infections

Oleic acid and related compounds act to replace biotin as unspecific stimulatory compounds in bacteria

Combines to lysine residues of proteins  
Only (+) isomer active  
Inactivated by rancid fats, choline

**4. Possible Relationships of Deficiency Symptoms to Metabolic Action**

Desquamation of skin—Decreased fatty acid synthesis, synergism with A, D, other B vitamins  
Hyperesthesia—Increased lactic acid levels  
Lassitude, somnolence—Decreased oxidation of pyruvate  
Muscle pain—Increased lactic acid levels, decreased fatty acid synthesis  
Seborrheic dermatitis—Decreased synergism with vits. A, D, other B vitamins

# 13

# Folic Acid

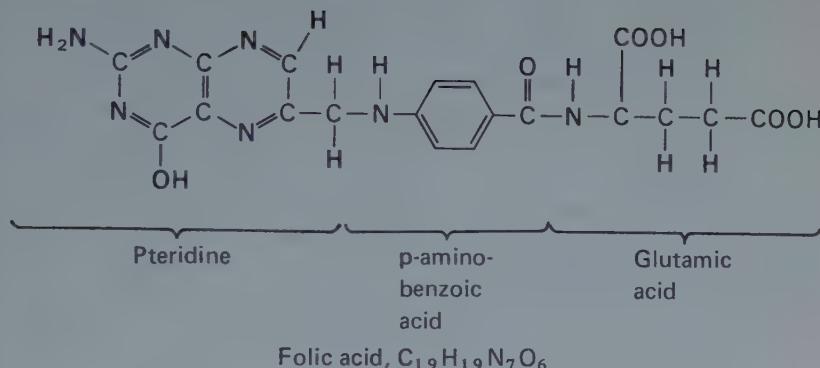
## GENERAL INFORMATION

1. **Synonyms:** Folacin, pteroylmonoglutamic acid, antianemia factor, *L. casei* factor, vit. B<sub>c</sub>, vit. M, PGA
2. **History**
  - 1931—Wills demonstrated a factor from yeast active in treating anemia
  - 1938—Day *et al.* found yeast or liver extracts active in treating anemia in monkeys
  - 1939—Hogan and Parrott prevented anemia in chicks with liver extract
  - 1940—Snell and Peterson isolated *L. casei* growth factor from liver and yeast
  - 1941—Hutchings *et. al.* found *L. casei* factor also essential for chicks
  - 1941—Mitchell, Snell, Williams isolated bacterial (*S. lactis R*) growth factor similar to *L. casei* factor from yeast; named it folic acid
  - 1943—Stokstad reported *L. casei* factor from liver more active than that from yeast; evidence for multiple factors
  - 1946—Angier *et al.* isolated pteroylmonoglutamic acid, proved structure and synthesized it
3. **Physiological Forms:** Tetrahydrofolic acid, pteroyltriglutamic acid, pteroylheptaglutamic acid, L-folinic acid (citrovorum factor), dihydrofolic acid (5-formyl-5,6,7,8-tetrahydro-PGA) (leucovorin)

4. **Active Analogs and Related Compounds:** Pteroic acid (bacteria), 10-formyl-FAH<sub>4</sub>, 5,10-methenyl-FAH<sub>4</sub>, diopterin, 5,10-methylene-FAH<sub>4</sub>, 5-formimino-FAH<sub>4</sub>, rhizopterin (bact.), xanthopterin (bact.), biopterin (urine), ichthyopterin (fish), leucopterin (invertebrates)
5. **Inactive Analogs and Related Compounds:** d-folinic acid
6. **Antagonists:** Aminopterin (4-amino-PGA), methotrexate (amethopterin) pyrimethamine, 4-amino-pteroylaspatic acid
7. **Synergists:** Biotin, pantothenic acid, niacin, Vits. B<sub>6</sub>, B<sub>2</sub>, C, B<sub>1</sub>, E, B<sub>12</sub>, STH, estradiol, testosterone
8. **Physiological Functions:** Synthesis of nucleic acid, coenzyme in purine-pyrimidine metabolism, serine-glycine conversion, intermediate in metabolism of purines and pyrimidines, differentiation of embryonic nervous system, one-carbon transfer mechanisms, metabolism of tyrosine and histidine, formation of active formate, and methionine, synthesis of choline
9. **Deficiency Diseases and Disorders:** Anemias (macrocytic, megaloblastic, pernicious), glossitis, diarrhea, G.I. lesions, intestinal malabsorption, sprue
10. **Sources for Species Requiring It**
  - Most animals require it
  - Exogenous sources—Vertebrates, invertebrates, some bacteria (intestinal bacteria provide it in man, rats, dogs, pigs, rabbits) required by monkey, guinea pig, mice, fox, chicken, geese, turkeys
  - Endogenous sources—Intestinal bacteria, fungi, yeast

## CHEMISTRY

### 1. Structure



### 2. Reactions

Heat—Labile (in soln.)

Acid—Labile

Alkali—Stable

Water—Stable (acid, pH 4.4)

Oxidation—Labile

Reduction—Stable

Light—Labile (in soln.) to UV

### 3. Properties

Appearance—yellow crystals

MW—441.2

MP—Chars at  $250^\circ\text{C}$

Crystal Form—Lenticular

Salts—Ba, Na, Pb

Important Groups for activity

Glutamic acid

$\text{N}^{10}, \text{N}^5, \text{N}^3, \text{N}^8$

Solubility

$\text{H}_2\text{O}$ —0.01 mg/ml

Acet., Alc.—Insol.

Benz., Chl., Eth.—Insol.

Absn. Max.—282, 350 m $\mu$

(pH 7.0)

Misc.— $\text{pK}_a = 8.2$

$\alpha_D^{25} = \pm 23^\circ$  (0.1 N NaOH)

Chemical Nature—Purine, amino acid, benzoic acid

### 4. Commercial Production

Extraction from yeast or liver; synthetic

### 5. Isolation

Sources—Spinach, liver, yeast, alfalfa, wheat bran

Method

Extract (aq.) liver at pH 3.0

Adsorb on norite, elute with  $\text{NH}_4\text{OH}$ -ethanol

Adsorb on superfiltrol pH 1.3, elute with NH<sub>4</sub>OH-ethanol  
 Ppt. with Ba<sup>++</sup>, pH 7.0 in alcohol  
 Esterify with methanol, extract with *n*-butanol  
 Adsorb on superfiltrol pH 7, elute ester with 75% acetone  
 Crystallize from hot methanol, hydrolyze ester  
 Recrystallize from hot H<sub>2</sub>O

## 6. Determination

### Bioassay

Animal—chick feathering, rat oviduct development

Microbial—Growth of *L. casei*, *S. fecalis*

### Physicochemical

Enzymatic—DPNH reductase activity

Fluorometric—Fluorescence at 470 m $\mu$

Colorimetric—Estimate aromatic amine on cleavage

Polarographic—Paper chromatography

## DISTRIBUTION AND SOURCES

### 1. Occurrence

#### Plants: Fruit—Low

Vegetables—Green leafy vegetables, dried beans

Nuts—Almonds, filberts, peanuts, walnuts

Miscellaneous—Green leaves, grass, barley, oats, rye, wheat

#### Animals

Liver, kidney

Butterflies (wing pigment, xanthopterin)

Fish scales (ichthyopterin)

Microorganisms: Intestinal bacteria, yeast, fungi, algae

Miscellaneous: Mushrooms

### 2. Dietary Sources

High: 90-300  $\mu$ g/100 gm

Liver (beef, lamb, pork, chicken)

Asparagus, spinach

Wheat, bran

Dry beans (lentils, limas, navy)

Yeast

Medium: 30-90  $\mu$ g/100 gm

Kidney (beef)

Low: 0-30  $\mu$ g/100 gm

Lima beans, snap beans, broccoli, corn, beet greens, chicory, endive, kale, parsley, chard, turnip greens, watercress  
Almonds, filberts, peanuts, walnuts  
Barley, oats, rye, wheat  
Low: 0.30 mg/100 g  
Beef (muscle, heart), lamb, pork, chicken, turkey (muscle)  
All fruit tested  
Cheese, milk  
Brazil nuts, coconuts, pecans  
Wax beans, beets, brussel sprouts, cabbages, carrots, brown rice, cauliflower, celery, cucumbers, eggplant, escarole, mustard, kohlrabi, lettuce, mushrooms, okra, onions, parsnips, peas, peppers, potatoes, pumpkins, radishes, rutabagas, squash, sweet potatoes, tomatoes, turnips

## MEDICAL AND NUTRITIONAL ROLE

1. Units: By weight, mg
2. Normal Blood Levels: 3.53 µg/100 ml (humans)
3. Recommended Allowances
  - Children and adults  
0.4 mg/day estimate  
Provided by intestinal synthesis in man  
Required by monkey, guinea pig, mice, fox, chicken, geese, turkeys
  - Special—Pregnancy, illness
4. Administration
  - Injection—subcutaneous
  - Topical—No data
  - Oral—Preferred route
5. Factors Affecting Availability
  - Decrease
    - High urinary excretion (75% ingested)
    - Destruction by certain intestinal bacteria
    - Increased urinary excretion caused by vit. C
    - Sulfonamides block intestinal synthesis
    - Poor absorption

Increase—Intestinal bacterial synthesis and release: man, rats, dogs, pigs, rabbits

## 6. Deficiency Symptoms

- Intestinal disturbances
- Leucopenia
- Glossitis
- Thrombocytopenia
- Macrocytic anemia
- Pernicious anemia
- Sprue
- Megaloblastic erythropoiesis
- Gingivitis, agranulosis (monkey)
- Hydrocephalus, splenic enlargement (rats)
- Endocrine disturbances, poor feathering (chick)
- Lethargy, convulsions (guinea pig)

## 7. Effects of Overdose

- Man—No toxicity reported
- Mice—Renal damage, convulsions:  $LD_{50} = 600 \text{ mg/kg}$
- Chick—Arrest cells in metaphase with high doses

## METABOLIC ROLE

### 1. Biosynthesis

- Precursors: Paraminobenzoic acid, glutamic acid, unknown pteridine
- Intermediates: Paraminobenzoylglutamic acid

### 2. Production: Species and Sites

- Plants—Leaves, seeds, cereal germ, algae
- Bacteria—Intestinal supply sufficient for man, rats, pigs, dogs, rabbits;  
Other species require exogenous sources
- Fungi—yeast

### 3. Storage: Liver (small amount)

### 4. Blood Carriers: Prefolic acid A

### 5. Half-life: 75% of ingested folic acid excreted in urine in 24 hr

### 6. Target Tissues: Liver, bone marrow, lymph nodes, kidneys

## 7. Reactions

Coenzyme forms: Folinic acid (citrovorum factor), 10-formyl-FH<sub>4</sub>, 5,10-methylene-FH<sub>4</sub>, 5-formimino-FH<sub>4</sub>, 10-formimino-FH<sub>4</sub>, 5-methyl-FH<sub>4</sub>, 5-hydroxymethyl-FH<sub>4</sub>

<i>Organ</i>	<i>Enzyme System</i>	<i>Effect</i>
Liver	<b>REDUCTASES</b> Dihydrofolate reductase: FH <sub>2</sub> → FH <sub>4</sub> N <sup>5</sup> N <sup>10</sup> -Methylene-FH <sub>4</sub> reductase: N <sup>5</sup> N <sup>10</sup> -methylene-FH <sub>4</sub> → N <sup>5</sup> -methyl-FH <sub>4</sub>	Activated
Liver	<b>TRANSFERASES</b> Formiminoglutamate formimino transferase: Formation of formimino glutamate Serine transhydroxymethylase: Glycine-serine interconversion Formylglutamate formyl transferase: Formation of glutamate	Activated
Liver	<b>ISOMERASES</b> N <sup>5</sup> -formyl-tetrahydrofolate isomerase: N <sup>5</sup> -formyl-FH <sub>4</sub> → N <sup>10</sup> -formyl-FH <sub>4</sub>	Activated
Liver	<b>SYNTHETASES</b> Formyl tetrahydrofolate synthetase: FH <sub>4</sub> → N <sup>10</sup> -formyl-FH <sub>4</sub>	Activated
Liver	<b>CONJUGASES</b> Folic acid conjugase: Converts pteroyltriglutamate → PGA	Activated

## 8. Mode of Action

Cellular

Anabolic

- Purine and pyrimidine synthesis
- Choline synthesis
- Methionine synthesis
- Formation of lignin, nicotine, betaine

Catabolic—Histidine metabolism, tryptophan metabolism

Other

- Mitotic step: Metaphase → anaphase requires folic acid
- Serine-glycine interconversion
- Formiminoglutamate formation

Organismal

- Erythropoiesis, growth
- Maintenance of sex organs
- Maintenance of intestinal tract

Leukopoiesis  
Differentiation of nervous system

## 9. Catabolism

Intermediates: Xanthopterin, leucopterin

Excretion products: Urine—Biopterin, leucovorin, pteroylglutamic acid, 10.8 µg/day (humans); feces—enterohepatic circulation of folate

## MISCELLANEOUS

### 1. Relationship to Other Vitamins

#### Vitamin C

Facilitates conversion of folic to folinic acid (CF-citrovorum factor)

Protects folinic acid from oxidation, increases urinary excretion of CF

Fundamental role with folic acid in erythropoiesis

#### Vitamin B<sub>12</sub>

Blood and marrow changes in pernicious anemia respond to folic acid or B<sub>12</sub>

Neurological changes in pernicious anemia involve B<sub>12</sub> and folic acid  
Involved with folic acid in formation of methionine from homocysteine

Biotin—Aids in storage and utilization of pantothenic acid in liver, (with folic acid)

Pantothenic acid—Utilization in CoA synthesis (with biotin and folic acid)

#### Niacin

Need folic acid for niacin metabolism

DPNH required for production of N<sup>5</sup>-methyl-FH<sub>4</sub>

DPN involved in methionine formation (with folic acid)

Vitamin B<sub>6</sub>—Required with folic acid for serine-glycine transformations and for methionine formation

Riboflavin—Required with DPN, folic acid, vit. B<sub>12</sub>, vit. B<sub>6</sub>, for methionine formation

### 2. Relationship to Hormones

Estradiol—Folic acid deficiency eliminates normal response of female reproductive organs to estrogens; pregnancies not normal

Testosterone—Folic acid increases action of testosterone on development of accessory sex organs

STH—Synergist in growth

### 3. Unusual Features

- Folic acid antagonists used in cancer therapy with temporary remissions
- Occurs in chromosomes
- Distributed throughout cell
- Needed for mitotic step metaphase → anaphase
- Antibody formation decreased in folic acid deficiency
- Choline-sparing effects
- Analgesic in man—pain threshold increased
- Low intravenous toxicity in man
- Antisulfonamide effects
- Enterohepatic circulation of folate
- Synthesized by psittacosis virus
- Concentrated in spinal fluid

### 4. Possible Relationships of Deficiency Symptoms to Metabolic Action

- Cytopenia—Decreased nucleic acid synthesis and porphyrin synthesis
- Intestinal disturbances—Indirect relationship with other vitamin deficiencies
- Thrombocytopenia—Decreased nucleic acid synthesis
- Leukopenia—Decreased nucleic acid synthesis
- Glossitis—Indirect effect of other vit. B deficiencies
- Macrocytic anemia and pernicious anemia—Vitamin B<sub>12</sub> lack and decreased porphyrin synthesis
- Sprue—Indirect effect of lack of other vitamins

# 14 Niacin

## GENERAL INFORMATION

1. **Synonyms:** Nicotinic acid, niacinamide, P-P factor, antipellagra factor, anti-blacktongue factor, B<sub>3</sub>
2. **History**
  - 1867—Huber first synthesized nicotinic acid
  - 1914—Funk isolated nicotinic acid from rice polishings
  - 1915—Goldberger demonstrated that pellagra is a nutritional deficiency
  - 1917—Chittenden and Underhill demonstrated that canine blacktongue is similar to pellagra
  - 1935—Warburg and Christian determined niacinamide essential in hydrogen transport as DPN
  - 1936—Euler *et al.* isolated DPN and determined its structure
  - 1937—Elvehjem *et al.* cured blacktongue with niacinamide from liver
  - 1937—Fouts *et al.* cured pellagra with niacinamide
  - 1947—Handley and Bond established conversion of tryptophan to niacin by animal tissues
3. **Physiological Forms:** Niacinamide, NAD (DPN, CoI), NADP (TPN, CoII), N<sup>1</sup>-methylnicotinamide
4. **Active Analogs and Related Compounds:** Niacin esters, coramine, β-picoline, 3-hydroxymethylpyridine
5. **Inactive Analogs and Related Compounds:** Trigonelline

6. **Antagonists:** Pyridine-3-sulfonic acid (bacteria), 3-acetylpyridine, 6-aminonicotinamide, 5-thiazole carboxamide
7. **Synergists:** Vitamins B<sub>1</sub>, B<sub>2</sub>, B<sub>6</sub>, B<sub>12</sub>, D, pantothenic and folic acids, STH
8. **Physiological Functions:** Maintenance of NAD, NADP; hydrogen and electron transfer agents in CHO metabolism; furnish coenzymes for dehydrogenase systems; coenzyme in lipid catabolism, oxidative deamination, photosynthesis
9. **Deficiency Diseases, Disorders:** Pellagra (man), blacktongue (dogs), malnutrition, dermatosis (man)
10. **Sources for Species Requiring It**  
Required by all species:  
Exogenous sources: Animals, some bacteria and fungi (not available from intestinal bacteria in man, but some conversion from tryptophan occurs in tissues)  
Endogenous sources: Plants: algae, some bacteria and fungi. Animals: (some species partly via tryptophan; other species completely via tryptophan)

## CHEMISTRY

### 1. Structure



### 2. Reactions

Heat—Stable	Oxidation—Stable
Acid—Stable	Reduction—Unstable
Alkali—Stable	Light—Stable
Water—Acidic	

### 3. Properties

Appearance—White crystalline powder	Salts—HCl, metallic, Na
MW—123.1	Important Groups for activity
MP—234–237°C (sublimes)	—N on ring
Crystal Form—needles	—COOH

Solubility	Chemical Nature—Carboxylic acid; amine; substituted pyridine
H <sub>2</sub> O—1 g/100 ml	
Alc.—Sol.	
Benz., Chl., Eth., Acet.—Insol.	Misc.—pKa = 4.8, 12.0
Absn. Max.—261.5 m $\mu$	$\alpha_D = 0$ (inactive)

#### 4. Commercial Production

Hydrolysis of 3-cyanopyridine  
Oxidation of nicotine, quinoline, or collidine

#### 5. Isolation

Sources—Liver, yeast

Method—Remove lipids with solvents; hydrolyze with acid or alkali; extract niacin from acidified hydrolysate; isolate as an acid, ester, or Cu salt; purify by recrystallization or sublimation

#### 6. Determination

Bioassay

Animal—Dogs, blacktongue (curative)

Microbial—*L. arabinosus*, growth

Physicochemical

Colorimetric—Cyanogen Br + reducing agent → color

Spectrophotometric—UV max. of DPN, TPN

### DISTRIBUTION AND SOURCES

#### 1. Occurrence

Plants:

Fruit—All low (exc. avocados and dried figs, dates, and prunes—medium)

Vegetables—All low (exc. beans, peas, potatoes, broccoli, asparagus, corn, parsley, kale—medium)

Nuts—All medium (exc. coconuts, pecans—low)

Animals: All medium [exc. livers, kidneys, beef heart, rabbit, turkey and chicken (white meat), tuna, halibut, swordfish—high]

Microorganisms—All high—intestinal bacteria, some other bacteria

#### 2. Dietary Sources

High: 10,000-100,000  $\mu\text{g}/100 \text{ g}$  (10-100 mg/100 g)

Peanuts (roasted), rice bran

Liver (beef, calf, chicken, pork, sheep)

Heart (calf), kidney (pork, beef)

Rabbit, turkey and chicken (white meat)

Meat extract

Tuna, halibut, swordfish

Yeast

Medium: 1000-10,000 µg/100 g (1-10 mg/100 g)

Avocados, dates (dry), figs (dry), prunes (dry)

Asparagus, beans (kidney, lima, snap, wax), broccoli, corn, kale, lentils (dry), parsley, peas, potatoes, soybeans (dry)

Almonds (dry), cashew nuts, chestnuts, walnuts

Barley, oats, wheat, rye, brown rice, wheat germ, molasses, cheeses (camembert, swiss, roquefort)

Beef, veal, chicken (dark meat), duck, lamb, fish (exc. tuna, halibut, swordfish), clams, shrimp, oysters

Mushrooms

Low: 100-1000 µg/100 g (0.1-1.0 mg/100 g)

Apples, apricots, bananas, berries (black-, blue-, cran-, rasp-, straw-), cherries, currants, figs, grapes, grapefruit, lemons, melons, oranges, peaches, pears, pineapples, plums, raisins (dry), tangerines

Beets, beet greens, brussels sprouts, cabbage, carrots, cauliflower, celery, chicory, endive, cucumbers, dandelion greens, eggplant, kohlrabi, lettuce, onions, parsnips, peppers, pumpkins, radishes, rhubarb, spinach, sweet potatoes, tomatoes, turnips, watercress

Coconuts, pecans

Eggs, milk

## MEDICAL AND NUTRITIONAL ROLE

### 1. Units—By weight, mg equivalents

### 2. Normal Blood Levels: 0.42-0.84 mg/100 ml

### 3. Recommended Allowances

Children—8-15 mg equivalents/day\*

Adults—18 mg equivalents/day—male\*; 13 mg equivalents/day—female\*

Special—Pregnancy, 15 mg equivalents/day; lactation, 20 mg equivalents/day

\* Depends on tryptophan content of diet; allow 10 mg equivalents for each 600 mg dietary tryptophan; assume 60 g/day protein in diet has 600 mg tryptophan.

#### 4. Administration

- Injection—I.V.
- Topical—No data
- Oral—Preferred route

#### 5. Factors Affecting Availability

Decrease

- Cooking losses
- Bound form in corn, greens, seeds, partially unavailable
- Oral antibiotics
- Decreased absorption—disease
- Decreased tryptophan converted in B<sub>6</sub> deficiency

Increase

- Alkali treatment of cereals
- Storage in liver, possibly muscle, kidney
- Increased intestinal synthesis

#### 6. Deficiency Symptoms

General (man)—Pellagra

Retarded growth, achlorhydria

Weakness, anorexia, indigestion, lassitude, dermatitis, pigmentation, diarrhea, tongue erythema, irritability, headaches, insomnia, memory loss

Histological changes in CNS (dog, cat—blacktongue)

Drooling (dog, cat—blacktongue)

Perosis (chickens)

Poor feathering (chickens)

#### 7. Effects of Overdose

Man—Limited toxicity starting approx. 1-4 g/kg dosage with individual variations in sensitivity. Burning, itching skin, peripheral vasodilation, decreased serum cholesterol, fatty liver, stimulated CNS, increased (pulse rate, respiratory rate, cerebral blood flow), decreased blood pressure

Rat—Respiratory paralysis, ketosis

Dogs—Death

Chick—Inhibition of growth, fatty liver

## METABOLIC ROLE

### 1. Biosynthesis

Precursors—Tryptophan (animals, bacteria). Glycerol and succinic acid (plants)

Intermediates—Kynurenone, hydroxyanthranilic acid, quinolinic acid

### 2. Production: Species and Sites

Fungi—*Neurospora*

Plants—Leaves, germinating seeds, shoots

Bacteria—Intestinal

Animals—Tissues (not intestinal)

### 3. Storage: Liver, heart, muscle

### 4. Blood Carriers: Mostly as DPN in blood corpuscles

### 5. Half-life—1/3 of intake excreted in 24 hr

### 6. Target Tissues: Liver (storage), heart, muscle, kidney, skin, G.I. tract, spinal cord

### 7. Reactions

Coenzyme forms—(DPN,NAD) and (TPN,NADP). Act as redox couples: oxid  $\rightleftharpoons$  reduced

<i>Organ</i>	<i>Enzyme System</i>	<i>Effect</i>
	More than 50 metabolic reactions known	
Liver	DEHYDROGENASES: Alcohol, lactate, malate, isocitrate, glucose-6-P-succinic, $\beta$ -hydroxybutyrate, 3 $\beta$ -hydroxysteroids, betaine aldehyde, glutamate, $\alpha$ -glycerophosphate, uridine DPG, reduced glutathione, glyceraldehyde-3-P	Activated
Liver	OXIDASES: $\alpha$ -keto glutaric oxidase microsomal mixed function oxidases (DPN + TPN), oxidation of steroids, fatty acids, drugs and carcinogens	Activated or completed

### 8. Mode of Action

Cellular

Anabolic—Maintains microsomal reductive biosynthesis; photosynthesis

**Catabolic**

- Furnishes coenzymes for lipid catabolism
- Oxidative deamination
- CHO metabolism—Dehydrogenation, oxidation
- Key reactions in glycolysis, TCA cycle, and HMP

**Other**

- Hydrogen and electron transfer agent
- A mobile hydrogen transfer agent
- Maintains respiratory chain in mitochondria

**Organismal**

- Maintains growth
- Maintains energy supply to organism from degradation of carbohydrates, proteins, and lipids
- Maintains terminal section of respiratory cycle
- Maintains manufacture of hormones (steroids) proteins, lipids
- Stimulates gastric secretion and bile secretion

**9. Catabolism**

Intermediates—*N*<sup>1</sup>-Methylnicotinamide (liver)

Excretion Products

Feces: Nicotinic acid

Urine: *N*<sup>1</sup>-Methylnicotinamide; *N*<sup>1</sup>-methyl-6-pyridone-3-carboxamide

**MISCELLANEOUS****1. Relationship to Other Vitamins**

Vitamin B<sub>2</sub>—Flavo-proteins reoxidize NAD, NADP

Vitamin B<sub>6</sub>—Decreased tryptophan conversion to niacin in B<sub>6</sub> deficiency

Vitamins B<sub>1</sub>, B<sub>2</sub>, B<sub>6</sub>, Pantothenic Acid, Folic Acid, Vitamin B<sub>12</sub>—General synergism with niacin in alleviating deficiencies and in CHO metabolism

Vitamins B<sub>1</sub>, B<sub>2</sub>, B<sub>6</sub>—Needed for conversion of tryptophan to niacin

**2. Relationship to Hormones**

Serotonin—Reduces tryptophan conversion to niacin (in cancer cases)

Thyroxine, Insulin—Affect mitochondrial metabolism (as do DPN and TPN), and energy production from CHO metabolism

Cortisol, Testosterone, Estradiol, Progesterone, Aldosterone—DPN and TPN involved in steroid oxidations in liver, in steroid hormone synthesis, and in cholesterol metabolism

STH—Synergist in growth

### 3. Unusual Features

- Has hormonal quality, being partially internally synthesized
- Vasodilator, causes flushing (not as niacinamide)
- High corn diets cause deficiency due to tryptophan deficiency in corn protein and unavailability of niacin in corn
- Prepared from nicotine using strong oxidizing agent
- Stereospecific action of dehydrogenases on DPN
- Serum cholesterol lowering with large doses
- Antagonist (6-aminonicotinamide) active against some rat tumors
- Other pyridine derivatives functional in DPN and TPN
- Conversion of tryptophan not in intestines
- Toxicity of overdose preventable by feeding methionine (rats)

### 4. Possible Relationships of Deficiency Symptoms to Metabolic Action

- Retarded growth—General synergism of all B vitamins
- Dermatitis, itching, pigmentation, tongue lesions; other B vitamins, esp.  $B_2$ , involved
- Irritability, mental disturbances, nervous lesions related to thiamine synergism with niacin
- G.I. lesions and disturbances related to thiamine deficiency and synergism
- Mottled liver, fatty liver are disturbances of cholesterol metabolism

# 15 Pantothenic Acid

## GENERAL INFORMATION

- 1. Synonyms:** Chick antidermatitis factor, B3, Bios IIa, antigray-hair factor
- 2. History**
  - 1901—Wildiers described Bios, essential for yeast growth
  - 1933—Williams isolated crystalline Bios from yeast; named it pantothenic acid
  - 1938—Williams isolated pantothenic acid from liver
  - 1939—Jukes determined liver antidermatitis factor (chick) identical to yeast factor
  - 1939—Woolley *et al.* demonstrated  $\beta$ -alanine a vital part
  - 1940—Harris, Folkers, *et al.* reported structure determination and synthesis of pantothenic acid; crystallization also
  - 1950—Lipmann *et al.* discovered CoA
  - 1951—Lynen characterized coenzyme A structure
- 3. Physiological Forms:** Coenzyme A, pantotheine, d(+)pantothenic acid
- 4. Active Analogs and Related Compounds:** Pantothenyl alcohol,  $\beta$ -alanine (bacteria), pantotheine (LBF), pantothine, pantothenylcystine, ethylmonoacetylpanothenate, ethyl pantothenate
- 5. Inactive Analogs and Related Compounds:** L-pantothenate,  $\alpha$ -alanine analogs

**6. Antagonists:** Pantoyltaurine,  $\omega$ -methylpantothenic acid, bis( $\beta$ -pantoyl-aminoethyl)disulfide, 6-mercaptopurine, pantoylaminoethanethiol

**7. Synergists:** Biotin, folic acid, vit. C,  $B_{12}$ ,  $B_1$ ,  $B_2$ , niacin, STH

**8. Physiological Functions:** Part of coenzyme A in carbohydrate metabolism (2 carbon transfer-acetate, or pyruvate), lipid metabolism (bio-synthesis and catabolism of fatty acids, sterols, + phospholipids), protein metabolism (acetylations of amines & amino acids), porphyrin metabolism, acetylcholine production, isoprene production

**9. Deficiency Diseases, Disorders:** Dermatitis (chick), achromotrichia (rat), adrenal necrosis (rats), bloody whiskers (rat), alopecia (mice)

#### 10. Sources for Species Requiring It

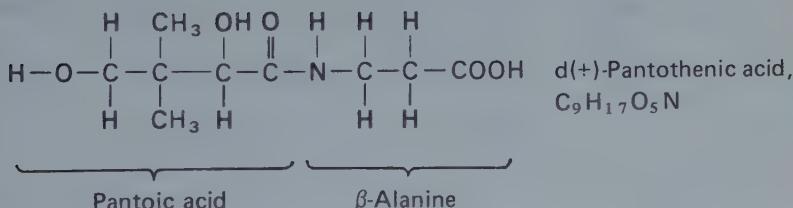
All organisms require it

Endogenous sources—Higher plants

Exogenous sources—All other organisms (not available from intestinal synthesis in man)

### CHEMISTRY

#### 1. Structure



#### 2. Reactions

Heat—Labile

Oxidation—Stable

Acid—Labile (warm)

Reduction—Stable

Alkali—Labile (warm)

Light—No data

Water—Sol. (acid)

#### 3. Properties

Appearance—yellow viscous oil

MP—unstable

MW—219.24

Crystal Form—No data

Salts—Calcium, sodium  
 Important Groups for activity  
 β-amino group  
 Solubility  
 H<sub>2</sub>O—7 g/100 ml  
 Acet., Alc.—Sol.  
 Benz., Chl., Eth.—Insol.

Absn. Max.—358 mμ  
 Chem. Nature—Conjugated amino acid, polyhydroxy acid  
 Miscellaneous:  
 $\alpha_D^{25} = (+37.5^\circ)$  (H<sub>2</sub>O)  
 $pK_a = 4.4$

#### 4. Commercial Production: Synthetic

Condensation of d-pantolactone with salt of β-alanine

#### 5. Isolation

Sources—Rice, bran, liver, yeast

Method

Extract liver with 90% ethyl alc.  
 Adsorb out organic bases on Fuller's earth  
 Adsorb vitamin on charcoal, pH 3.6, elute with ammonia  
 Form brucine salts, extract selectively with CHCl<sub>3</sub>  
 Convert brucine salt to calcium salt  
 Purify by fractional ppt. from organic solvents

#### 6. Determination

Bioassay

Animal—Growth rate of chicks

Microbiol—Growth of *L. casei*

Physicochemical—Estimate of β-alanine after hydrolysis; estimate CoA by citrate cleavage enzyme

### DISTRIBUTION AND SOURCES

#### 1. Occurrence

Plants

Fruit—All (low)  
 Vegetables—All (medium and low)  
 Nuts—All (high and low)

Animals

All (medium and high)  
 Organs (brain, heart, kidney, liver)

Microorganisms

Yeast (high), Rumen bacteria in sheep and cattle

Molds

**2. Dietary Sources**

High: 2.0 mg-10.0 mg/100 g

Beef (brain, heart, liver, kidney), pork (liver, kidney), sheep liver,  
chicken liver, lamb kidney

Eggs

Herring, cod ovary

Wheat germ, bran, dried peas, peanuts

Yeast, royal jelly

Medium: 0.5 mg-2.0 mg/100 g

Salmon, clams, mackerel

Walnuts

Broccoli, soybeans, oats, lima beans, cauliflower, peas, avocado,  
carrots, kale, dried lentils, spinach, rice

Beef, pork (ham, bacon), chicken, lamb

Mushrooms, wheat, cheese

Low: 0.1-0.5 mg/100 g

Bananas, oranges, peaches, pears, pineapples, tomatoes, apples, grapes,  
grapefruit, lemons, plums

Onions, kidney beans, cabbage, lettuce, peppers, white and sweet  
potatoes, turnips, watercress

Almonds

Oysters, lobster, shrimp

Veal

Milk, honey, molasses

**MEDICAL AND NUTRITIONAL ROLE****1. Units:** By weight, mg**2. Normal Blood Levels:** 19-32 µg/100 ml**3. Recommended Allowances**

Children—no data

Adults—Exact values unknown, estimate 10-15 mg/day

Special—Increased needs in stress situations

**4. Administration**

Injection—Parenteral

Topical—No data

Oral—Preferred route

**5. Factors Affecting Availability**

Decrease

Cooking—Up to 44% loss

Heat instability

Difficult release of bound forms

Increase: Intestinal bacteria synthesis (very little in man)

**6. Deficiency Symptoms**

General

Neuromotor disturbances

Cardiovascular disorders

Digestive disorders

Infection susceptibility

Physical weakness, depression

Stress susceptibility—rats

Skin disorders (cornea)—rats, chicks

Liver disorder—rat, chick

Reproductive failure—chick

Decreased antibody production—rat

**7. Effects of Overdose**

10 g/kg in mice, respiratory failure

Essentially nontoxic in man

**METABOLIC ROLE****1. Biosynthesis**

Precursors

 $\alpha$ -Ketoisovaleric acid (pantoic acid)Uracil ( $\beta$ -alanine)Aspartic acid ( $\beta$ -alanine)

Intermediates

Ketopantoic acid

Pantoic acid

 $\beta$ -alanine**2. Production: Species and Sites**

Plants—Green plants, fungi

Bacteria—Intestinal

**3. Storage:** Possibly liver, heart, kidney (all small amounts)

**4. Blood Carriers:** Blood proteins

**5. Half-life:** Estimate average loss: 25% of daily requirements

**6. Target tissues:** All, esp. brain, heart, kidney, liver

## **7. Reactions**

Coenzyme form: CoA (adenine -3'-P-Ribose-P-P-pantothenic acid- $\beta$ -mercapto ethylamine)

<i>Organ</i>	<i>Enzyme System</i>	<i>Effect</i>
Liver	TRANSFERASE: Citrate condensing enzyme $\beta$ -Ketothiolase, CoA transferase	Activated
Brain	TRANSACYLASES: Choline acetylase, lipoic transacetylase, phosphotransacetylase	Activated
Liver	ISOMERASES: Methylmalonyl isomerase, $\beta$ -hydroxyacyl racemase, enoyl isomerase	Activated
Liver	ESTERASES: Acetyl CoA deacylase, succinyl CoA deacylase	Activated
Liver	HYDRASES: Enoylhydrase	Activated
Liver	SYNTHETASES: Acetic thiokinase, fatty acid thiokinases, succinic thiokinase, acetyl carboxylase, propionyl carboxylase, methyl crotonylcarboxylase	Activated
Muscle and liver	DEHYDROGENASES: Hydroxyacyldehydrogenase, pyruvate dehydrogenase, $\alpha$ -ketoglutarate dehydrogenase acyl dehydrogenases	Activated

## **8. Mode of Action**

Cellular

Anabolic

Lipid synthesis increased

Active in synthesis of porphyrins, acetylcholine and isoprenoid groups

Sterol and hormone synthesis increased

Catabolic—Regulates CHO metabolism

Other—As coenzyme A in CHO, lipid, and protein metabolism. Acyl transfer agent.

Organismal

Fat synthesis and breakdown

Respiratory pigment synthesis

Water metabolism regulator

Energy metabolism regulator

## 9. Catabolism

Intermediates—Not destroyed in body

Excretion Products

Urine—Pantothenic acid (1-7 mg/day)

Feces—Variable

## MISCELLANEOUS

### 1. Relationship to Other Vitamins

Folic acid—Required for utilization of pantothenic acid

Biotin—Required for utilization of pantothenic acid; acts with pantothenic acid in fatty acid biosynthesis; reduces severity of pantothenic acid deficiency in rats

Vitamin C—Compensates partly for deficiency of pantothenic acid

CoQ—Decreased in pantothenic acid deficiency

Vitamin A and Vitamin E—Synthesis promoted by pantothenic acid (isoprene production)

Pantothenic acid and biotin involved in synthesis of niacin

### 2. Relationship to Hormones

Aldosterone, Deoxycorticosterone, Cortisol, Testosterone, Progesterone—Cholesterol precursors for sterol hormones in adrenal cortex require pantothenic acid for synthesis; pantothenic acid deficiency produces cortical necrosis

Cortisone—Relieves certain pantothenic acid deficiency symptoms in humans

STH—Produces pantothenic acid deficiency in rats; synergist in growth

### 3. Unusual Features

Promotes amino acid uptake

Anticarcinogenic agent (?) (A. E. Needham)

Potentiated by Zn in preventing graying of hair in rats

Resistance to stress of cold immersion

Deficiency of pantothenic acid in tumors

Chick hatchability depends on pantothenic acid

Useful in treating vertigo, postoperative shock, poisoning with isoniazid and curare

Useful in acceleration of wound healing

Useful in treating Addison's disease, liver cirrhosis, and diabetes

**4. Possible Relationships of Deficiency Symptoms to Metabolic Action**

Neuromotor Disturbances

Decreased phospholipid and acetylcholine synthesis

Has effect on membranes, degeneration of nerves

Cardiovascular disorders—Disturbances of fat and CHO metabolism due to degeneration of liver

Digestive disorders—Decreased bile acid production due to decreased sterol production; atrophy of intestinal mucosa

Infection susceptibility—Decreased antibody production due to decreased ATP synthesis

Physical weakness and depression—Decreased ATP synthesis

# 16

# Hypothalamic- Releasing Factors

## CORTICOTROP(H)IN-RELEASING HORMONE (CRH)

1. **Synonyms:** CRF, cortical-releasing factor (hormone), (adreno) corticotrop(h)in-releasing factor
2. **History**
  - 1955—Saffran *et al.* first demonstrated release of ACTH by crude hypothalamic extract
  - 1962—Schally *et al.* proposed structure for CRH
  - 1963—Critchlow *et al.* reported CRH preparation maintains ACTH synthesis in pituitary transplants
3. **Forms:**  $\alpha_1$ ,  $\alpha_2$ , and  $\beta$
4. **Analogs:** Vasopressin, oxytocin
5. **Functions:** Chemical stimulant; messenger from hypothalamus to ACTH-producing cells in anterior pituitary; stimulates production of ACTH
6. **Structure**
  - Peptide with disulfide ring system
  - $\alpha_1$ —16 amino acids, similar to  $\alpha$ -MSH
  - $\alpha_2$ —13 amino acids, almost identical to  $\alpha$ -MSH
  - $\beta$ —11 amino acids, similar to arginine vasopressin

7. MW—Approx. 1100 ( $\beta$ ), 1500 ( $\alpha$ )
8. Extraction; Purification: Acid acetone, pH 1.5, ppt. with  $(\text{NH}_4)_2\text{SO}_4$ , chromatography, countercurrent distribution
9. Determination  
Bioassay—Release of corticosteroids in rat plasma on injection of CRH
10. Factors Affecting Release of CRH  
Stimulators—Stress, low level of cortisol, sympathomimetic amines  
Inhibitors—Cerebral cortex factors
11. Production Sites and Storage Location  
Hypothalamus—Ventral area, neurohypophysis
12. Target Tissues: Anterior pituitary (ACTH-producing cells)
13. Reactive Intermediate: Cyclic AMP
14. Unusual Features: Very unstable

### LUTEINIZING HORMONE-RELEASING HORMONE (LRH)

1. Synonyms: LRF, LH-releasing factor (hormone)
2. History  
1941—Guillemin first postulated existence of LH-releasing factor  
1964—McCann and Ramirez caused depletion of ovarian ascorbic acid with extracts of hypothalamus  
1964—Campbell *et al.* infused hypothalamic extract into anterior pituitary and produced ovulation
3. Functions: Chemical stimulant: messenger from hypothalamus to LH-producing cells in anterior pituitary
4. Structure: Peptide containing Asp., Glu., Gly., Ala., Lys., His., Arg., Thr., Prol., Leu., Ser.
5. MW—1200-2500
6. Extraction; Purification: Acetic acid extraction; gel filtration on sephadex G-25, chromatography

7. Determination: Bioassay—Depletion of ovarian vit. C

8. Factors Affecting Release of LRH

Stimulators—Low levels of estradiol, testosterone, norepinephrine, catecholamines

Inhibitors—High levels of LH, testosterone

9. Production Sites and Storage Location: Hypothalamus

10. Target Tissues: Anterior pituitary (LH-producing cells)

11. Reactive Intermediate: Cyclic AMP

### THYROTROP(H)IN-RELEASING HORMONE (TRH)

1. Synonyms: TRF, TSH-releasing factor (hormone)

2. Antagonists: T3, T4 (large doses)

3. History

1958—Harris and Woods produced thyroidal  $I_{131}$  release on stimulation of hypothalamus

1958—Nikitovich *et al.* produced TSH after reimplanting pituitary graft near median eminence, but not in temporal lobe area

1969—Byler *et al.* determined structure of porcine TRH

4. Functions: Chemical stimulant: messenger from hypothalamus to TSH-producing cells in anterior pituitary

5. Structure: Porcine TRH: Tripeptide

L-pyroglutamyl—L-histidyl—L-proline amide

6. MW: Approx. 400

7. Extraction: Purification: Gel filtration; high-voltage electrophoresis

8. Factors Affecting Release of TRH

Stimulators—Low level of T4, cold, stress, light,  $Ca^{++}$  ion

Inhibitors—No data

9. Production Sites and Storage Location: Suprachiasmatic area, median eminence, neurohypophysis

10. Target Tissue: Anterior pituitary (TSH-producing cells)
11. Reactive Intermediate: Cyclic AMP
12. Unusual Properties: Destroyed in human serum in 15 min at 37°C

## FOLLICLE STIMULATING HORMONE-RELEASING HORMONE (FRH)

1. Synonyms: FSH-RF, FSH-releasing factor (hormone), FRF, FSH-RH
2. History
  - 1932—Hollweg and Junkmann proposed CNS involved in secretion of gonadotropins
  - 1964—Igarishi *et al.* demonstrated FSH-releasing activity of hypothalamic extracts
  - 1964—Mittler and Meites demonstrated FRH increases release of FSH in pituitary culture
3. Functions: Chemical stimulant: messenger from hypothalamus to FSH-producing cells in anterior pituitary
4. Structure: Polyamine, MW = < 300
5. Extraction: Purification: Similar to LRH, plus long columns of sephadex G-25.
6. Factors Affecting Release of FRH
  - Stimulators—Estrogen level (cyclic), K<sup>+</sup> ion
  - Inhibitors—Stress, FSH
7. Production Sites and Storage Location: Median eminence
8. Target Tissues: Anterior pituitary (FSH-producing cells)
9. Reactive Intermediate: Cyclic AMP

## PROLACTIN RELEASE-INHIBITING HORMONE (PIH)

1. Synonyms: PIF, RIH, prolactin inhibiting factor (hormone)

**2. History**

1963—Meites showed increased prolactin secretion by pituitaries in tissue culture while other hormones decreased

1962-63—Talwalker; Basteels *et al.* reduced prolactin in pituitary culture by adding hypothalamic extract

**3. Functions:** Chemical inhibitor: messenger from hypothalamus to prolactin-producing cells in anterior pituitary

**4. Structure:** Some similarity to LRH, probably a peptide

**5. Extraction: Purification:** 0.1 N HCl extract, concentrate and separate on sephadex G-25

**6. Factors Affecting Release of PIH**

Stimulator—Prolactin

Inhibitor—Reserpine

**7. Production Sites and Storage Location:** Satiety center, appetite suppressor in hypothalamus

**8. Target Tissues:** Prolactin-producing cells in anterior pituitary

**9. Reactive Forms:** No data

**10. Unusual Features:** Stable to boiling

**GROWTH HORMONE-RELEASING HORMONE (GRH)**

**1. Synonyms:** GRF, somatotrop(h)in-releasing factor (hormone), growth-hormone-releasing factor (hormone), SRF, GHRF

**2. History**

1964—Deuben and Meites released GH in rat pituitary in tissue culture using rat hypothalamic extracts

1965—Schally *et al.* stimulated release of GH by incubating rat pituitaries with beef, pig, hypothalamic extracts

**3. Functions:** Chemical stimulant; messenger from hypothalamus to STH-producing cells in anterior pituitary

4. **Structure:** Acidic polypeptide
5. **MW:** 2500 (approx.)
6. **Extraction: Purification:** 0.1 N HCl extraction; gel filtration, CMC chromatography
7. **Factors Affecting Release of GRH**
  - Stimulators—No data
  - Inhibitors—No data
8. **Production Sites and Storage Location:** Hypothalamus, neurohypophysis
9. **Target Tissues:** Anterior pituitary cells producing STH
10. **Reactive Intermediate:** Cyclic AMP

### PROLACTIN-RELEASING HORMONE (PRH)

1. **Synonyms:** PRF, prolactin-releasing factor (hormone)
2. **History**

1965—Kragt and Meites increased prolactin release in pigeon pituitary culture by pigeon hypothalamic extracts
3. **Functions:** Stimulates release of prolactin from anterior pituitary (probably only in birds)
4. **Structure:** Not obtained pure
5. **Extraction: Purification:** No data
6. **Factors Affecting Release of PRH**
  - Stimulators—No data
  - Inhibitors—No data
7. **Production Sites and Storage Location:** Hypothalamus of birds
8. **Target Tissues:** Anterior pituitary cells secreting prolactin

## MELANOCYTE STIMULATING HORMONE RELEASE-INHIBITING HORMONE (MIH)

1. **Synonyms:** MIF, MSH-inhibiting factor (hormone), MRIH
2. **History**
  - 1962—Etkin produced frog blackening by repositioning pituitary in other locations in body
  - 1964—Kastin and Ross produced coloration in albino rat by repositioning pituitary
3. **Functions:** Inhibits release of MSH from intermediate lobe of pituitary
4. **Structure:** Not obtained pure
5. **Extraction: Purification:** 2 N acetic acid extraction; gel filtration on sephadex G-25
6. **Factors Affecting Release of MIH**
  - Stimulators—No data
  - Inhibitors—No data
7. **Production Sites and Storage Location:** Hypothalamus (paraventricular nucleus)
8. **Target Tissues:** Cells of intermediate pituitary lobe secreting MSH

## MELANOCYTE STIMULATING HORMONE-RELEASING HORMONE (MRH)

1. **Synonyms:** MRH, MSH-releasing factor (hormone)
2. **History**
  - 1965—Taliesnik and Orios found evidence for existence of MRH
3. **Functions:** Stimulates release of MSH from intermediate lobe of pituitary
4. **Structure:** Not obtained pure
5. **Extraction: Purification:** No data

**6. Factors Affecting Release of MRH**

Stimulators: No data

Inhibitors: No data

**7. Production Sites and Storage Location:** No data

**8. Target Tissues:** Cells of intermediate pituitary lobe secreting MSH

# 17 Growth Hormone

## GENERAL INFORMATION

1. **Synonyms:** Somatotrop(h)in, GH, STH, phyone, (anterior) pituitary growth hormone, adenohypophyseal growth hormone, somatotropic hormone, hypophyseal growth hormone
2. **History**
  - ✓ 1921—Evans and Long induced growth in rats with pituitary extract
  - ✓ 1930—Smith restored growth in hypophysectomized rats with hypophyseal implants
  - 1945—Li *et al.* isolated growth hormone from anterior pituitary (beef)
  - 1962—Reisfeld *et al.* isolated growth hormone from human anterior pituitary
  - 1964—Glick, Roth, Berson, and Yallow developed accurate immunoassay of growth hormone in serum
  - 1966—Li *et al.* determined amino acid sequence for human growth hormone, 188 amino acid residues
  - 1971—Li *et al.* synthesized human growth hormone
3. **Physiological Forms:** "Sulfation factor"
4. **Active Analogs and Related Forms:** Prolactin (human). Chorionic factor
5. **Inactive Analogs and Related Forms:** Primate GH minus 10% A.A. residues, bovine GH minus 25% A.A.'s, human GH minus C-terminal phenylalanine

**6. Antagonists:** Cortisone, cortisol, insulin (all concentration dependent), plasma inhibitors

**7. Synergists:** Adrenal corticoids (fat metabolism), ACTH, T4, insulin, testosterone

### 8. Physiological Functions

General growth of organism

Promotes skeletal growth, protein anabolism, fat metabolism, CHO metabolism, water and salt metabolism

### 9. Deficiency Diseases and Disorders

Deficiency—Progeria, pituitary dwarf, hypopituitarism

✓ Excess—Acromegaly, gigantism

**10. Essentiality for Life:** Absence results in stunted, abnormal growth, with  
✓ possible decrease in normal lifespan

## CHEMISTRY

### 1. Structure—Growth hormone, structure known and synthesized (Human)

Human—Coiled, unbranched protein, 188 A.A. residues, 2S-S-bridges  
(Phe ——— Phe)

Bovine—Coiled, 1-branch protein, 400 A.A. residues, 4S-S-bridges



### 2. Reactions

Heat—Stable to 100°C 15 min

Acid—Unstable (strong)

Alkali—Unstable (strong)

Water—Soluble, acidic

Oxidation—Oxidizes S—S bonds

Reduction—Reduces S—S bonds

Light—No data

Proteolysis—15% limit of digestion of human growth hormone before loses activity

### 3. Properties

Appearance—No data

MW—21,500 (human)

48,000 (bovine)

MP—None

Crystal Form—None

Salts—None

Important Groups for activity

—S—S—; Phe (terminal)

Solubility

H<sub>2</sub>O—Sol.

Acet. Alc.—Insol.

Benz., Chl., Eth.—Insol.

Absn. Max.—Approx. 280 m $\mu$

Chemical Nature—Simple protein, globulin

Misc- pl = 4.9 (human)

= 6.8 (bovine)

✓ 4. Commercial Production: Not available

5. Isolation

Sources—Pituitary glands of sheep, ox, pig, monkey

Methods

Extract with borate buffer, pH 8.8, DEAE chromatography

✓ Ppt. with  $(\text{NH}_4)_2\text{SO}_4$ , column chromatog.  $\text{IRC}_5\text{O}$ , pH 5.1

Treat with acetic acid-acet., ppt. with acet.; column chromatog., ppt. with alc.

Additional purification: Counter-current distribution and gel filtration

6. Determination

Bioassay

Tibia test (rat) (5  $\mu\text{g}$ -120  $\mu\text{g}$ )

Increased weight (rat)

Increased N retention (rat)

$\text{S}^{35}$  incorporation into cartilage (rat)

Physicochemical

Immunoassay

Radioimmunoassay

## MEDICAL AND BIOLOGICAL ROLE

1. Species Occurrence, Specificity and Antigenicity

Occurrence—All vertebrates except birds

Specificity—No crossing of species lines for primates or guinea pigs.

Other vertebrates slightly more tolerant

Antigenicity—Monkey, sheep, rat, pig hormones antigenically different.

2. Units: 1 USP unit = 1 I.U. = 1 mg

3. Normal Blood Levels: 20-50  $\mu\text{g}/100 \text{ ml serum}$  (man)

4. Administration

Injection—Preferred route

Topical—Not used

Oral—Not used, inactivated

5. Factors Affecting Release

Inhibitors—Inadequate dietary protein, sleeplessness, hyperglycemia

Stimulators—Plasma amino acids, hypoglycemia, GHRH, vasopressin (fish), adequate protein in diet, fasting, exercise, sleep

## 6. Deficiency Symptoms

Humans

- Dwarfism
- Failure of long bones to close
- Failure of sexual maturation
- Increased fat deposition

## 7. Effects of Overdose, Excess

- Tumors,  $\beta$ -cell destruction
- Pituitary giants
- Bone thickening

## METABOLIC ROLE

### 1. Biosynthesis

- Precursors—Amino acids. All 20 standard
- Intermediates—Unknown
- Site(s) in Cell—Unknown

2. Production Sites: Anterior pituitary acidophils

3. Storage Areas: Anterior pituitary

4. Blood Carriers:  $\alpha_2$ -Macroglobulin,  $\beta$ -lipoprotein

5. Half-life: 20 min

6. Target Tissues: All except nervous tissue, esp. bone, viscera, muscle, epiphyseal cartilage

### 7. Reactions

- Reactive form—Sulfation factor (?)

<i>Organ</i>	<i>Enzyme System</i>	<i>Effect</i>
Most tissues and organs	RNA-polymerase	Activated
Blood cells	Protein-synthetic Alk. phosphatase	Activated

## 8. Mode of Action

Cellular

Anabolic

Increases rate of protein and RNA synthesis

Increases glycogen deposition (muscles)



Catabolic—Mobilizes unsaturated fatty acids

Other—Increases amino acid permeability of cells; increases salt and H<sub>2</sub>O transport in kidney

#### Organismal

Increases muscle, skin, viscera, lymph glands, bone and cartilage size

Decreases urea formation

Increases blood sugar

Increases tissue nitrogen

Mobilizes fatty acids from adipose tissue

### 9. Catabolism

Intermediates—Liver destruction, to peptides; plasmin in blood inactivates GH

Excretion Products—Small amounts of GH in urine

## MISCELLANEOUS

### 1. Relationship to Vitamins

All vitamins—All concerned with growth

### 2. Relationship to Other Hormones

Insulin—Inhibited by GH in certain concentrations. Synergist with GH at other (low) concentrations

GHR—GH-releasing factor of hypothalamus

Vasopressin—A hypothalamic release factor (in fish)

Cortisol—Antagonist to GH (protein metabolism). Also a synergist (fat metabolism)

Testosterone—Synergist with GH

T4—Synergist with GH (differentiation)

ACTH—Synergist with GH

### 3. Unusual Features

Rat GH lacks tryptophan; contaminated with protease

Lactogenic and growth activity present in human GH

Guinea pig not sensitive to own GH

HGH withstands 15 min at 100°C

Increases capacity to form tumors

Lactogenic action in humans, similarity in structure to prolactin

**4. Possible Relationships of Deficiency Symptoms to Metabolic Action**

Dwarfism—Lack of protein synthesis due to lack of GH activity

Failure of long bones to close—Lack of major metabolic action of GH

Failure of sexual maturation—Lack of synergism of sex hormones and GH

Increased fat deposition—Lack of catabolic action of GH

# Thyroid-Stimulating Hormone (TSH)

## GENERAL INFORMATION

1. **Synonyms:** Thyroid-stimulating hormone, thy(e)otrop(h)ic hormone, TTH, thyrotrop(h)in
2. **History**
  - 1921—Evans and Long first noted effects of pituitary extracts on growth
  - 1927-30—Smith reported that hypophysectomy in rat causes atrophy of thyroids (and other organs) correctable by hypophyseal implants
  - 1929—Basset; Aron and Loeb defined properties of a thyrotrophic hormone
  - 1945—Ciereszko isolated crude TSH from beef pituitaries
  - 1960—Wynston *et al.* obtained purified TSH from beef, sheep, and whale pituitaries
  - 1963—Carsten *et al.* determined amino acid composition of beef TSH
3. **Physiological Forms:** Unknown
4. **Active Analogs and Related Compounds:** LATS (long-acting thyroid stimulator)
5. **Inactive Analogs and Related Compounds:** TSH minus CHO moiety, oxidized TSH
6. **Antagonists:** Acetylated TSH, *p*-aminosalicylic acid, perchlorate, sulfathiazole, thiocyanate, thiouracil, thiourea

**7. Synergists:** STH, ACTH, MSH, TH

**8. Physiological Functions**

- Regulation of body temperature via T4
- Maintains thyroid gland and its secretory activity (colloid discharge)
- Maintains iodine uptake by thyroid gland
- Promotes differentiation in embryo during development (via T4)
- Stimulates coupling of diiodotyrosine to form thyroxine (T4)

**9. Deficiency Diseases, Disorders**

- Thyrotoxicosis (excess), goiter (excess or deficiency), exophthalmos (excess), Sheehan's syndrome (deficiency)

**10. Essentiality for Life:** Required by all vertebrates for proper development; possible shortening of lifespan in absence of TSH

## CHEMISTRY

**1. Structure**

Glycoprotein—Unpurified (contaminated with LH). Contains 2.5% CHO—Glucosamine, galactosamine, hexose, fucose

**2. Reactions**

Heat—Inactivates	Oxidation—Inactivates using bromine, iodine, and permanaganate
Acid—Easily inactivates	
Alkali—Inactivates	Reduction—May potentiate effects of TSH
Water—Basic	Light—No data
	Proteolysis—inactivates with pepsin or trypsin

**3. Properties**

Appearance—No data	Solubility
MW—26-30,000 (300 amino acids)	H <sub>2</sub> O—Sol.
MP—No data	Acet., Alc.—Insol.
Crystal Form—No data	Benz., Chl., Eth.—Insol.
Salts—No data	Absn. Max.—Approx 280 m $\mu$
Important Groups for activity	Chemical Nature—Basic
$\alpha$ -NH <sub>2</sub> , tyrosine, CHO moiety	glycoprotein, globulin
—S—S—	MISC—pI = 7.8

**4. Commercial Production:** Extract bovine pituitary glands

**5. Isolation**

Sources—Bovine pituitary glands

Methods

Extract pituitary (freeze, dried) in 2% NaCl, pH 7.6. Precipitate at pH with acetone (1 I.U./mg)

Precipitate from 3.6 M ammonium sulfate

Purification

Chromatog. on IRC-50, elute with 1 M NaCl

Chromatog. on CM cell, elute with 0.2 M NaCl 0.05 M formate, pH 3-4

Gel filtration on sephadex G-50, G-100

Chromatog. on IRC-50 in urea (60 I.U./mg)

**6. Determination**

Bioassay

Height of secretory epithelium in thyroid—guinea pig

Number colloid droplets in guinea pig thyroid

I<sub>2</sub> depletion of 1-day chick

Uptake I<sup>131</sup> by thyroid of rats

In vitro assay, slice uptake of I<sup>131</sup>

Physicochemical—Radioimmunoassay

## MEDICAL AND BIOLOGICAL ROLE

**1. Species Occurrence, Specificity, and Antigenicity**

Occurrence—All vertebrates

Specificity—Incomplete; bovine TSH active in all species  
(chick and guinea pig most sensitive)

Antigenicity—High; bovine TSH antigenic in rabbits

**2. Units:** 1 I.U. = 13.5 mg of standard = 1 USP unit

**3. Normal Blood Levels (Man):** 5-20 milliunits/100 ml plasma

**4. Administration**

Injection—Preferred route

Topical—Inactive

Oral—Inactive

## 5. Factors Affecting Release

### Inhibitors

- Feedback via hypothalamus from high serum T4
- High serum iodide, massive doses vit. A
- High temperature
- Inhibition of hypothalamus
- Nerve stimuli

### Stimulators

- Release factor of hypothalamus (TRH)
- Decreased serum T4 via hypothalamus
- Low temperature
- Stimulation of hypothalamus
- Nerve stimuli

## 6. Deficiency Symptoms

- Decreased synthesis of thyroid hormones
- Low serum protein-bound iodine (PBI)
- Decreased iodine uptake by thyroid
- Secondary symptoms of thyroxine deficiency

## 7. Effects of Overdose, Excess

- Exophthalmic effect
- Increased synthesis of thyroid hormones
- Increased PBI
- Increased iodide uptake by thyroid
- Increased basal metabolic rate
- Decreased thyroid iodine
- Decreased blood cholesterol
- Goiter

## METABOLIC ROLE

### 1. Biosynthesis

- Precursors—17 of 20 standard amino acids. No glutamine, asparagine, tryptophan
- Intermediates—Unknown
- Site(s) in cell—Basophilic cytoplasm

### 2. Production Sites: S<sup>2</sup> type cell, anterior pituitary

### 3. Storage Areas: Not stored

**4. Blood Carriers:**  $\beta$ -globulins

**5. Half-life:** 54 min

**6. Target Tissues:** Thyroid, reproductive glands, liver, probably muscles

### **7. Reactions**

Reactive intermediate—Cyclic AMP (secondary messenger)

<i>Organ</i>	<i>Enzyme System</i>	<i>Effect</i>
Thyroid	Proteolytic enzymes (on colloid)	Activated
Thyroid	Synthetic enzymes for T4	Activated
Thyroid	Adenyl cyclase	Activated
Thyroid	DPN kinase	Activated
Thyroid	HMP enzymes	Activated

### **8. Mode of Action**

Cellular

Anabolic

RNA and protein synthesis (thyroid)

Thyroid hormone synthesis (thyroid)

Catabolic

Lipolytic activity increased

Proteolytic activity increased (thyroid)

Glucose oxidation increased via TCA, HMP, and glycolysis

Other

Activates thyroid cell membrane enzymes

Increases oxidase granules (thyroid), and O<sub>2</sub> consumption by thyroid cells

Increases glucose and iodine entry into cells

No increase in NADP<sup>+</sup>

Organismal

Mobilization of thyroid hormones

Increases serum bound iodine

Maintains body temperature via T4

### **9. Catabolism**

Intermediates—Hydrolyzed in liver

Excretion products—Present in urine

## MISCELLANEOUS

### 1. Relationship to Vitamins

Vitamin A—Massive doses of vit. A inhibit secretion of TSH; thyroid hormones required for carotene and retinene conversions

Vitamins B<sub>1</sub>, B<sub>2</sub>, B<sub>12</sub>, C—Requirements increased in hyperthyroidism; tissue concentrations reduced

Vitamin B<sub>6</sub>, Niacin—Conversion to phosphorylated reactive forms impaired in hyperthyroidism

Vitamins A, D, E, K—Requirements increased in hyperthyroidism; tissue concentrations reduced in hyperthyroidism

### 2. Relationship to Other Hormones

T4—TSH stimulates production of T4; synergist in lactation

LH—Contained frequently as a contaminant in TSH

### 3. Unusual Features

Not inactivated by neuraminidase

CHO moiety needed for activity

Different functions in lower species

Rapid loss of potency in solution

Inactivation by freeze drying

Reduction may potentiate activity

High cystine content

Phospholipase activity of TSH reported

### 4. Possible Relationships of Deficiency Symptoms to Metabolic Action

Decreased synthesis of thyroid hormones—Insufficient activation of thyroid cell membrane enzymes

Low serum PBI—Reduction of T4 output due to decreased TSH

Decreased iodide uptake by thyroid—Decreased reactivity of thyroid gland

# 19 Follicle- Stimulating Hormone (FSH)

## GENERAL INFORMATION

1. **Synonyms:** Follotropin, Luteoantine, Thylakentrin, Prolan A, gonadotropin I, gametogenic hormone, follicle ripening hormone, gametokinetic hormone
2. **History**
  - 1921—Evans and Long first noted gonadotropic effect of pituitary extracts on rats
  - 1927-30—Smith reported that hypophysectomy in rat causes atrophy of gonads (and other organs) correctable by hypophyseal implants
  - 1928—Aschheim and Zondek discovered a follicle-stimulating gonadotropin in menopausal urine
  - 1933—Fevold *et al.* identified a separate follicle-stimulating hormone in the pituitary
  - 1939—Chow *et al.* demonstrated FSH to be resistant to inactivation by proteolytic enzymes
  - 1940—Fevold *et al.*    } Described isolation procedures
  - 1949—Li, Simpson and Evans } for animal FSH
  - 1965—Roos and Gemzell prepared human FSH from menopausal urine
3. **Physiological Forms:** Unknown
4. **Active Analogs and Related Forms:** PMSG, HMG (mixture of FSH and LH)

5. Inactive Analogs and Related Forms: FSH without sialic acid moiety
6. Antagonists: No data
7. Synergists: LH, STH, T4
8. Physiological Functions: Gametogenic
  - Female—Stimulates ovarian follicles to grow and to develop, forming multiple layers and antra
  - Male—Stimulates seminiferous tubules; stimulates spermatogenesis
9. Deficiency Diseases, Disorders: Klinefelter's syndrome (deficiency), Turner's syndrome (deficiency), hypogonadotropic eunuchoidism (deficiency)
10. Essentiality for Life: Not required for life of organism, but required for reproduction by all vertebrates analyzed

## CHEMISTRY

1. Structure: Unknown
  - Glycoprotein—7.4% sialic acid; impure preparations (contam. with LH)
  - 0.6% hexosamine; 1.3% hexose
2. Reactions
 

Heat—No data Acid—Stable Alkali—Stable Water—Acidic	Oxidation— $\text{H}_2\text{O}_2$ , periodate —inactivate Reduction—Cysteine, ketene—inactivate Light—No data Proteolysis—Inactivates on 60-75% digestion with trypsin Urea—Stable in 6 M urea
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3. Properties
 

Appearance—No data MW—30,000 (pig) 28,000 (sheep) MP—No data Crystal Form—No data Salts—No data	Important Groups for activity Sialic acid (complex CHO) —S—S—, terminal $\text{NH}_2$ Solubility $\text{H}_2\text{O}$ —soluble Acet., Alc.—Insol. Sol. 50% Acet.
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Sol. 70% Alc.  
 Benz., Chl., Eth.—Insol.  
 Absn. Max.—Approx 280 m $\mu$   
 Chemical Nature—Acidic  
 glycoprotein

Misc—pl = 5.1 (pig)  
 = 4.5 (sheep)

**4. Commercial Production:** Extracted from human and sheep pituitaries

**5. Isolation**

Sources—Human, horse, sheep, swine pituitary  
 Method—Extract frozen pituitaries in aqueous salts; fractional precipitation from ammonium sulfate; DEAE cellulose; sephadex G-100; polyacrylamide gel electrophoresis

**6. Determination**

Bioassay—Problems with LH contamination  
 Ovarian weight change  
 Stimulation of young ovarian follicles (rabbit)  
 Increase in weight of testes  
 Physicochemical  
 Immunoassay  
 Radioimmunassay

## MEDICAL AND BIOLOGICAL ROLE

**1. Species, Occurrence, Specificity, and Antigenicity**

Occurrence—Found in all species of vertebrates studied  
 Specificity—Strong species specificity (Fish FSH inactive in mammals)  
 Antigenicity—Moderately antigenic

**2. Units:** 1 I.U. = 38.5  $\mu$ g sheep FSH (NIH-S<sub>1</sub>, Std.)

**3. Normal Blood Levels (Man):** Males: 0.02 I.U./100 ml plasma, females 0.015 I.U./100 ml plasma (Menopausal female: 0.20 I.U./100 ml plasma)

**4. Administration**

Injection—Preferred route  
 Topical—inactive  
 Oral—inactive

## 5. Factors Affecting Release

Inhibitors—Estradiol, cortisol, stress, hyperthyroidism, feedback by sex hormones via hypothalamus

Stimulators—FRH from hypothalamus, castration, menopause, low sex hormone levels, female—rhythmic control by hypothalamus via FRH secretion, male—continuous secretion of FRH by hypothalamus

## 6. Deficiency Symptoms

Decreased gametogenic function and development (nonfunctional)

Atrophy of gonads

No maturation of ova, sperm

Obesity

Decreased libido, potency, hair growth

Decreased blood levels of estrogen

## 7. Effects of Overdose, Excess

Hypertrophy of secondary sex organs

Increased growth and maturation of numerous follicles

Increased estrogen secretion (with LH)

Follicular cysts

## METABOLIC ROLE

### 1. Biosynthesis

Precursors—All 20 standard amino acids except methionine

Intermediates—Unknown

### 2. Production Sites: Anterior pituitary—basophilic cells (peripheral)

### 3. Storage Areas: Anterior pituitary

### 4. Blood Carriers: $\alpha$ , $\beta$ -plasma proteins

### 5. Half-Life: Approx. 1 hr

### 6. Target Tissues: Ovary, testis

### 7. Reactions

Reactive Form—Unknown

Enzyme Systems—Unknown

**8. Mode of Action**

Cellular

Anabolic—Unknown

Catabolic—Unknown

Other—Stimulates incorporation of glucose and  $\alpha$ -aminoisobutyric acid into rat ovaries

Organismal

Promotes growth of ovarian follicles

Promotes development of ovarian follicle

Promotes growth of seminiferous tubules

Promotes spermatogenesis

**9. Catabolism**

Intermediates—Liver hydrolysis

Excretion Products—Free in urine (active)—small amounts

**MISCELLANEOUS****1. Relationship to Vitamins**

Vitamin C—Depletion in ovary due to LH and FSH action

Vitamin E—Needed for maintenance of membranes in sex organs

**2. Relationship to Other Hormones**

STH, LH—Synergists to FSH

PMSG, HMG—Active analogs to FSH

ACTH—Inhibitor of FSH

T4—Inhibitor of FSH

**3. Unusual Features**

Increased instability with purer preparations

Only pituitary hormone not precipitated with 50% saturated  $(\text{NH}_4)_2\text{SO}_4$ 

Bird migration, ovulation, sex behavior controlled by FSH via light and temperature

Gonadotropins of mammals stimulate thyroids of fish

CHO groups needed for activity—neuraminidase inactivates

Cyclic release in females (spontaneous ovulators)

**4. Possible Relationships of Deficiency Symptoms to Metabolic Action**

Decreased gametogenesis and development of gonads, atrophy of gonads, no maturation of ova or sperm, decreased potency—lack of FSH function (unknown)

Obesity—Unknown

Decreased libido—decreased synergism with testosterone and LH

Decreased hair growth—decreased synergism with sex hormones and LH

Decreased blood levels of estrogen—decreased synergism with LH

# 20

# Luteinizing Hormone (LH)

## GENERAL INFORMATION

1. **Synonyms:** Luteotrop(h)in, interstitial cell-stimulating hormone, ICSH, Prolan B, gonadotrop(h)in II, Metakentrin, corpus luteum-ripening hormone
2. **History**
  - 1921—Evans and Long first noted gonadotropic effect of pituitary extracts on rats.
  - 1927-30—Smith noted hypophysectomy in rat caused atrophy of gonads (and other organs) correctable by hypophyseal implants
  - 1933—Fevold *et al.* identified a separate luteinizing hormone in pituitaries
  - 1940—Li, Simpson, and Evans isolated LH from sheep pituitaries
  - 1940—Shedlovsky *et al.* }                            Isolated LH from pig pituitaries
  - 1942—Chow *et al.*                                    }
  - 1962—Squire *et al.* isolated a purified LH from human pituitaries
3. **Physiological Forms:**  $\alpha$  and  $\beta$ -forms
4. **Active Analogs and Related Compounds**
  - HCG, HMG (mixture of FSH and LH)
  - PMSG (properties of FSH and LH)
5. **Inactive Analogs and Related Compounds:** LH minus CHO moiety

**6. Antagonists:** Prolactin, insulin (both concentration dependent)

**7. Synergists:** FSH, prolactin, TH, insulin

## **8. Physiological Functions**

### Female

Promotes estrogen and progesterone secretion, ovulation, maintains ovarian tissues

Stimulates rupture of follicles and formation of corpora lutea

### Male

Stimulates Leydig cells to secrete testosterone, gametogenic with FSH

Promotes growth of seminal tubules and accessory sex organs

**9. Deficiency Diseases, Disorders:** Hypogonadism; irregular sexual development

**10. Essentiality for Life:** Not required for life of organism, but required for reproduction by all analyzed vertebrates

## **CHEMISTRY**

### **1. Structure**

Globular glycoprotein with S-S bridges (2-5% CHO)

Ser-Val-Asp—human

Ser-Val-Phe—Ser-Lys (porcine)

### **2. Reactions**

Heat—Inactivates

Acid—Picric, TCA, picrolonic, and  
flavianic acids ppt. LH without  
loss of activity

Alkali—No data

Water—Sol., acidic

Oxidation— $H_2O_2$ , periodate,  
performic acid—inactivate

Reduction—Cysteine, ketene—  
inactivate

Light—No data

Proteolysis—Inactivates

Urea—Unstable in 6 M urea

### **3. Properties**

Appearance—White powder

MW—26,000 (human)

30,000 (sheep)

MP—No data

Crystal Form—No data

Salts—No data

Important Groups for activity

Cys., Pro.

CHO moiety

—S—S—

Solubility	Chemical Nature—Acidic, globular
H <sub>2</sub> O—soluble	glycoprotein
Alc.—Sol. 4% alc.,	Misc—pl = 5.4 (human)
Acet., Benz., Chl., Eth.—Insol.	= 7.3 (sheep)
Absn. Max.—Approx 280 m $\mu$	= 7.45 (pig)

#### 4. Commercial Production: Extraction of human or sheep pituitaries

#### 5. Isolation

Sources—Pituitary of human, sheep, swine, and beef

Method

- Aqueous extract at pH 5.5
- Ammonium sulfate precipitation
- Metaphosphoric acid precipitation
- Ethanol fractionation
- IRC-50; sephadex G-100

#### 6. Determination

Bioassay

- Vitamin C depletion of rat ovary
- Increased hyperemia in immature rat ovary
- Increased weight in male sex accessory organs
- Weaver-Finch test
- Physicochemical—Radioimmunoassay

### MEDICAL AND BIOLOGICAL ROLE

#### 1. Species Occurrence, Specificity, and Antigenicity

Occurrence—Found in all vertebrate species studied

Specificity—Slight species specificity

Antigenicity—Definite

#### 2. Units: 1 I.U. = 0.67 $\mu$ g ovine LH (NIH-S<sub>1</sub>, Std.)

#### 3. Normal Blood Levels (Man): 1.5-3.0 I.U./100 ml plasma (males and females) preovulatory and menopausal women 7.5-15.0 I.U./100 ml plasma

#### 4. Administration

Injection—Preferred route

Topical—Inactive

Oral—Inactive

## 5. Factors Affecting Release

Inhibitors

Cortisol

Stress

High sex hormone levels

Feedback to hypothalamus by sex hormones

Hyperthyroidism

Stimulators

Low sex hormone levels

External stimuli

Male—Continuous LRH from hypothalamus

Female—Continuous LRH (hypothalamus) in induced ovulators—  
rabbit

Cyclic LRH (hypothalamus) in spontaneous ovulators—human and  
dog

## 6. Deficiency Symptoms

Estrogen or androgen secretion inhibited

Atrophy of interstitial tissue in ovary or testis

Lack of ovulation, luteinization in female

## 7. Effects of Overdose, Excess

Hypertrophy, then atrophy of Leydig cells in male

Increases estrogen or androgen secretion (with FSH)

Precocious ovulation and luteinization of prepared follicles

## METABOLIC ROLE

### 1. Biosynthesis

Precursors—19 of 20 standard amino acids, tryptophan missing

Intermediates—Unknown

### 2. Production Sites:

Anterior pituitary, central cells, basophilic cells

### 3. Storage Areas:

Stored in pituitary prior to ovulation in female

### 4. Blood Carriers:

Complex with inactive protein

### 5. Half-life:

Approx. 1 hr

### 6. Target Tissues:

Gonads

**7. Reactions**

Reactive intermediate—Cyclic AMP (secondary messenger)

<i>Organ</i>	<i>Enzyme System</i>	<i>Effect</i>
Gonads	Adenyl cyclase Enzymes incorporating acetate into squalene	Activated Activated

**8. Mode of Action**

Cellular

Anabolic—Increased synthesis of steroid hormones

Female—Interstitial ovarian cells synthesize estradiol

Male—Leydig cells synthesize testosterone

Catabolic—Increased CHO catabolism to produce NADH, NADP

Organismal

Promotes gametogenesis

Promotes growth of accessory sex organs

Stimulates rupture of follicles in ovary

**9. Catabolism**

Intermediates—Hydrolysis in liver

Excretion products—Active hormone in urine

**MISCELLANEOUS****1. Relationship to Vitamins**

Vitamin C—Ovarian depletion on LH stimulation

Vitamin E—Involved in spermatogenesis

**2. Relationship to Other Hormones**

FSH—Synergist to LH

Prolactin—Synergist to LH

HMG—Mixture of FSH and LH

PMSG—Properties of FSH and LH

HCG—Analog to LH

**3. Unusual Features**

More stable on freeze-drying than FSH

LH causes multiple ovulation in birds

Insensitive to neuraminidase

Inactivated by trypsin and carboxypeptidase, pepsin, chymotrypsin

Not inactivated by CHO splitting enzymes; CHO moiety unharmed  
CHO moiety needed for activity  
Cyclic release in certain females (spontaneous ovulators)

**4. Possible Relationships of Deficiency Symptoms to Metabolic Action**

Estrogen or androgen secretion inhibited—lack of cyclic AMP to stimulate ovary or testis production

Atrophy of interstitial tissue in ovary or testis—lack of stimulus by cyclic AMP

Lack of ovulation or luteinization in female—lack of cyclic AMP to initiate events leading to ovulation

# 21 Prolactin

## GENERAL INFORMATION

1. **Synonyms:** Lactogenic hormone, luteotrop(h)ic hormone, LTH, luteotrop(h)in, lactogen, galactin, mammotropin
2. **History:**
  - 1928—Stricker and Grüter discovered prolactin
  - 1933—Riddle *et al.* coined term prolactin
  - 1937—Lyons isolated prolactin from pituitary glands of ox, sheep, and pig
  - 1939—Astwood, Fevold suggested luteotropin distinct from LH
  - 1941—Evans, Simpson, Lyons suggested identity of prolactin and luteotropin in rat
  - 1942—Li crystallized prolactin (first pituitary hormone to be crystallized)
  - 1967—Sherwood showed chemical similarity of human growth hormone to placental lactogenic hormone
3. **Physiological Forms:** In man, prolactin is a part of very pure growth hormone complex
4. **Active Analogs and Related Forms:** 50% digested residue—"active core"
5. **Inactive Analogs and Related Forms**
  - Reduced molecule (with cysteine)
  - Acetylated molecule—(on lysine residues)
  - Iodinated molecule—(tyrosine residues iodinated)

6. **Antagonists:** Progesterone, testosterone, estradiol, LH (all concentration dependent)
7. **Synergists:** STH, T4, prednisone, estradiol, progesterone, cortisol, oxytocin, PTH, LH
8. **Physiological Functions**
  - Initiation of lactation
  - Development of mammary glands in female
  - Increases weight and growth (similar to somatotropin) (some species)
  - Nidation of zygote
  - Protein anabolism (some species)
  - Growth and secretion of crop gland (birds)
  - Luteotropic (only in mouse and rat)
  - Promotes maternal behavior
9. **Deficiency Diseases, Disorders:** Mammary carcinoma, galactorrhea, failure of lactation
10. **Essentiality for Life:** Not essential except where it functions as a growth hormone in certain species (birds, reptiles)

## CHEMISTRY

1. **Structure**

Single chain protein, 205 amino acids  
 Pig: Ala.—Cys—Tyr—Leu—Asn—Cys  
 Sheep: Thre.—Cys—Tyr—Leu—Asn—Cys
2. **Reactions**

Heat—Stable	Oxidation—Inactivates
Acid—Ppt. with 0.5% TCA	Reduction—Inactivates
Alkali—Unstable	Light—Not reported
Water—Soluble, acidic	Proteolysis: 50% digestion leaves active core
3. **Properties**

Appearance—Crystalline powder	Salts—Not reported
MW—25,000 (pig)	Important Groups for activity
23,300 (sheep)	Tyr
MP—Not reported	Lys
Crystal Form—Not reported	Cys (S—S bridges)

Solubility:	Chemical Nature—Single chain
H <sub>2</sub> O—Slightly soluble	simple acidic protein
Alc.—Sol.	$\alpha_D^{25} = -40.5^\circ$ (H <sub>2</sub> O)
Acet., Benz., Chl., Ether—Insol.	Misc.—pl = 4.97 (pig)
Absn. Max.—Approx. 280 m $\mu$	= 5.74 (sheep)

#### 4. Commercial Production

Extraction of pituitary glands of ox, sheep, swine

#### 5. Isolation

Sources—Pituitary glands of sheep

Methods

Ovine acetone powder extracted with pH 3 buffer

Precipitate prolactin with 0.06 saturated NaCl

Fractional precipitation, pH 5.6

Probability of protease contamination

Purify by: Countercurrent distribution. DEAE chromatography

#### 6. Determination

Bioassay

Crop sac thickening (pigeons)

Mammary gland growth in pseudopregnant rabbit

Luteotropic, inhibition of estrus (mice)

Physicochemical Assay

Immunoassay

Radioimmunoassay

### MEDICAL AND BIOLOGICAL ROLE

#### 1. Species Occurrence, Specificity, and Antigenicity

Occurrence—Found in all vertebrates

Specificity—Some tolerance in crossing species lines

Antigenicity—Moderate; bovine X rabbit no antigenicity

#### 2. Units: 1 I.U. = 0.1 mg international standard

#### 3. Normal Blood Levels (Man)

Not detectable in male or nonlactating female

Detectable in lactating women

**4. Administration**

- Injection—Currently used
- Topical—Not active
- Oral—Not active

**5. Factors Affecting Release**

- Inhibitors—Hypothalamus (PIH factor), CNS, progesterone
- Stimulators—CNS, suckling stimulus, oxytocin, tranquilizers, PRH (in birds)

**6. Deficiency Symptoms**

- Lactation not maintained
- Growth inhibited (some species)

**7. Effects of Overdose, Excess**

- Corpus luteum maintained past normal regression time
- Precocious lactation

**METABOLIC ROLE****1. Biosynthesis**

- Precursors—Amino acids, 20 standard
- Intermediates—Unknown
- Site(s) in cell—Not reported

**2. Production Sites**

- Anterior pituitary—acidophils, E cells
- Placenta

**3. Storage Areas: Pituitary****4. Blood Carriers: Free and combined with blood proteins****5. Half-life: Unknown****6. Target Tissues: Mammary gland, ovary, crop sac (pigeons)****7. Reactions**

- Reactive form—Unknown
- Enzyme systems—Unknown

**8. Mode of Action**

Cellular

Anabolic—Protein synthesis (some species)

Catabolic—Unknown

Other—Unknown

Organismal

Initiates and maintains lactation

Increases life of corpus luteum

Increases weight and growth

Releases progesterone (in mouse and rat)

**9. Catabolism**

Intermediates—Unknown

Excretion Products—Free in urine; also breakdown products

**MISCELLANEOUS**

**1. Relationship to Vitamins:** None specifically; all indirectly via growth action in species where applicable

**2. Relationship to Other Hormones**

Progesterone, STH, T4, PTH, Estradiol, Cortisol, Oxytocin—Synergists with prolactin [STH, prolactin, ACTH (or adrenal steroids) needed for lactation in rats]

**3. Unusual Features**

Not stimulated, but is inhibited, by hypothalamus (PIH) (except in birds)

Only anterior pituitary hormone precipitated with 0.5% TCA

Present in male pituitary (human) and probably in blood of male

Human prolactin not separated from HGH

HGH stimulates pigeon crop, lactogenic activity in rabbits + luteotrophic activity in mouse

New plumage stimulated in birds by prolactin.

Antigonadal in male bird; otherwise no known functions in male

Terminal ring similar to oxytocin ring structure

Different functions in various species

**4. Possible Relationships of Deficiency Symptoms to Metabolic Action**

Lactation not maintained—Metabolic functions of prolactin absent

Growth inhibited—Prolactin needed to synergise growth hormone in certain species

# **22**

## **Adrenocortico- tropic Hormone (ACTH)**

## GENERAL INFORMATION

5. Inactive Analogs and Related Compounds:  $\alpha$ -MSH,  $\beta$ -MSH, ACTH sequence 2-39
6. Antagonists: Insulin; concentration dependent for corticosterone, cortisol; STH (protein metabolism)
7. Synergists: Epinephrine, cortisol, corticosterone, STH (fat metabolism)
8. Physiological Functions
  - Maintenance of adrenal cortex
  - Promotes secretion of steroids, oxidative phosphorylation in adrenal cortex
  - Mobilizes and increases oxidation of free fatty acids in adipose tissue
  - Increases gluconeogenesis in liver; increases cyclic AMP in adrenal cortex
  - Decreases urea formation in liver
9. Deficiency Diseases, Disorders: Adrenal insufficiency; hypopituitarism; Addison's disease (deficiency); Cushing's syndrome (excess); Simmonds' disease (deficiency)

#### 10. Essentiality for Life

One of the most essential hormones—absence causes notable shortening of normal life span

## CHEMISTRY

#### 1. Structure

Straight chain, simple polypeptide, 39 amino acids,  $C_{214}H_{386}O_{93}N_{56}S$ .

Structure known and synthesized. Human ACTH: Ser—Tyr—Ser—Met—Glu—His—Phe—Arg—Try—Gly—Lys—Pro—Val—Gly—Lys—Lys—Arg—Arg—Pro—Val—Lys—Val—Tyr—Pro—Asp—Ala—Gly—Glu—Asp—Glu—Ser—Ala—Glu—Ala—Phe—Pro—Leu—Glu—Phe

No S-S bridges

Amino acids #1-24 essential, same in all species

#### 2. Reactions

Heat—Stable

Alkali

Acid

Inactivates

Weak—stable

Hydrolysis

Strong—hydrolysis

Water—Soluble, acidic

Oxidation	Light-Stable
Irreversibly inactivates using periodate	Proteolysis—50% digestion of C-terminal end leaves active core
Reversibly inactivates using $H_2O_2$	
Reduction—Stable	

### 3. Properties

Appearance—White powder	Solubility
MW—4500 (39 amino acids)	$H_2O$ —Freely sol.
MP—No data	Acet., Alc.—Sol. in 60% alc., 60% Acet.
Crystal Form—No data	Benz., Chl., Eth.—Insol.
Salts—No data	Absn. Max.—Approx. 280 m $\mu$
Important Groups for Activity	Chemical Nature—Acidic polypeptide
Methionine—redox center—reacts with thiol; if change proline at #12, 19, 24 or serine #1, lose activity; 1-24 essential	Misc.—pl = 4.65-4.80

### 4. Commercial Production

Extract pig, cattle, sheep, whale pituitaries  
Synthetic production possible

### 5. Isolation

Sources—Pituitaries of various animals  
Method  
Extract with 1 N acetic acid; precipitate with ethanol  
Adsorb on and elute from oxycellulose; freeze-dry  
Countercurrent distribution—500X purification using *s*-butanol—0.2% TCA  
Zone electrophoresis, end group analysis, analytical ultracentrifugation

### 6. Determination

Bioassay  
Maintenance of weight of adrenal gland in hypophysectomized rats  
Depletion of vit. C in adrenals of hypophysectomized rats  
Involution of thymus  
Physicochemical  
Immunoassay  
Radioimmunoassay

## MEDICAL AND BIOLOGICAL ROLE

### 1. Species Occurrence, Specificity, Antigenicity

Occurrence—All vertebrates

Specificity—Slight biological differences, species differences located in sequence of amino acids 25-34

Antigenicity—Slight

### 2. Units: 1 USP unit = 1 I.U. = 1.14 mg

### 3. Normal Blood Levels (Man): 0.1-0.6 mu/100 ml plasma

### 4. Administration

Injection—Intravenous, intramuscular, subcutaneous

Topical—No data

Oral—Active (stimulates release of cortisol)

### 5. Factors Affecting Release

Inhibitors—Increased plasma level glucocorticoids (feedback)

Stimulators

Cortical release factors (CRH)—diurnal rhythm

Vasopressin, increased hepatic inactivation

Epinephrine, histamine

Stimulation of median eminence

Psychic trauma (via hypothalamus)

Decreased level of glucocorticoids

### 6. Deficiency Symptoms

Decreased weight of adrenal (atrophy)

Decreased mobilization of free fatty acids

Decreased steroids in blood, urine (17-hydroxy and 17-keto)

Fasting hypoglycemia

Increased insulin sensitivity

### 7. Effects of Overdose, Excess

Increased cortical secretions → hypertrophy → destruction

Increased pigmentation

Death

Hypersensitivity

## METABOLIC ROLE

### 1. Biosynthesis

Precursors—16 of 20 standard amino acids. No Cys, Thr, Ile or Asn  
 Intermediates—MSH (?)

2. Production Sites: Anterior pituitary—basophilic cells; placenta

3. Storage Areas: Anterior pituitary

4. Blood Carriers: Free and combined with plasma proteins

5. Half-life: 15 min

6. Target Tissues: Adrenal cortex, perirenal cells, embryonic rest cells

### 7. Reactions

Reactive intermediate: cyclic AMP—Secondary messenger

<i>Organ</i>	<i>Enzyme System</i>	<i>Effect</i>
Adrenal cortex	Adenyl cyclase	Activated
	Phosphorylase b	Activated
	Cholesterol 20-Hydroxylase	Activated

### 8. Mode of Action

Cellular—

Anabolic—

Increases melanin synthesis in skin

Increases steroid synthesis in adrenal

Increases protein synthesis in liver (via cortisol)

Catabolic

Increases glycogenolysis (adrenal cortex)

Increases gluconeogenesis (liver) (via cortisol)

Increases lipolysis and oxidation of fatty acids in adipose tissue

Other:

Increases oxidative phosphorylation in adrenal cortex

Increases production of cyclic AMP to produce NADPH<sub>2</sub> in adrenal cortex

Decreases cholesterol in adrenal cortex

Organismal

Increases weight of adrenals, depletes cortex of vit. C.

Mobilizes free fatty acids from adipose tissue

- Hypoglycemic, reduces urea formation
- Increases iodine uptake by thyroid
- Stimulates secretion of gluco- and mineralocorticoids by adrenal cortex
- Stimulates melanophores, darkening of skin

## 9. Catabolism

- Intermediates—Liver destruction
- Excretion Products—Free in urine (very little)

## MISCELLANEOUS

### 1. Relationship to Vitamins

- Vitamin C—Depleted in adrenal cortex on stimulation by ACTH
- Niacin—Production of NADPH<sub>2</sub> by ACTH via cyclic AMP
- Vitamin D—Antagonized indirectly by ACTH via cortisol action
- Biotin and Vitamin A—Adrenocortical insufficiency noted in biotin and vitamin A deficiency
- Pantothenic acid, niacin—Synergistic with ACTH in steroid hormone synthesis

### 2. Relationship to Other Hormones

- Epinephrine—Synergist, stimulates release of ACTH.
- Cortisol, corticosterone—Synergists or antagonists depending on concentration. Production stimulated by ACTH
- CRH—Stimulates release of ACTH
- Vasopressin—Similar to CRH, in action
- T4 and TSH—ACTH stimulates iodine uptake by thyroid
- MSH—MSH is a part of ACTH molecule
- Insulin—Antagonist to ACTH
- STH—Antagonist (protein metab.) synergist (fat metab.)

### 3. Unusual Features

- Reversible loss of activity on oxidation with H<sub>2</sub>O<sub>2</sub>
- Reacts with thiols
- Irreversible deactivation by periodate
- First 13 amino acids essential for corticotropin activity
- Full activity at first 20 amino acids
- MSH, a part of ACTH, and its activity increased by *N*-acetylation
- Second messenger (cyclic AMP) involved in adrenal cortex

**4. Possible Relationships of Deficiency to Metabolic Action**

- Atrophy of adrenal cortex—Lack of stimulus from ACTH
- Decreased mobilization of fatty acids—Decreased glucocorticoids, increased insulin activity
- Decreased steroids in blood and urine—Decreased production of adrenal corticoids
- Fasting hypoglycemia—Decreased gluconeogenesis
- Increased insulin sensitivity—Insulin antagonism to ACTH and cortisol

# 23

# Melanocyte- Stimulating Hormone (MSH)

## GENERAL INFORMATION

1. **Synonyms:** Melanophore (affecting) hormone, melanophore-stimulating hormone, melanotrophin, melanotrophic hormone, chromatophoretic hormone, melanosome-dispersing hormone, pigmentation hormone,  $\beta$ -hormone
2. **History**
  - 1932—Zondek and Krohn noted factor in intermediate lobe mediating pigmentary responses in lower vertebrates
  - 1954—Lerner proposed term melanocyte-stimulating hormone for above factor
  - 1956—Geschwind *et al.* isolated  $\beta$ -MSH from pig pituitary
  - 1957—Harris and Lerner isolated  $\alpha$ -MSH from pig pituitary tissue
  - 1959—Harris and Roos isolated  $\beta$ -MSH from bovine pituitary
  - 1960—Dixon isolated  $\beta$ -MSH from human pituitary
  - 1960—Hofmann *et al.* synthesized derivatives of  $\beta$ -MSH
  - 1960—Li, Dixon isolated  $\alpha$ -MSH from horse pituitary
  - 1960—Lee *et al.* determined structure of  $\alpha$ -MSH
  - 1963—Schwyzer *et al.* synthesized  $\alpha$ -MSH and  $\beta$ -MSH

## 3. Physiological Forms

I- $\alpha$ -MSH, I- $\beta$ -MSH (intermedin) (approx equal biological activity)

**4. Active Analogs and Related Compounds**

Acetylated *N*-terminal ( $\beta$ -MSH and ACTH)

Common heptapeptide (Met—Glu—His—Phe—Arg—Try—Gly) of  $\alpha,\beta$ -MSH and ACTH

**5. Inactive Analogs and Related Compounds**

ACTH (1% of MSH activity)

Hydrolyzed fragments of MSH

**6. Antagonists:** Cortisone, d-amino acid analogs (competitive inhibitors), melatonin**7. Synergists:** STH, TSH (amphibia), caffeine, theophylline**8. Physiological Functions**

Function in mammals is obscure (protection from sunlight?), small effect on skin pigmentation

Expands or contracts pigments in various chromatophores

Expands melanophore pigments with color changes in amphibia (adaptation to environment); weak ACTH activity; adipokinetic effect, stimulates T4 secretion

Increases sensitivity to light, decreases dark adaptation time (lower vertebrates)

**9. Deficiency Diseases, Disorders**

Excess—Addison's disease, adrenal insufficiency (darkening)

Deficiency—Hypopituitarism (light)

**10. Essentiality for Life:** Not required; present in all vertebrates with differing functions**CHEMISTRY****1. Structure**

Polypeptide—purified, synthesized,  $\alpha$  and  $\beta$ -forms, straight chains  
 $\alpha$ , 13 amino acids—Ser—Tyr—Ser—[Met—Glu—His—Phe—Arg—Try—  
 Gly]—Lys—Pro—Val

*N*-terminal =  $\text{CH}_3\text{CO}-$ , C-terminal =  $-\text{NH}_2$  similar all species

$\beta$ 18 amino acids in all species except 22 in human—Ala—Glu—Lys—  
 Lys—Asp—Glu—Gly—Pro—Tyr—Arg—Met—Glu—His—Phe—Arg—  
 Try—Gly—Ser—Pro—Pro—Lys—Asp

No S—S bridges

**2. Reactions**

Heat-Stable  
Acid-Stable  
Alkali-Stable (potentiates)  
Water-Sol., basic

Oxidation— $\text{H}_2\text{O}_2$  reversibly  
inactivates  
Reduction—thiols reversibly  
inactivate  
Light—No effect  
Proteolysis—Decreases activity

**3. Properties**

Appearance—White powder  
MW— $\alpha$  1500 (13 A.A.)  
 $\beta$  2100-2600 (18-22 A.A.)  
Crystal Form—No data  
Salts—No data  
Important Groups for Activity  
Met (redox center)  
Tyr  
Common heapeptide in all  
 $\alpha$ 's,  $\beta$ 's, and ACTH  
(Met---Gly)

Solubility  
 $\text{H}_2\text{O}$ -Sol.  
Acet., Alc.—Insol.  
Benz., Chl., Eth.—Insol.  
Absn. Max.—Approx. 280 m $\mu$   
Chemical Nature  
Simple, peptides ( $\alpha$ -acidic,  
 $\beta$ -basic)  
 $\alpha$ -MSH:  $\alpha_D^{25} = 58.5^\circ\text{C}$  (10% acetic  
acid)  
Misc—pl =  $\alpha$  5.5-7.0,  $\beta$  11.0

**4. Commercial Production: Synthetic****5. Isolation**

Sources—Human, pig, bovine, pituitary glands, urine, blood  
Methods  
 $\beta$ -MSH  
Extract with KCl at pH 5.5; precipitate with salt; adsorb on  
oxycellulose  
Purify via carboxylic acid resin  
Countercurrent distribution (1.2 M urea, 0.2 M ethylenediamine, 0.1  
N HCl)

**6. Determination**

Bioassay—Darkening of frog skin ( $\alpha > \beta$ )  
Physicochemical  
Photoelectric reflectance assay  
Immunoasay  
Radioimmunoassay

## MEDICAL AND BIOLOGICAL ROLE

### 1. Species Occurrence, Specificity, and Antigenicity

Occurrence: All vertebrates ( $\alpha$ -MSH,  $\beta$ -MSH). All preparations similar in activity from all animals

#### Specificity

$\alpha$ -MSH—Slight species differences in activity

$\beta$ -MSH—Definite species differences in activity

Antigenicity:  $\alpha$ —None.  $\beta$ —Slight

### 2. Units: Relative to posterior pituitary standard or by weight

### 3. Normal Blood Levels (Man): 0.09 m $\mu$ g/ml or less

### 4. Administration

Injection—Subcutaneous

Topical—Active, used in amphibian experiments

Oral—Active, used in amphibian experiments

### 5. Factors Affecting Release

Inhibitors—MIF via hypothalamus, epinephrine, nervous controls, melanotropin

Stimulators—Metabolic, nervous controls, MRH via hypothalamus

### 6. Deficiency Symptoms

Lightened skin color (amphibians)

Chromatophore contraction

Guanophore expansion

### 7. Effects of Overdose, Excess

Darkening of skin (amphibians and humans), temporary

Hyperglycemia

## METABOLIC ROLE

### 1. Biosynthesis

Precursors—13-14 of 20 standard amino acids. Missing (Cys, Asn, Gln, Leu, Ile, Thr, Val)

Intermediates—Unknown

### 2. Production Sites

Intermediate lobe of pituitary, except in birds, whales, elephants, armadillos, where it is in anterior lobe

Also in posterior lobes

3. Storage Areas: In intermediate lobe of pituitary
4. Blood Carriers: Free and combined with plasma proteins
5. Half-life: 1–2 hrs.
6. Target Tissues: Skin (melanophores) (amphibia)

#### 7. Reactions

Reactive intermediates: Cyclic AMP (secondary messenger)

<i>Organ</i>	<i>Enzyme System</i>	<i>Effect</i>
Skin	Adenyl cyclase Tyrosinase, see ACTH enzymes	Activated Activated

#### 8. Mode of Action

Cellular

Anabolic—Melanin formation

Catabolic—Blocks glycolytic pathways

Other—Increases permeability to  $\text{Na}^+$ , changes protoplasmic viscosity.  
Expands pigments in melanophores

Organismal

ACTH function (weak)

Blocks action of melatonin

Regulates skin color changes, light adaptations

#### 9. Catabolism

Intermediates—Unknown

Excretion products—Free in urine; also breakdown products

## MISCELLANEOUS

#### 1. Relationship to Vitamins

Vitamin C—Adrenal cortex depleted on ACTH and MSH activity

Vitamin A—MSH decreases dark adaptation time

#### 2. Relationship to Other Hormones

STH, TSH—Synergists to MSH

T4—Secretion stimulated by MSH

Cortisone, melatonin—Antagonist to MSH

Epinephrine—Inhibitor of MSH release

**3. Unusual Features**

- Very resistant to degradation or inactivation
- Reversibly inactivated by oxidation ( $H_2O_2$ )
- Reduced with thiols
- Heptapeptide 4-10 similar to ACTH
- $\alpha$  and  $\beta$  forms with similar activity but different a.a. contents

**4. Possible Relationships of Deficiency to Metabolic Action**

- Lightened skin color (amphibia)—No MSH available to promote melanin dispersion

# 24

# Oxytocin

## GENERAL INFORMATION

1. **Synonyms:** Oxytocic hormone, postlobin-O, posterior-lobe principle, Pitocin, lactogogin, uteracon,  $\alpha$ -hypophamine
2. **History**
  - 1906—Dale noted effect of posterior pituitary factor in stimulating uterine contraction
  - 1928—Kamin *et al.* separated two active fractions from neural lobe: one was active in raising blood pressure in mammals; the other promoted uterine contractions
  - 1952—Pierce *et al.* isolated oxytocin
  - 1953—du Vigneaud *et al.* synthesized oxytocin
  - 1965—Flouret *et al.* synthesized d-oxytocin
3. **Physiological Forms:** L-oxytocin
4. **Active Analogs and Related Compounds**
  - Vasopressin
  - Isotocin (some fishes)
  - 8-Isoleucine oxytocin (other fishes, amphibia)
  - Arginine vasotocin (all vertebrates, except mammals)
5. **Inactive Analogs and Related Compounds**
  - Reduced form of oxytocin, enlarged or smaller ring forms, forms with side chains removed

**6. Antagonists:** 2'-*o*-methyltyrosine oxytocin

**7. Synergists**

Uterus—Prolactin, relaxin, estradiol

Mammary gland—STH, progesterone, estradiol, T4, cortisol

**8. Physiological Functions**

Uterine contraction, milk ejection, facilitates sperm ascent in female tract

Decreases: Membrane potential of myometrium; BMR, liver glycogen

Stimulates oviposition in hen, releases LH

Increases: Blood sugar, urinary Na and K

**9. Deficiency Diseases, Disorders**

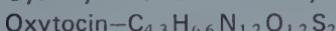
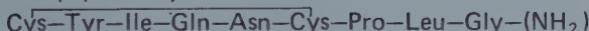
Insufficiency of labor, atonic uterine bleeding

**10. Essentiality for Life:** Not essential

## CHEMISTRY

**1. Structure:**

Octapeptide—synthesized



**2. Reactions**

Heat—No data

Acid—Stable, (weak), unstable  
(strong)

Alkali—Unstable

Water—Sol., basic

Oxidation—Stable

Reduction—Inactivates (ring opens)

Light—No data

Proteolysis by chymotrypsin,  
trypsin or tyrosinase  
inactivates

**3. Properties**

Appearance—Amorphous white powder

MW—1007

MP—No data

Crystal Form—No data

Salts—Citrate, flavianate

Important Groups for Activity

Ile, Glu, Asp, Leu, Gly, Cys

Ring (opening inactivates)

Solubility

H<sub>2</sub>O—Soluble

Acet., Alc.—Sl. Sol., Sol.

Benz., Chl., Ether—Insol.

Absn. Max.—Approx. 280 m $\mu$

Chemical Nature—Basic octapeptide

$\alpha_D^{22} = -26.2^\circ$

Misc.—pI = 7.7

**4. Commercial Production**

- Synthetic, from amino acids
- Posterior pituitary lobe of cattle, sheep (extraction)

**5. Isolation**

Sources—Posterior lobe of pituitary, cattle

Methods

- Dissociate from protein with acid hydrolysis
- Electrodialysis, precipitation
- DEAE cellulose, pH 5.5

**6. Determination**

Bioassay

Blood pressure drop in chick

Milk ejection in rat

Contraction of isolated, uterus of virgin guinea pig

Physicochemical—No information

**MEDICAL AND BIOLOGICAL ROLE****1. Species Occurrence, Specificity, and Antigenicity**

Occurrence: Found in most vertebrates, in slightly different forms

Specificity: Interspecies reactivity—Decrease in action in lower forms

Antigenicity: Low

**2. Units:** 1 USP unit = approx. 2 µg of pure hormone**3. Normal Blood Levels (Man):** 0.15-1.5 milliunits/100 ml plasma**4. Administration**

Injection—intramuscular, subcutaneous, I.V. drip

Topical—Nasal spray

Oral—Inactivated by chymotrypsin in intestine

**5. Factors Affecting Release**

Inhibitors: No data

Stimulants: Reflex arcs—Chemical and neural reflexes from suckling, milking, from cervix, vagina (dilatation of birth canal); psychic events; relaxin

**6. Deficiency Symptoms**

Delayed uterine contraction in pregnancy  
Decreased milk flow

**7. Effects of Overdose, Excess**

Tetanic contraction of pregnant uterus  
Increase in milk flow

**METABOLIC ROLE****1. Biosynthesis**

Precursors—8 of 20 std amino acids. Missing are Glu, Asp, Met, Arg, Lys, His, Pro, Try, Phe, Ala, Thr, Ser  
Intermediates: Neurophysin—Peptide complex

**2. Production Sites:** Hypothalamus (paraventricular nuclei?)**3. Storage Areas:** Posterior pituitary and hypothalamus**4. Blood Carriers:** Unbound and in loose association with plasma proteins**5. Half-life:** 9 min in pregnant woman**6. Target Tissues:** Uterus (pregnant), mammary gland, other smooth muscle**7. Reactions:** Reactive form—No data**8. Mode of Action**

## Cellular

Anabolic—No data

Catabolic—No data

Other—Contraction of myoepithelial cells around mammary alveoli.

Contraction of uterine smooth muscle

## Organismal

Uterine contraction

Milk ejection

Vasodilator }  
Antidiuretic }

in large doses only

**9. Catabolism**

Intermediates

In pregnancy, plasma oxytocinase inactivates

Oxytocinase formed in placenta breaks down oxytocin

Removed from plasma by liver, kidney, and mammary gland

Excretion products: A little, free in urine

**MISCELLANEOUS****1. Relationship to Vitamins:** No data**2. Relationship to Hormones**

Vasopressin

Structurally similar to vasopressin

Always secreted with vasopressin irrespective of stimulus

Prolactin—Oxytocin may stimulate release of prolactin

STH, TSH, ACTH, LH, FSH, Prol.—Anterior pituitary hormones; related  
in milk production

Estradiol—Uterine effect dependent on estrogen presence.

LH—oxytocin stimulates LH release

Norepinephrine      }

Serotonin              } Occur with oxytocin in posterior pituitary

CRH—Structural similarity to oxytocin

Relaxin—Stimulates oxytocin release

**3. Unusual Features**

Very similar structurally to vasopressin but main physiological actions  
very different (only two amino acids differ)

No known function in male mammal

Protein, neurophysin, binds neurohypophyseal hormones specifically

Always secreted with vasopressin irrespective of nature of stimulus

Nonpregnant uterus is more sensitive to ADH than to oxytocin

Vasodilator effect of oxytocin is blocked by ADH

Releases anterior pituitary hormones in fish

Increases oviposition in birds and reptiles

Increases spawning reflex in fish

**4. Possible Relationships of Deficiency Symptoms to Metabolic Action:** No  
data

# 25 Vasopressin

## GENERAL INFORMATION

1. **Synonyms:** Arginine vasopressin, ADH (antidiuretic hormone) anti-diuretin, Pitressin,  $\beta$ -hypophamine, Tonephin, Vasophysin
2. **History**
  - 1895—Oliver and Schafer noted effect of posterior pituitary factor on rise in blood pressure
  - 1937—Gilman and Goodman showed dehydration increased plasma and urine levels of vasopressin
  - 1942—Van Dyke isolated crude protein fraction possessing oxytocin and vasopressin activities from oxen pituitaries
  - 1953-54—DuVigneaud *et al.* determined structure and synthesized ADH
3. **Physiological Forms:** I-vasopressin
4. **Active Analogs and Related Compounds**
  - Arginine vasopressin (most mammals)
  - Lysine vasopressin (pig)
  - Vasotocin (birds, amphibia, fish)
5. **Inactive Analogs and Related Compounds**
  - Opening of ring; removal of side chain
  - Change in size of ring
6. **Antagonists:** Norepinephrine, certain prostaglandins

**7. Synergists:** Aldosterone, STH, prolactin, corticosterone, T4, testosterone, epinephrine

### **8. Physiological Functions**

- Elevates blood pressure (mammals) (reverse effect in birds)
- Decreases kidney blood flow
- Antidiuretic, acts as CRF, releases ACTH
- Increases NaCl and urea excretion
- Regulates water balance
- Stimulates contraction of smooth muscles
- Increases renal tubular H<sub>2</sub>O reabsorption
- Releases anterior pituitary hormones

### **9. Deficiency Diseases, Disorders**

- Deficiency—Diabetes insipidus
- Excess—Schwartz-Bartter syndrome (oat-cell carcinoma)

### **10. Essentiality for Life:** Not essential

## **CHEMISTRY**

### **1. Structure**

Octapeptide—synthesized  
Cys—Tyr—Phe—Gln—Asn—Cys—Pro—Arg—Gly(NH<sub>2</sub>)  
 Arginine vasopressin, C<sub>46</sub>H<sub>65</sub>N<sub>15</sub>O<sub>12</sub>S<sub>2</sub>

### **2. Reactions**

- |                           |  |
|---------------------------|--|
| Heat—Degrades in solution | Oxidation—Stable   |
| Acid—Stable               | Reduction—Inactivates (ring opens)   |
| Alkali—Unstable           | Light—Unstable   |
| Water—Soluble, basic      | Proteolysis inactivates (by trypsin<br>(which removes terminal glycine<br>amide group), but not by pepsin) |

### **3. Properties**

- Appearance—amorphous white powder
- MW—1084 (arginine-vasopressin)
- MP—No data
- Crystal Form—No data
- Salts, Esters—Tannate

- Important Groups for Activity
- Cyclic pentapeptide (opening inactivates)
- Tripeptide side chain
- Cys

<b>Solubility</b>	Absn. Max.—Approx. 280 m $\mu$
H <sub>2</sub> O—Soluble	Chemical Nature—Basic peptide
Alc.—Sol.	Misc.—pI = 10.9
Acet., Benz., Chl., Eth.—Insol.	

#### 4. Commercial Production

Synthesized from amino acids.

Posterior lobe of pituitary of domestic animals (hog, beef)

#### 5. Isolation

Sources: Posterior pituitary glands (hog, beef)

Methods:

Acetic acid extraction of posterior pituitary powder

Percolation through Celite using 70% ethanol and gradually increasing concentrations of water and acetic acid

Or the neurophysin peptide complex is extracted with acetic acid and the protein precipitated with NaCl. Treatment with trichloroacetic acid then dissociates the complex and precipitates the protein

#### 6. Determination

Bioassay

Blood pressure measurements on cats, dogs, or chickens

Diuretic studies on dogs, rats, and rabbits

Weight gain in frogs

Physicochemical: Radioimmunoassay

### MEDICAL AND BIOLOGICAL ROLE

#### 1. Species Occurrence, Specificity, and Antigenicity

Occurrence

Vasopressin-like substances found in vertebrates from cyclostomes through mammals

Loss of activity as go to amphibia and fish

Specificity—Decreasing interspecies reactivity in lower vertebrates

Antigenicity—Low

2. Units: 1 USP posterior pituitary unit = 1 international posterior pituitary unit = 0.5 mg of the international standard oxytocic, vasopressor, and antidiuretic substances (ox posterior pituitary)

3. Normal Blood Levels (Man): 3.7 milliunits/100 ml

**4. Administration**

Injection—Intravenous, intramuscular, or subcutaneous

Topical—Inhalation of powders or sprays

Oral—No data

**5. Factors Affecting Release**

Inhibitors

Low osmotic pressure in blood

Ethyl alcohol

High extracellular fluid volume

Stimulators

High blood osmotic pressure

Acetylcholine, lobeline

Physostigmine

Cold, low fluid volume

Hemorrhage

Morphine, nicotine, ether, some barbiturates, tranquilizers, and general anesthetics

$\text{Ca}^{++}$ -ion-(inhibits binding to protein)

Stress

Exercise, psychic events

**6. Deficiency Symptoms**

Diuresis

Polydipsia

Decreased NaCl and urea excretion

**7. Effects of Overdose, Excess**

Increased water reabsorption, blood pressure

Smooth muscle contraction—G.I. activity

Facial pallor

Uterine cramps

Coronary circulation complications

## **METABOLIC ROLE**

**1. Biosynthesis**

Precursors—Eight of standard 20 amino acids. Missing are Glu, Asp, Met,

Lys, His, Leu, Prol, Try, Ile, Ala, Thre, Ser

Intermediates—Neurophysin-peptide complex

2. **Production Sites:** Hypothalamus, esp. supraoptic nuclei. Secreted into neurohypophysis
3. **Storage Areas:** Hypothalamus and posterior pituitary
4. **Blood Carriers:** Unbound, and loose association with plasma protein
5. **Half-life:** In plasma, 8 min
6. **Target Tissues:** Capillaries, arterioles, coronary vessels, kidney tubules, smooth muscle

### 7. Reactions

Reactive intermediate: Cyclic AMP—secondary messenger

<i>Organ</i>	<i>Enzyme System</i>	<i>Effect</i>
Kidney	Hyaluronidase	Activated
Kidney (distal tubule)	Adenyl cyclase	Activated

### 8. Mode of Action

#### Cellular

Anabolic—No data

Catabolic—Depolymerizes hyaluronic acid

#### Other

Increases passive permeability of epithelium of distal segment of nephron to water; allows osmotic forces to operate more freely

Increases intracellular water in muscle; decreases Na and K

Increases pore size or number in cell membrane

#### Organismal

Antidiuretic

Decreases coronary blood flow

Increases motility of bowel

Arterial smooth muscle sensitized to effects of norepinephrine by physiological amounts of ADH

Renal blood flow reduced by ADH

### 9. Catabolism

Intermediates—Inactivated in kidney and liver

Excretion Products: Some free in urine

## MISCELLANEOUS

### 1. Relationship to Vitamins: No data

### 2. Relationship to Other Hormones

Oxytocin, Hypertensin—Structurally very similar to vasopressin but main physiological effect is very different

Aldosterone, Corticosterone—Synergistic with vasopressin; related to antidiuretic activity of vasopressin

CRF—Vasopressin suggested to have CRF (corticotropin release factor) properties

STH, T4, Testosterone, Prolactin—Synergistic with vasopressin

Aldosterone—ADH and aldosterone may interact in water and electrolyte conservation

Norepinephrine, Prostaglandins—Norepinephrine and certain prostaglandins inhibit ADH activity in kidney

### 3. Unusual Features

Thiazides which act as diuretics, paradoxically reduce polyuria in both pituitary diabetes insipidus and nephrogenic diabetes insipidus. May act by reducing filtration rate

Nonpregnant uterus is more sensitive to ADH than to oxytocin. Rare form of diabetes insipidus is not caused by lack of ADH but by inability of kidney tubule to respond to ADH. (An inborn error of metabolism)

Reverse effects in birds

Increases skin permeability in amphibia

### 4. Possible Relationships of Deficiency Symptoms to Metabolic Action

Decreased NaCl and urea excretion—Permeability of epithelium of distal segment of nephron to water is reduced and water reabsorption is decreased

# 26

# Thyroxine

## GENERAL INFORMATION

1. **Synonyms:** T<sub>4</sub>, 3,5,3',5'-tetraiodothyronine

2. **History**

16th Century—Anon. Cretinism described

1825—Parry associated enlarged thyroid with exophthalmia, tachycardia

1874—Gull associated atrophy of thyroid with characteristic syndrome

1891—Murray treated hypothyroidism with injection of thyroid extract

1896—Baumann showed that thyroid contains iodine

1911—Baumann demonstrated diiodotyrosine in thyroid

1915—Kendall isolated and crystallized thyroxine

1926—Harington determined structural formula

1927—Harington and Barger synthesized thyroxine

1951—Gross *et al.* isolated and identified triiodothyronine as active factor in thyroid

3. **Physiological Forms:** I-thyroxine, 3',3,5-triiodothyronine (T<sub>3</sub>, TRIT), tetraiodothyroacetic acid (TETRAC), triiodothyroacetic acid (TRIAC)

4. **Active Analogs and Related Compounds**

d-thyroxine (fractional activity of I-thyroxine)

Triiodothyropropionic acid (very active in tadpole metamorphosis)

5. Inactive Analogs and Related Compounds: Deiodinated T4; T4 with esterified hydroxyl group
6. Antagonists: 3,3',5'-triiodothyronine, guanethidine; 2',6'-diiodotyrosine, insulin, PTH
7. Synergists: STH, cortisol, epinephrine, prolactin, MSH, oxytocin, progesterone, vasopressin

### 8. Physiological Functions

Regulates growth, differentiation, oxidative metabolism, electrolytic balance  
 Increases CHO metabolism, calorigenesis, protein anabolism, BMR, O<sub>2</sub> consumption, fat catabolism, fertility  
 Sensitizes nervous system

### 9. Deficiency Diseases, Disorders

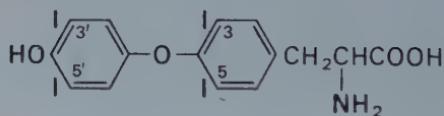
Deficiency—Cretinism, goiter (deficient), Hashimoto's disease, Gull's disease, myxedema  
 Excess—Grave's disease, thyrotoxicosis, thyroiditis, goiter

### 10. Essentiality for Life

Required for development and growth of all vertebrates  
 Deficiency in adult shortens life span

## CHEMISTRY

### 1. Structure:



Thyroxine, C<sub>15</sub>H<sub>11</sub>I<sub>4</sub>NO<sub>4</sub>

### 2. Reactions

Heat—Decomposes at 231°C	Oxidation—Unstable
Acid—Unstable (Sol. in acid alc.)	Reduction—Stable
Alkali—Sol. in alk. alc.	Light—Unstable
Water—Insol.	Enzyme action: Unstable to deiodinating enzymes.

### 3. Properties

Appearance—White crystalline powder  
 MW—776.9  
 MP—231-233°C decomp.  
 Crystal Form—needle-like  
 Salts—Sodium  
 Important Groups for Activity  
 —I-Alanine  
 —O—  
 —I (all 4 positions)  
 —OH

Solubility  
 H<sub>2</sub>O—Insol.  
 Acet.—Insol.  
 Alc.—Sol. at acid or alk. pH  
 Benz., Chl., Eth.—Insol.  
 Absn. Max.—231 m $\mu$   
 Chemical Nature  
 Acidic substituted amino acid  
 $\alpha_D = -4.4^\circ$  (aq. alk. EtOH)  
 Misc.—pK<sub>a</sub> = 2.2, (COOH), 6.45 (OH),  
 10.1 (NH<sub>2</sub>)  
 pI = 3.5

### 4. Commercial Production

Synthetic and from pig thyroid by defatting and drying with acetone—thyroid, U.S.P.

Sodium salts

Sodium levothyroxine, USP (synthroid)

Sodium liothyronine, USP (cytomel)

### 5. Isolation

Sources—Pig thyroid

Method—Extraction:

Proteolysis, pH 8.4, (pancreatin and trypsin) of thyroid, 24 hr at 37°C

Extract with *n*-butanol saturated with *N* HCl

Paper chromatography or ion-exchange resin

Partition chromatography (kieselguhr in 0.5 *N* NaOH) separates T<sub>4</sub> from T<sub>3</sub>

### 6. Determination

Bioassay

Metamorphosis in tadpoles

Increased oxidative metabolism

Physicochemical—Protein-bound iodine (PBI) in plasma. Radioassay

## MEDICAL AND BIOLOGICAL ROLE

### 1. Species Occurrence, Specificity, and Antigenicity

#### Occurrence

All vertebrates have thyroid tissue, but follicles dispersed in lampreys and bony fish

Thyroxine and precursors found in various invertebrates but no follicles

#### Specificity

Interreactive all vertebrates; no loss in potency (i.e. no specificity)

No response in invertebrates; different functions in lower vertebrates

#### Antigenicity—No antigenicity

### 2. Units: In mg

### 3. Normal Blood Levels (Man): 3.0-6.5 µg/100 ml serum

### 4. Administration:

Injection—No data

Topical—No data

Oral—Thyroid tablets, sodium levothyroxine, sodium liothyroxine

### 5. Factors Affecting Release

#### Inhibitors

High blood I<sub>2</sub>

High blood T<sub>4</sub>—feedback via hypothalamus

Stress, pain

#### Stimulators

TSH

Low blood T<sub>4</sub>—feedback via hypothalamus

Cold

Direct nervous control

### 6. Deficiency Symptoms (Humans)

Tumors of pituitary

Decreased BMR

Accumulation of mucoprotein

Increase in blood lipid and cholesterol

Increase in liver gluconeogenesis

Extracellular retention of NaCl and H<sub>2</sub>O

## 7. Effects of Overdose, Excess

Acceleration of growth, maturation

Increased BMR, esp. liver, skin, kidney, smooth muscle, gastric mucosa

Decreased tissue glycogen

Increased blood sugar

Exophthalmos

Hyperthyroidism, Graves's disease

Thyrotoxicosis

## METABOLIC ROLE

**1. Biosynthesis:** Tyrosine → Monoiodotyrosine → Diiodotyrosine → Thyroxine Site(s) in Cell—Data not conclusive

**2. Production Sites:** Thyroid gland

**3. Storage Areas:** Colloid in thyroid follicles = thyroglobulin

**4. Blood Carriers**

α-Globulin

Acid glycoprotein

Albumin

**5. Half-life:** 6-7 days

**6. Target Tissues:** Systemic—All tissues, esp. adenohypophysis, hypothalamus

**7. Reactions**

Reactive intermediate: Cyclic AMP—secondary messenger

Organ	Enzyme System	Effect
67 tissue enzymes affected <i>in vivo</i>		
Thyroid	Mitochondrial enzyme systems	Activated
Thyroid	TCA cycle—oxidative phosphorylating enzymes	Uncoupled
Thyroid	Adenyl cyclase	Activated

**8. Mode of Action**

Cellular

Anabolic

Increases protein synthesis on the ribosomes and <sub>m</sub> RNA synthesis  
in muscle, kidney, reticulocytes, liver

**Catabolic**

Increases protein catabolism in brain, spleen, and testis

Increases glucose and fat catabolism

Other—Swells mitochondria, affects permeability, regulates redox potential, chelates metals that inhibit enzymes

Uncouples mitochondrial oxidative phosphorylation at 2 points

Decreases mucoprotein synthesis

**Organismal**

Stimulates hematopoiesis, oogenesis, spermatogenesis, lactation, intestinal absorption

Regulates growth, differentiation, electrolyte balance, heat production, O<sub>2</sub> consumption, BMR

Sensitizes nervous system

**9. Catabolism****Intermediates**

Iodine split off in liver, kidney, salivary glands, and recycled

Residue coupled with glucuronic acid or sulfate and excreted. Also oxidative deamination of amino acid residues

**Excretion Products**

Compounds containing diphenyl ether and at least two carbons of side chain excreted as glucuronides and sulfates in bile

Very small amounts free in urine and bile

**MISCELLANEOUS****1. Relationship to Vitamins**

Vitamin A—T<sub>4</sub> needed for vit. A synthesis in liver

B-Complex vitamin deficiencies develop in hyperthyroidism

Vit B<sub>12</sub>—T4 aids in B<sub>12</sub> absorption

Vitamin C—Synergist in cold survival

Niacin—Synergist in mitochondrial metabolism

**2. Relationship to Other Hormones**

STH, ACTH, FSH, LH, TSH, Prolactin—synergists to T4 esp. in lactation

ACTH—Antagonist in proper relative concentration

Insulin—T4 stimulates secretion of insulin

TSH—Stimulates production of T4

FSH—Inhibited by T4

MSH, ACTH—Stimulate iodine uptake by thyroid

PTH—Antagonist to T<sub>4</sub>  
Cortisol—Synergist to T<sub>4</sub>

### 3. Unusual Features

Powerful chelating agent, esp. with Mg  
Free OH participates in quinonoid formation  
Regulates metamorphosis in amphibia  
Osmoregulatory in fish  
Iodinated tyrosine found in invertebrate exoskeleton—inactive  
Diffuse thyroid gland in teleosts & other lower forms  
TRIAC—potent stimulant for metamorphosis  
TETRAC—potent metabolic stimulant  
Decreased activity if I is replaced with Br or Cl  
Decreased activity if OH is removed or I position changed

### 4. Possible Relationships of Deficiency Symptoms to Metabolic Action

Decreased BMR—Lack of T<sub>4</sub> stimulus for anabolism  
Accumulation of Mucoprotein—Lack of T<sub>4</sub> control of mucoprotein synthesis  
Increase in Blood Lipid and Cholesterol—Decreased fat catabolism  
Increase in Liver Gluconeogenesis—Antagonism by ACTH (cortisol)  
Extracellular Retention of NaCl and H<sub>2</sub>O—Antagonism by ACTH and aldosterone (?)

# 27

# Parathyroid Hormone

## GENERAL INFORMATION

1. **Synonyms:** PTH, Parathormone

2. **History**

1900—Vassale and Generali reported convulsions and tetany from removal of parathyroids only

1909—MacCallum and Voegtlin reported effect of parathyroidectomy on plasma Ca

1924-25—Hanson, Collip prepared active extracts from parathyroid gland

1942—Patt and Luckhardt demonstrated that blood Ca level controls parathyroid secretion

1959—Rasmussen, Aurbach prepared pure parathyroid hormone peptides

3. **Physiological Forms:**  $\alpha$ -Parathormone

4. **Active Analogs and Related Compounds:** No data

5. **Inactive Analogs and Related Compounds:** No data

6. **Antagonists:** T4, STH, estradiol, testosterone, TCT

7. **Synergists:** Vitamin D, estrogens (birds), cortisol

## 8. Physiological Functions

- Increases blood Ca, kidney Ca reabsorption, PO<sub>4</sub> excretion, blood citrate
- Mobilizes Ca and PO<sub>4</sub> from bone.
- Activates Ca and PO<sub>4</sub> absorption from G.I. tract (requires vitamin D)
- Increases osteoclast formation

## 9. Deficiency Diseases, Disorders

- Deficiency—Tetany, hypoparathyroidism
- Excess—von Recklinghausen's disease, hyperparathyroidism

## 10. Essentiality for Life:

One of the most essential hormones. Absence rapidly leads to tetany and death of adult

## CHEMISTRY

### 1. Structure

- Simple polypeptide (83 amino acids), sequence determined
- Straight chain—No S—S bridges
- Ala—Leu

### 2. Reactions

- |                            |   |
|----------------------------|---|
| Heat—No data               | Oxidation—H <sub>2</sub> O <sub>2</sub> , performic acid inactivate |
| Acid—Stable, dilute, acid  | Reduction—Stable  |
| Alkali—Relatively unstable | Light—No data   |
| Water—Sol., acidic         | Proteolysis—Loses activity  |

### 3. Properties

- |                               |                                    |
|-------------------------------|------------------------------------|
| Appearance—No data            | Solubility                         |
| MW—8500                       | H <sub>2</sub> O—Sol.              |
| MP—No data                    | Acet., Alc.—Insol.                 |
| Crystal Form—No data          | Benz., Chl., Eth.—Insol.           |
| Salts—No data                 | Absn. Max.—Approx. 280 m $\mu$     |
| Important Groups for Activity | Chemical Nature—Acidic polypeptide |
| Met, Try, Tyr                 | Misc—pI = 4.8                      |

### 4. Commercial Production:

From bovine parathyroid

### 5. Isolation

- Sources—Bovine parathyroid

**Methods****Extraction**

Extract with 80% acetic acid

Precipitate in 86% acetone

Ultrafilter at pH 2.4

**Purification**

Column chromatography on Dowex 50

Countercurrent distribution

Gel filtration

**6. Determination****Bioassay**

Serum Ca increase in dogs

Increase in urine P output

**Physicochemical**

Radioimmunoassay

**MEDICAL AND BIOLOGICAL ROLE****1. Species Occurrence, Specificity, and Antigenicity**

Occurrence—Found in all vertebrates above fish and cyclostomes

Specificity—Interspecific potency high, e.g. bovine and human Parathormone—Isoactive

Antigenicity—Low

**2. Units:** 1 USP unit = 1/100 the amount of PTH to increase dog blood Ca 1 mg/100 ml in 18 hr after subcutaneous injection**3. Normal Blood Levels (Man):** Est. 4000 USP units/100 ml plasma**4. Administration**

Injection—Parathyroid USP (Paroidin) usually subcutaneous; occasionally I.V.

Topical—No data

Oral—Destroyed by proteolytic enzymes

**5. Factors Affecting Release**

Inhibitors—High serum Ca; vasomotor nerve control

Stimulators—Low serum Ca feedback; vasomotor nerve control

**6. Deficiency Symptoms**

Decreased blood (Ca, citrate), urine (PO<sub>4</sub>, Ca).

Increased blood PO<sub>4</sub>.

Irritability of nervous system, muscle twitch, tetany, death

Cataracts

**7. Effects of Overdose, Excess**

Increased blood (Ca, citrate, alkaline phosphatase), urine PO<sub>4</sub>, demineralization of skeleton, osteoclast activity

Decreased blood PO<sub>4</sub>, muscle sensitivity

Metastatic deposits of Ca in tissues, notably kidney

**METABOLIC ROLE****1. Biosynthesis**

Precursors—17 of 20 standard amino acids. No Cys, Asn, or Gln

Intermediates—No data

Site(s) in cell—No data

**2. Production Sites:** Parathyroid gland. Principal cells (?)**3. Storage Areas:** No data**4. Blood Carriers:**  $\alpha$ -globulin and albumin**5. Half-life:** 20 min**6. Target Tissues:** Bone, kidney, muscle, mammary gland, gut**7. Reactions:** Reactive intermediate—Cyclic AMP—secondary messenger

<i>Organ</i>	<i>Enzyme System</i>	<i>Effect</i>
Bone and Kidney	Adenyl cyclase	Activated

**8. Mode of Action**

Cellular

Anabolic—No data

Catabolic—Bone resorption

Other

Mitochondrial PO<sub>4</sub> increased

Mitochondrial swelling  
Increased conversion pyruvate to citrate

**Organismal**

Raises renal Ca threshold  
Lowers renal PO<sub>4</sub> threshold

**9. Catabolism**

Intermediates—Partial digestion in liver  
Excretion Products—1% in urine

**MISCELLANEOUS**

**1. Relationship to Vitamins**

Vitamin D—Synergistic with PTH in maintenance of serum calcium

**2. Relationship to Other Hormones**

Estradiol—Synergizes PTH in birds

Cortisol—Synergizes PTH in vertebrates

T4, STH, Estradiol, Testosterone, Calcitonin—Antagonists to PTH

**3. Unusual Features**

Activity increased with molecular weight of analog

Demineralization of skeleton, formation of cysts with excess PTH

High citrate produced in bone action

**4. Possible Relationships of Deficiency Symptoms to Metabolic Action**

Decreased blood Ca, citrate—Lack of PTH mobilization of bone calcium

Increased blood PO<sub>4</sub>—Urine threshold for PO<sub>4</sub> high without PTH

Irritability of nervous system—Decrease of blood calcium

Cataracts—?

# Thyrocalcitonin

## GENERAL INFORMATION

1. **Synonyms:** TCT, calcitonin

2. **History**

1962—Copp discovered and named hormone with effects opposite to those of Parathormone

1963—Munson extracted thyrocalcitonin from rat thyroids

1964—Foster *et al.* reported that calcitonin originated in thyroid gland in goats

1966—Pearse identified thyroid "C" cells as source of calcitonin

3. **Physiological Forms:** I-Thyrocalcitonin

4. **Active Analogs and Related Compounds:** No data

5. **Inactive Analogs and Related Compounds:** No data

6. **Antagonists:** Parathyroid hormone, vit. D

7. **Synergists:** Estradiol

8. **Physiological Functions**

Decreases blood Ca [balances PTH (parathyroid hormone)]

Inhibits bone resorption

- Increases  $\text{PO}_4$  excretion
- Increases proline incorporation into bone

**9. Deficiency Diseases, Disorders:** Medullary carcinoma of the thyroid (excess)

**10. Essentiality for Life:** Not demonstrated

## CHEMISTRY

**1. Structure**

Polypeptide, 32 amino acids, synthesized

Straight chain, one S-S ring: Porcine TCT Cys—Ser—Asn—Leu—Ser—Thr—Cys—Val—Leu—Ser—Ala—Try—Trp—Arg—Asn—Leu—Asn—Asn—Phe—His—Arg—Phe—Ser—Gly—Met—Gly—Phe—Gly—Pro—Glu—Thr—Pro

**2. Reactions**

Heat—Relatively stable

Oxidation—No data

Acid—Sol., Inactivates (conc.)

Reduction—No data

Alkali—Inactivates (conc.)

Light—No data

Water—Sol., acidic

Proteolysis—Pepsin and trypsin inactivates

**3. Properties**

Appearance—No data

Solubility

MW—3604

$\text{H}_2\text{O}$ —Sol.

MP—No data

Acet., Alc.—Insol.

Crystal Form—No Data

Benz., Chl., Eth.—Insol.

Salts—No data

Absn. Max.—Approx 280 m $\mu$

Important Groups for Activity

Chemical Nature—Acidic

S—S ring 1 + 7 position

polypeptide

Tyr and Try in

Misc.—pl = 4.8

positions 12 and 13

**4. Commercial Production:** Not available

**5. Isolation**

Sources—Pork thyroid

**Method****Extraction**

- (a) Extract with 0.2 *N* HCl 60-70°C for 5 min, filter after 1 hr
- (b) Dialyze, pH 4.6, against 0.1 *M* acetate buffer at 4°C
- (c) Precipitate from 1.5 *M* NaCl

**Purification**

- (a) Gel filtration—Sephadex G-100, pH 4.6
- (b) Ultrafiltration—if complexed to proteins earlier

**6. Determination**

Bioassay—Effect on plasma Ca level in rat

Physicochemical—Radioimmunoassay

**MEDICAL AND BIOLOGICAL ROLE****1. Species Occurrence, Specificity, and Antigenicity**

Occurrence—Found in most vertebrates

Specificity—High, great variation in interspecific potency

Antigenicity—Not antigenic

**2. Units**

MRC units or by weight

5-10 MRC milliunits lowers plasma Ca in rat by about 10%

**3. Normal Blood Levels:** 0.01 µg/100 ml plasma (rabbit)**4. Administration**

Injection—Active

Topical—Inactive

Oral—Inactive

**5. Factors Affecting Release**

Inhibitors—No data

Stimulators—High plasma calcium level, glucagon

**6. Deficiency Symptoms:** Blood Ca increase**7. Effects of Overdose, Excess:** Blood Ca decrease

## METABOLIC ROLE

### 1. Biosynthesis

Precursors—18 of 20 standard amino acids; Lys, Ile absent  
 Intermediates—Unknown  
 Site(s) in cell—Unknown

### 2. Production Sites

Thyroid, parathyroid, and thymus (man)  
 Parafollicular C cells derived from ultimobranchial body

### 3. Storage Areas: Unknown

### 4. Blood Carriers: Unknown

### 5. Half-life: 5-15 min (rabbit)

### 6. Target Tissues: Bone, kidney, muscle

### 7. Reactions

Reactive intermediate—Cyclic AMP—secondary messenger

<i>Organ</i>	<i>Enzyme System</i>	<i>Effect</i>
Thyroid	Adenyl cyclase Phosphorylase b	Activated Activated

### 8. Mode of Action

Cellular

Anabolic—Increases proline incorporation into bone

Catabolic—No data

Other—No data

Organismal

Decreases blood calcium

Inhibits bone resorption and citrate formation

Increases PO<sub>4</sub> excretion

Decreases glucose utilization and lactate production in bone

### 9. Catabolism

Intermediates—Liver proteolysis

Excretion products—Products of protein metabolism

## MISCELLANEOUS

- 1. Relationship to Vitamins:** Vitamin D antagonizes TCT
- 2. Relationship to Other Hormones**
  - PTH—Antagonist to thyrocalcitonin
  - Glucagon—Stimulates release of TCT
  - Estradiol—Synergises and releases TCT
- 3. Unusual Features:** Birds have a gland separate from thyroid containing TCT
- 4. Possible Relationships of Deficiency to Metabolic Action**
  - Blood calcium increase—Unknown

# 29 Insulin

## GENERAL INFORMATION

**1. Synonyms:** None

**2. History**

10 A.D.—Celsus described diabetic syndrome

1899—Von Mering and Minkowski demonstrated relationship between pancreatectomy and diabetes mellitus

1922—Macleod determined that islet cells produce insulin

1922—Banting and Best prepared potent insulin extracts from dog pancreas

1926—Abel *et al.* isolated crystalline insulin

1955—Sanger *et al.* determined structure of insulin

1966—Katsoyannis synthesized insulin (human and sheep)

**3. Physiological Forms:** I-Insulin

**4. Active Analogs and Related Compounds:** No data

**5. Inactive Analogs and Related Compounds**

Oxidized, reduced insulin, proinsulin

Alkali inactivated insulin

**6. Antagonists:** Cortisol, glucagon, epinephrine, norepinephrine, STH (CHO and fat metabolism), T4

**7. Synergists:** STH (protein metabolism), testosterone, estradiol

## 8. Physiological Function

- Regulates CHO and fat metabolism, esp. glucose and fat oxidations
- Stimulates amino acid and glucose transport into cells and protein synthesis
- Stimulates glycogen and mucopolysaccharide formation

**9. Deficiency Diseases, Disorders:** Diabetes mellitus (faulty  $\beta$ -cells), azoturia, hyperlipemia, ketonemia

**10. Essentiality for Life:** Essential for survival

## CHEMISTRY

### 1. Structure

Structure known and synthesized—51 amino acids

Polypeptide, 2 parallel straight chains, -3—S—S bridges

2 chains (ox insulin)

$\alpha$ -21 amino acids—acidic: Gly—Ile—Val—Glu—Glu—  
 Cys—Cys—Ala—Ser—Val—Cys—Ser—Leu—Tyr—Glu—Leu—Glu—  
 Asp—Tyr—Cys—Asp  
 $\beta$ -30 amino acids—basic: Phe—Val—Asp—Glu—His—Leu—Cys—Gly—  
 Ser—His—Leu—Val—Glu—Ala—Leu—Tyr—Leu—Val—Cys—Gly—  
 Glu—Arg—Gly—Phe—Phe—Tyr—Thr—Pro—Lys—Ala

### 2. Reactions

Heat—Unstable

Acid—Stable

Alkali—Inactivates

Water—Soluble, acidic

Oxidation—Inactivates

Reduction—Inactivates

Light—No data

Proteolysis—Trypsin inactivates

### 3. Properties

Appearance—White crystalline powder

MW—5734 monomer

Polymer: 12,000-48,000,  
 depending on pH

MP—No data

Crystal Form—Hexagonal system

Salts—Zinc, Protamine

### Important Groups for Activity

2 Disulfide bridges (S—S ring)

Active groups unknown

Key positions—19-21 on  $\alpha$ -chain;  
 22-30 on  $\beta$ -chain

Tyr, Asn

Solubility	Absn. Max.—Approx. 280 m $\mu$
H <sub>2</sub> O—Soluble	Chemical Nature—Acidic
Acet., Alc.—Sol.	polypeptide
Benz., Chl., Eth.—Insol.	Misc.—pI = 5.3

#### 4. Commercial Production: Extraction of beef or pork pancreas

##### 5. Isolation

Sources—Pancreas—beef, pork

Method

Extract pancreas in 80% EtOH, pH 3 (H<sub>3</sub>PO<sub>4</sub>)

pH to 8 with NH<sub>4</sub>OH precipitates impurities

Precipitate insulin with EtOH and ether

Dissolve in EtOH—H<sub>3</sub>PO<sub>4</sub> buffer and precipitate insulin as picrate

Dissolve in acetone HCl

Precipitate with acetone

Wash and dry

Purification

Crystallize at pI in acetate buffer with 0.15-0.60% zinc

Precipitate with alc.

Salting out

Gel filtration and crystallization or electrophoresis

#### 6. Determination

Bioassay

Isolated rat diaphragm; perfused heart; *in vitro* systems, for measuring glucose uptake

Lowering blood sugar in rabbit

Physicochemical

Radioimmunoassay

Immunoassay—Very sensitive for plasma insulin concentration

### MEDICAL AND BIOLOGICAL ROLE

#### 1. Species Occurrence, Specificity, and Antigenicity

Occurrence—Found in all vertebrates

Specificity—Moderate interspecific potency

Antigenicity—Moderate antigenicity. Pig and human sequence alike yet antigenic differences exist

#### 2. Units: 1 I.U. = 1 USP unit = 0.04167 mg international standard

**3. Normal Blood Levels:**  $0.1\text{--}3.0 \times 10^{-3}$  I.U./ml**4. Administration****Injection—Subcutaneous**

Amorphous Insulin, Crystalline Insulin—Fast acting, short duration

Protamine Insulin, Protamine Zn insulin—Slow, steady absorption

**Topical—Not used****Oral**

Sulfonylureas—Stimulate secretion of insulin

Hypoglycemic agents—Stimulate secretion of insulin

Biguanides—Stimulate secretion of insulin

**5. Factors Affecting Release****Inhibitors**

Low blood sugar—Feedback

Epinephrine

Norepinephrine

**Stimulators**

High blood sugar—Feedback

Elevated blood amino acid level

Vagal stimulation

Glucagon, ACTH, secretin, STH,

Ketone bodies, sulfonylureas, biguanides

Hypoglycemic agents

Cortisol, T4

**6. Deficiency Symptoms**

Polyphagia

Decreases respiratory quotient

Decreases tissue protein

Polydipsia

Hyperglycemia, Glycosuria—Underutilization and overproduction of glucose

Polyurea

Hyperlipemia

Ketonemia

Azoturia

**7. Effects of Overdose, Excess**

Convulsions

Increases glycogen storage

Mental confusion

Coma  
Headache  
Tremor  
Sweating  
Apprehensiveness

## METABOLIC ROLE

### 1. Biosynthesis

Precursors—17 of 20 standard amino acids (aspartic acid, tryptophan, and methionine missing)

Intermediates—Proinsulin

Site(s) in cell—Unknown

### 2. Production Sites: $\beta$ -cells of islets of pancreas

### 3. Storage Areas: $\beta$ -granules in $\beta$ -cells

### 4. Blood Carriers: Circulating proteins; $\alpha,\beta$ -macroglobulins

### 5. Half-life in Plasma: Nonlabeled insulin, < 9 min; insulin $^{131}\text{I}$ , 40 min

### 6. Target Tissues: Systemic, esp. liver, adipose tissue, muscle, kidney.

### 7. Reactions: Reactive form—unknown

<i>Organ</i>	<i>Enzyme System</i>	<i>Effect</i>
Liver	Lipase Adenyl cyclase Glycogen synthetase	Inhibited Inhibited Activated
Tissues	Hexokinase Phosphorylases	Activated Activated

### 8. Mode of Action

Cellular

Anabolic—Increases mucopolysaccharide synthesis, protein synthesis, fatty acid synthesis,  $m$  RNA synthesis

Catabolic—Inhibits gluconeogenesis. Increases glucose oxidation

Other—Increases transport glucose and A.A. across cell membrane (does not affect glucose entrance into hepatic cells, brain, blood cells). Inhibits cyclic AMP formation

**Organismal**

- Inhibits mobilization of fat from peripheral reservoirs
- Decreases blood (sugar, K, PO<sub>4</sub> ketones), liver gluconeogenesis, polyuria
- Increases liver and muscle glycogen, glucose absorption in gut, fat formation, nitrogen balance

**9. Catabolism**

- Intermediates—Insulinase in liver (antagonized by insulinase inhibitor)
- Excretion products—Metabolic products of amino acids

**MISCELLANEOUS****1. Relationship to Vitamins:** Vitamin C acts similarly to alloxan (i.e., antagonist)**2. Relationship to Other Hormones**

- Cortisol, Glucagon, Epinephrine, Norepinephrine, T4, STH (CHO and fat metabolism)—Antagonistic to insulin
- Estradiol, Testosterone, STH (protein metabolism)—Synergistic with insulin

**3. Unusual Features**

- Contains 0.4% zinc in crystals
- First synthetic polypeptide hormone
- Multiple insulins in rat, bonito
- Forms fibrils when heated at low pH
- Antibody sites not identical with biological activity sites
- Frog—Pancreas not active until mid-metamorphosis
- Urodeles—Only  $\beta$ -cells in pancreas
- Vigorous exercise increases rate of transport of glucose into muscle cells even in absence of insulin

**4. Possible Relationships of Deficiency Symptoms to Metabolic Action**

- Hyperglycemia, decrease in respiratory quotient—Inability to metabolize and transport glucose into cells
- Hyperlipemia—Mobilization of fat from peripheral reserves
- Ketonemia—Incomplete oxidation of mobilized fat
- Azoturia (decrease in tissue protein)—Induced gluconeogenesis producing urea and ammonia
- Polydipsia—Thirst produced by glycosuria (polyuria)
- Polyphagia—Hunger produced by loss of urinary glucose

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# Glucagon

## GENERAL INFORMATION

1. **Synonyms:** HGF, HG-Factor, hyperglycemic-glycogenolytic factor, glukagon
2. **History**

1922—McLeod  
1923—Collip } Described hyperglycemic effect of pancreatic extracts  
1923—Kimball and Murlin suggested a second pancreatic hormone;  
named it glucagon  
1955—Staub, Sinn, and Behrens isolated and crystallized glucagon  
1956—Bromer *et al.* determined structure of glucagon  
1967—Wunsch synthesized glucagon
3. **Physiological Forms:**  $\alpha$ -glucagon
4. **Active Analogs and Related Compounds:** Serotonin (G.I. tract, spleen, skin, tongue); isoproterenol, G.I. glucagon
5. **Inactive Analogs and Related Compounds:** UV-inactivated glucagon
6. **Antagonists:** Insulin
7. **Synergists:** Epinephrine (liver, muscle), norepinephrine, cortisol, cortisone

## 8. Physiological Functions

- Increases—Blood sugar, blood K<sup>+</sup>, O<sub>2</sub> consumption, liver glycogenolysis, gluconeogenesis, nitrogen and salt excretion, glucose-1-P  
Decreases—Liver glycogen, protein formation, gastric juice, fatty acid synthesis

## 9. Deficiency Diseases, Disorders: Hypoglycemic coma

## 10. Essentiality for Life: Not essential for life of vertebrate organisms

## CHEMISTRY

### 1. Structure

Polypeptide (sequence determined): His—Ser—Glu—Gly—Thr—Phe—  
Thr—Ser—Asp—Tyr—Ser—Lys—Tyr—Leu—Asp—Ser—Arg—Arg—  
Ala—Glu—Asp—Phe—Val—Glu—Try—Leu—Met—Asp—Thr  
Straight single chain—His. . . . Thr., 29 amino acids  
No S—S bridges

### 2. Reactions

Heat—Stable to 100°C	Oxidation—No data
Acid—Stable, pH 2	Reduction—Stable to cysteine (removes contaminating insulin)
Alkali—Stable, pH 9	
Water—Sol., basic	Light—UV Inactivates
	Proteolysis—Leucine amino peptidase, pepsin, trypsin, chymotrypsin at pH = 6-8 hydrolyze

### 3. Properties

Appearance—White powder	Solubility
MW—3500 (29 A.A.)	H <sub>2</sub> O—Insol.
MP—No data	Acet., Alc.—Insol.
Crystal Form—Rhombic dodecahedra	Benz., Chl., Eth.—Insol.
Salts—HCl	Absn. Max.—278 m $\mu$
Important Groups for Activity	Chemical Nature—Basic polypeptide
Try, Met	Misc.—pI = 7.5-8.5

### 4. Commercial Production: Hog pancreas

**5. Isolation**

Sources—Crude pork insulin

Methods

Ppt. with acetone and salts at low pH

Crystallize from 0.033 M glycine buffer, pH 8.6 with 0.67 M urea

Purification: Starch zone electrophoresis

**6. Determination**

Bioassay

Hyperglycemic response in cats

Glycogenolysis of liver slices

Reaction of phosphorylase in liver slices

Physicochemical—Radioimmunoassay, immunoassay

**MEDICAL AND BIOLOGICAL ROLE****1. Species Occurrence, Specificity, and Antigenicity**

Occurrence—Found in fish through mammals

Specificity—Interspecies potency—Interreactive

Antigenicity—Antigenic in rabbit or bovine x porcine glucagon, but not guinea pig glucagon

**2. Units:** By weight, also 1 I.U. = amount to increase blood sugar to 30 mg/100 ml**3. Normal Blood Levels (Man):** 0.02-0.05 µg/100 ml plasma**4. Administration**

Injection—Glucagon HCl intravenous, intramuscular, or subcutaneous

Used to treat insulin-induced hypoglycemia

Topical—Inactive

Oral—Inactive

**5. Factors Affecting Release**

Inhibitors—High blood sugar, CoCl<sub>2</sub> ( $\alpha$ -cells)

Stimulators—Hypoglycemia, fasting

**6. Deficiency Symptoms:** Low blood glucose**7. Effects of Overdose:** Metaglucagon diabetes (destroy  $\beta$ -cells), increased food consumption, high blood glucose

## METABOLIC ROLE

### 1. Biosynthesis

Simple precursors—16 of standard 20 amino acids (no cysteine, isoleucine, proline, glutamic acid)

Intermediates—Unknown

Site(s) in cell—No data

### 2. Production Sites— $\alpha$ -cells in pancreas

### 3. Storage Areas: Granules in $\alpha$ -cells

### 4. Blood Carriers: Plasma proteins

### 5. Half-life: Less than 10 min

### 6. Target Tissues: Liver, adipose tissues, kidney

### 7. Reactions

Reactive intermediate—Cyclic AMP—secondary messenger

<i>Organ</i>	<i>Enzyme System</i>	<i>Effect</i>
Liver	Glucokinase	Inhibited
	Glycogen synthetase	Inhibited
	Glycogenolysis enzymes	Activated
	Glucoseogenesis enzymes	Activated
	Adenyl cyclase	Activated
	Dephosphophorylase kinase	Activated
	Phosphorylase b	Activated
	Carbamoyl phosphate synthetase	Activated
	Argino-succinase	Activated
	Argino-succinic synthetase	Activated
Heart	Adenyl cyclase	Activated

### 8. Mode of Action

Cellular

Anabolic—No data

Catabolic

Decreased protein and fatty acid synthesis

Increased lipolysis

Increased CHO glycogenolysis

Increased protein catabolism

Other

Increased cyclic AMP formation

Decreased adrenal ascorbic acid

**Organismal**

- Stimulates hepatic glycogenolysis and gluconeogenesis
- Increases adipose tissue lipolysis
- Stimulates release of catecholamines by adrenal medulla
- Increases nitrogen K, Na, Cl, PO<sub>4</sub> excretion
- Increases blood sugar, ketone bodies
- Decreases gastric juice flow
- Increases heart rate, ventricular contractility
- Decreases atrio-ventricular conduction time
- Retards G.I. contractions

**9. Catabolism**

- Intermediates—Proteolysis in liver, kidney, blood—glucagonase (protease), recycling
- Excretion products—End products of protein metabolism (urea, CO<sub>2</sub>)

**MISCELLANEOUS****1. Relationship to Vitamins**

- Vitamin C—Depletion of adrenal ascorbic acid by glucagon

**2. Relationship to Other Hormones**

- Epinephrine, Norepinephrine—Secretion stimulated by glucagon, also synergistic
- Cortisol, Cortisone—Synergistic to glucagon
- Insulin—Antagonistic to glucagon

**3. Unusual Features**

- Tissue differences in glucagon response
- More conc. in female than male pancreas
- G.I. glucagon not identical with pancreatic glucagon
- Traces of heavy metals (Cu, Co) found in glucagon preparations

**4. Possible Relationships of Deficiency Symptoms to Metabolic Action**

- Low blood glucose—lack of glucose-releasing activity by glucagon into plasma

# 31 Aldosterone

## GENERAL INFORMATION

1. **Synonyms:** Electrocortin, mineralocorticoid, aldocortin, 18-oxocorticosterone
2. **History**

1953—Simpson *et al.*      }      Isolated crystalline aldosterone  
1954—Mattox *et al.*      }      from adrenals  
1954—Wettstein and Anner devised highly sensitive test for mineralocorticoid activity  
1954—Simpson *et al.* determined structure of aldosterone  
1955—Schmidlin *et al.* synthesized dl-aldosterone  
1956—Vischer *et al.* synthesized d-aldosterone  
1956—Neher and Wettstein isolated 15 more steroids similar to aldosterone and cortisol
3. **Physiological Forms:** Hemiacetal form (11,18-semiacetal), aldehyde form
4. **Active Analogs and Related Forms (Mineralocorticoids)**

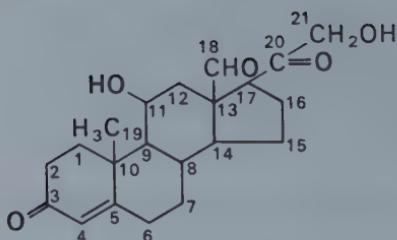
Natural—11-Deoxycorticosterone, corticosterone  
Synthetic— $2\alpha$ -Methylcortisol,  $9\alpha$ -fluorocortisol,  $2\alpha$ -methyl- $9\alpha$ -fluorocortisol
5. **Inactive Analogs and Related Forms (for Aldosterone Function):** Cortisol, dexamethasone, prednisolone

**6. Antagonists**

Natural—Cortisol, pineal factor, estradiol, progesterone, vasopressin (kidney), prostaglandins  
 Synthetic—3-Spironolactone, aldactone-A

**7. Synergists:** 11-deoxycorticosterone, vasopressin, oxytocin, angiotensin II, renin, STH**8. Physiological Functions**

Maintenance of normal electrolyte blood balance  
 Prolongs survival of adrenalectomized animals  
 Accelerates gluconeogenesis  
 Regulates kidney function

**9. Deficiency Diseases, Disorders:** Addison's disease, (deficiency), Cushing's syndrome (excess), adrenocortical insufficiency, primary hyperaldosteronism**10. Essentiality for Life:** One of the most essential of all hormones. Absence can be fatal in short time period**CHEMISTRY****1. Structure**

Aldosterone (aldehyde form),  
 $C_{21}H_{28}O_5$

**2. Reactions**

Heat—Stable  
 Acid—Decomposes  
 Alkali—Fluoresces (conc.)  
 Isomerizes to 17-iso-aldosterone  
 Water—Slightly sol.

Oxidation—Loses aldehyde group  
 Reduction—Unstable  
 Light—Stable

### 3. Properties

Appearance—Colorless crystals	Solubility
MW—360.4	H <sub>2</sub> O—Sparingly
MP—164° C	Acet., Alc.—Sol.
Crystal Form—Needles (acetate)	Benz., Chl., Eth.—Sol.
Salts, Esters—Acetate	Absn. Max.—240 m $\mu$
Important Groups for Activity	Chemical Nature
—C(18)HO	Hemiacetal, aldehyde
—C(21)H <sub>2</sub> OH	Alc., ketone—Reducing steroid
—C(11)OH	$\alpha_D^{23} = +145$ (acet.)

### 4. Commercial Production: Microbiological (stereospecific hydroxylation)

### 5. Isolation

Sources: Beef adrenal extract

Methods

- (1) Partition aqueous extract with pentane-methanol
- (2) Chromatograph on kieselguhr, elute with petroleum ether-benzene-CHCl<sub>3</sub>
- (3) Rechromatograph on powdered cellulose, elution with toluene-petroleum ether-methanol
- (4) Recrystallize from methanol

### 6. Determination

Bioassay

Life maintenance in adrenalectomized animals

Increase muscular work performance

Cold stress reactions on adrenalectomy

*In vitro* incubation of perfused tissues

Physicochemical—Monitor Na/K ratios in urine

## MEDICAL AND BIOLOGICAL ROLE

### 1. Species Occurrence, Specificity, and Antigenicity

Occurrence: All vertebrate species studied, except cyclostomes

Specificity: Same electrolyte regulator, all species

Antigenicity: None reported

### 2. Units: mg or $\mu$ g

### 3. Normal Blood Levels (Man): 0.03 $\mu$ g/100 ml

**4. Administration**

Injection—Main route

Topical—No reports

Oral—Active

**5. Factors Affecting Release**

Inhibitors

Decreased  $K^+$  in blood

Increased  $Na^+$  in blood

Hemodilution

Stimulators

Angiotensin II—Renin

Stress, decreased  $Na^+$ , decreased blood vol.

Pregnancy

ACTH (slightly)

Increased blood pressure in carotid arteries

Increased  $K^+$  in blood

**6. Deficiency Symptoms (Humans)**

Decreased—Blood (pressure, sugar, pH), weight, liver glycogen, urinary  $K^+$ , temperature, reproductive functions

Increased—Urinary ( $Na^+$ ,  $Cl^-$ ,  $HCO_3^-$ )

Kidney failure, muscular weakness, GI disturbances, hemoconcentration, stress intolerance, acidosis

**7. Effects of Overdose, Excess**

Hypertension

Congestive heart failure

Increased  $Na^+$  and  $H_2O$  in blood, muscles

Hemodilution

Hypokalemia

Edema

Alkalosis

Diabetes insipidus (type of)

**METABOLIC ROLE**

- Biosynthesis:** Acetate  $\rightarrow$  Mevalonate  $\rightarrow$  Squalene  $\rightarrow$  Cholesterol  $\rightarrow$  Pregnenolone  $\rightarrow$  Progesterone  $\rightarrow$  Aldosterone  
Site(s) in Cell—Membranes

**2. Production Sites:** Adrenal cortex (zona glomerulosa), embryonic rest cells

**3. Storage Areas:** None

**4. Blood Carriers**

Lipoproteins, albumin

Conjugates, Free Steroid—Combined with above proteins

**5. Half-life:** 25 min

**6. Target Tissues:** Distal renal tubules, sweat and salivary glands, intestinal mucosa, gills (fish), skin (amphibia), nasal gland (bird), rectal gland (sharks)

**7. Reactions**

Reactive form—Equilibrium (hemiacetal-aldehyde) redox couple

Organ	Enzyme System	Effect
Kidney	1. Unknown enzymes involved in sodium transport 2. Also enzymes similar to cortisol (glucocorticoid function) 3. RNA polymerase	Activated Activated Activated
Liver, muscle, plasma, general	Similar to cortisol; see Cortisol	Activated

**8. Mode of Action**

Cellular

Anabolic—Liver (proteins, CHO, nucleic acids)

Catabolic—Extrahepatic (proteins, fats, CHO, nucleic acids)

Other—Increases  $\text{Na}^+$  active transport in renal tubules, activates redox pump,  $\text{H}_2\text{O}$  transported with  $\text{Na}^+$

Organismal

Increases blood  $\text{Na}^+$ , volume, pressure; urinary  $\text{K}^+$ ,  $\text{H}^+$ ; cold tolerance, muscle work performance, liver glycogen

Decreases blood  $\text{K}^+$ ,  $\text{H}^+$ ; urine  $\text{Na}^+$ ,  $\text{H}_2\text{O}$ , volume; eosinophils, lymphocytes

**9. Catabolism**

Intermediates—Tetrahydro derivative (inactive)

Excretion Products—30-40% Glucuronides, 4-8% free, 52-66% other conjugates

## MISCELLANEOUS

### 1. Relationship to Vitamins

Vitamin C—Adrenal cortex depleted of vit. C on production of aldosterone

Niacin—NADPH involved in synthesis of aldosterone

Biotin—Prolongs life in adrenalectomized rats

### 2. Relationship to Other Hormones

Cortisol—Synergistic to aldosterone in glucocorticoid activity; antagonistic to aldosterone in water metabolism

ACTH—Trigger for small release of aldosterone

Vasopressin, Oxytocin—Synergists for aldosterone action in water metabolism

Angiotensin II, Renin—Stimulate production of aldosterone

Other hormones antagonistic or synergistic with cortisol (glucocorticoid action)—see Cortisol

### 3. Unusual Features

Not a glucocorticoid even though it has —OH on C-11 and 1/3 of glucocorticoid power of cortisol

Redox couple—Hemiacetal-aldehyde equilibrium

No nervous controls

Active on oral administration

Most water soluble of all steroids

Largely independent of ACTH control

### 4. Possible Relationships of Deficiency Symptoms to Metabolic Action

Loss of mineralocorticoid functions. Failure of sodium pump and sodium-water reabsorption mechanisms in kidney tubules

Increased—Urinary ( $\text{Na}^+$ ,  $\text{Cl}^-$ ,  $\text{HCO}_3^-$ ). Decreased urinary  $\text{K}^+$ , blood pH and pressure

Acidosis, kidney failure

Hemoconcentration

Weight loss

Loss of glucocorticoid functions; decreased gluconeogenesis

Muscular weakness

G.I. disturbances

Stress intolerance

Decreased blood sugar

Decreased liver glycogen

Decreased temperature

# 32 Cortisol

## GENERAL INFORMATION

1. **Synonyms:** Hydrocortisone, Compound F, 17-hydroxycorticosterone, Substance M
2. **History**
  - 1937—Reichstein isolated cortisol from adrenal glands
  - 1942—Von Euw, Reichstein determined configuration of cortisol
  - 1948—Mason, Sprague isolated cortisol from urine
  - 1950—Reich *et al.* isolated cortisol from blood
  - 1950—Wendler *et al.* synthesized cortisol
  - 1951—Zaffaroni *et al.* demonstrated biosynthesis of cortisol in adrenals
3. **Physiological Forms:** Cortisol, cortisone
4. **Active Analogs and Related Compounds (Glucocorticoids)**
  - Natural—Deoxycorticosterone, cortexolone, cortisone ("E"), cortisterone ("B"), dehydrocorticosterone ("A")
  - Synthetic—Dexamethasone, 9 $\alpha$ -F-cortisol, prednisone, prednisolone
5. **Inactive Analogs and Related Compounds:** Estrone, progesterone, 17- $\alpha$ -hydroxyprogesterone, cortexolone, adrenosterone
6. **Antagonists:** Protein and CHO metabolism—Insulin; STH, estrogens, testosterone

**7. Synergists:** Fat metabolism—STH; epinephrine, norepinephrine, PTH, T4

### 8. Physiological Functions

Increases—Protein catabolism (exc. liver) gluconeogenesis, carbohydrate anabolism (liver), blood sugar, glucose absorption, brain excitation, spread of infections, urinary glucose and nitrogen, stress tolerance, lactation, water diuresis

Decreases—Fat anabolism, growth rate, inflammation, eosinophils, lymphocytes, antigen sensitivity, respiratory quotient, ketosis, wound healing, skin pigmentation, RBC hemolysis

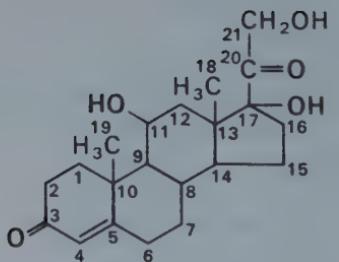
Regulates—General adaptation syndrome, water balance, blood pressure, hormone release

**9. Disorders and Deficiency Diseases:** Addison's disease (deficiency), Cushing's syndrome (excess), adrenal insufficiency, adrenogenital syndrome, rheumatic arthritis, inflammation

**10. Essentiality for Life:** Absence causes shortening of life span due to inability to respond to stress situations

## CHEMISTRY

### 1. Structure:



Cortisol,  $C_{21}H_{30}O_5$

### 2. Reactions

Heat—Oxidizes

Acid—Esterifies

Fluorescent in  $H_2SO_4$  (conc.)

Alkali—Stable (dilute)

Fluorescent (conc.)

Water—very sl. sol.

Oxidation—Forms cortisone

C-11 Hydroxyl  $\rightarrow$  Keto

Reduction—Stable

Light—Stable

### 3. Properties

Appearance—White powder	Solubility
MW—362.5	H <sub>2</sub> O—0.28 mg/ml
MP—217-220°C	Acet., Alc.—15, 6.2 mg/ml
Crystal Form—Rectilinear plates	Chl., Eth.—9.3, 0.35 mg/ml
Salts, Esters—	Absn. Max.—242 m $\mu$
Acetate	Chemical Nature
Important Groups for Activity	Reducing agent
-C(17)OH	Alcohol, ketone
-C(11)OH	$\alpha_D^{22} = 167$ (EtOH)
-C(21)H <sub>2</sub> OH	

### 4. Commercial Production: Extraction and isolation from beef and hog adrenals

### 5. Isolation

Sources—Adrenal cortex

Methods

    Free

        Extract with dil. alkali, partition between 2 solvents

    Chromatography—Glass, paper, thin layer, gas, liquid

    Columns—Florasil

    Countercurrent distribution

Conjugates—Extract tissue, paper chromatography, alumina columns

### 6. Determination

Bioassay:

    Increased—Liver glycogen, lifespan in cold, tolerance to trauma, isotope uptake.

    Decreased—Eosinophils, lymphocytes

Physicochemical

    Reduction to red formazan

    Oxidation to 17-oxosteroids

    Phenylhydrazone formation

    Fluorescence at 550 or 570 m $\mu$

    Polarography

## MEDICAL AND BIOLOGICAL ROLE

### 1. Species Occurrence, Specificity, and Antigenicity

Occurrence—Cortisol major form of glucocorticoids in primates, dog, fish, decreasing in activity in lower forms. Corticosterone major glucocorticoid in rodents, birds, amphibians, reptiles

Specificity—Can cross species lines without loss of activity

Antigenicity—Not antigenic

### 2. Units: By weight, $\mu\text{g}$

### 3. Normal Blood Levels: $10 \mu\text{g}/100 \text{ ml}$ (man)

### 4. Administration

Injection—Intramuscular

Oral—Active. Prednisone form used

Topical—Acetonides in creams, lotions

### 5. Factors Affecting Release

Inhibitors

Pituitary hypofunction

Diurnal rhythm—Low in afternoon

Decreased ACTH

Increased plasma-glucocorticoids

Stimulators

Pregnancy, infancy, stress

ACTH ingestion and ACTH increase

Adrenal hyperfunction

Angiotensin II, insulin, estrogens

Glucagon, vasopressin

Decreased plasma glucocorticoids

### 6. Deficiency Symptoms (Humans)

Decreased

Growth, secondary sex characteristics

Blood pressure, body temperature

Kidney function, leading to death

Liver glycogen, gluconeogenesis

Intestinal absorption, blood sugar

Stress response—ultimately death

Increased

Glucose oxidation, ACTH levels, respiratory quotient

Fat anabolism, hemoconcentration  
Muscular weakness  
Skin pigmentation  
Insulin sensitivity

### 7. Effects of Overdose (Excess)

Buffalo obesity, bruising, moon-face  
Osteoporosis (demineralization of bone)  
Adrenal regression  
Anesthesia  
Atherosclerosis, hypercholesterolemia, lipemia  
Diabetes  
Alkalosis  
Decreased growth  
Inhibition of inflammatory responses and wound healing

## METABOLIC ROLE

1. Biosynthesis: Acetate → Mevalonate → Squalene → Cholesterol  
→ Pregnenolone → Progesterone → 17 $\alpha$ -Hydroxyprogesterone  
→ Cortisol  
Sites in cell—Mitochondria, microsomes
2. Production Sites: Adrenal cortex, placenta, embryonic rest cells
3. Storage: Adrenal cortex (small amount)
4. Blood Carriers: Lipoproteins, conjugates,  $\alpha$ -globulins (transcortin), albumin; also free
5. Half-life: 1½-3 hr
6. Target Tissues: Liver, central nervous system, hypothalamus, thymus, lymph nodes, intestine, connective tissues, skin, mammary gland, vascular system, general systemic
7. Reactions  
Reactive Form: Cortisol ⇌ cortisone (redox couple)

**Enzyme Systems:**

<i>Organ</i>	<i>Enzyme Systems</i>	<i>Effect</i>
Liver	Phosphoenolpyruvate carboxykinase	Activated
	Pyruvate carboxylase	Activated
	Tryptophan pyrolase	Activated
	Glycolytic cycle enzymes	Activated
	Krebs cycle enzymes	Activated
	Urea cycle enzymes Deaminases and transaminases	Activated
Liver, kidney	Glucose-6-phosphatase	Activated
	Glycogen synthetase	Activated
	Arginase	Activated
Liver, plasma	Alkaline phosphatase	Activated
Muscle	Aminopeptidase	Activated
General	Histidine decarboxylase	Inhibited
	Hexokinase	Inhibited

**8. Mode of Action**

## Cellular

- Anabolic—Increases liver (protein, nucleic acid, CHO, fat) synthesis
- Catabolic—Increases extrahepatic (protein, lipid, and nucleic acid) breakdown; decreases extrahepatic CHO breakdown
- Other—Redox mechanisms maintained; water and sodium membrane transport regulated in kidney glomerulus (with aldosterone)

## Organismal

- Maintains circulation and blood pressure (with aldosterone)
- Maintains fluid balance (with aldosterone)
- Maintains renal function (with aldosterone)
- Releases other hormones
- Maintains stress reactions
- Regulates ACTH output of pituitary
- Maintains collagen, capillary permeability

**9. Catabolism**

Intermediates—Bile salts, 17-hydroxy steroids

Excretion products

## Urine

- 100 (approx.) different steroids in urine
- 87% Glucuronides or sulfates—Cortols, cortolones, 17-hydroxy steroids
- 4% Free metabolites—Cortols, cortolones, 17-hydroxy steroids
- 1% Free cortisol—Cortols, cortolones, 17-hydroxy steroids
- Feces—Bile salt derivatives

## MISCELLANEOUS

### 1. Relationship to Vitamins

- Vitamin C—May be needed for steroid hormone biosynthesis; depleted from adrenal cortex on cortical secretion
- Niacin—NADPH required for steroid hormone biosynthesis
- Vitamin D—Action antagonized by cortisol, i.e., reduces Ca absorption in intestine
- Pantothenic acid, folic acid maintain secretions of steroids by adrenal cortex
- Biotin—Adrenocortical insufficiency noted in biotin deficiency
- Vitamin A—Deficiency of vitamin A causes cortical necrosis

### 2. Relationship to Other Hormones

- Estradiol- $17\beta$ —Antagonist to cortisol protein metabolic effects
- Insulin—Antagonist to cortisol (CHO, protein, lipid) metabolic effects
- STH—Antagonist to cortisol protein metabolic effects
- Testosterone—Antagonist to cortisol protein metabolic effects
- Cortisone—Converted to cortisol in body (redox couple)
- T4, Norepinephrine, Epinephrine—Potentiated by cortisol, synergistic
- ACTH—Production stopped via feedback mechanism of cortisol
- PTH—Synergist to cortisol in bone resorption
- Vasopressin, Oxytocin—Antagonist to cortisol water balance effects, stimulants for production of glucocorticoids
- Glucagon—Stimulant for production of cortical hormones

### 3. Unusual Features

- Production of euphoria, anesthetic action
- Decreased activity if side chain is lengthened
- Substituents on C-20, C-18, determine antihemolytic activity
- Suppression of mast cell activity, migration of lymphocytes and phagocytes
- Inhibition of wound healing and collagen formation by fibroblasts
- Inhibition of antibody production, regression of thymus tissue
- Suppresses mitosis in lymphoid tissue
- Species difference in sensitivity

### 4. Possible Relationships of Deficiency Symptoms to Metabolic Action

- Osteoporosis—Antagonism to vit. D; synergism with PTH
- Diabetes—Inhibition of glucose oxidation
- Alkalosis—Retention of sodium
- Bruisability—Depletion of vit. C (?)

- Buffalo obesity, Moon-face—Antagonism to insulin (?)
- Adrenal regression—Shut-off of ACTH production
- Anesthesia—Effects on membranes (?)
- Atherosclerosis—Diabetogenic effect (?)

# 33 Estradiol

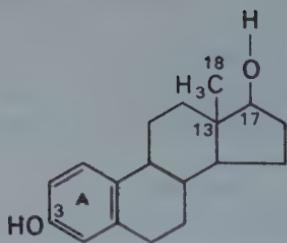
## GENERAL INFORMATION

1. **Synonyms:** Estradiol- $17\beta$ , female hormone,  $\beta$ -estradiol, dihydrotheelin, dihydrofollicular hormone, dihydrofolliculin
2. **History**
  - 1929—Doisy, Butenandt, *et al.* isolated and crystallized estrone from pregnancy urine
  - 1930—Marrian isolated estriol from pregnancy urine
  - 1932—Marrian, Butenandt determined structure of estrone and estriol
  - 1936—McCorquodale isolated crystalline estradiol from pregnancy urine and sow ovaries
  - 1940—Inhoffen synthesized estradiol from cholesterol
  - 1948—Anner and Miescher totally synthesized estrone
3. **Physiological Forms:** Estrone, estriol, estradiol (Estrogens)
4. **Active Analogs and Related Compounds (Estrogens)**
  - Synthetic—Diethylstilbestrol, hexestrol, dienestrol, benzestrol, ethinyl-estradiol, chlorotrianisene
  - Natural—Estriol, estrone, equilin
5. **Inactive Analogs and Related Compounds (Estrogen function)**
  - Pregnandiol, lumiestrone, progesterone,  $17\alpha$ -estradiol,  $17\alpha$ -hydroxy-progesterone,  $17\alpha$ -hydroxypregnenolone

6. **Antagonists:** Progesterone, cortisol, testosterone (all concentration dependent); uterine factor, melatonin, ethamoxypyriphetol, aldosterone
7. **Synergists:** Prolactin, progesterone, androgens, corticoids, STH, oxytocin, T4, relaxin, insulin
8. **Physiological Functions**
  - Regulates menstrual cycle, female sex behavior
  - Maintains secondary sex characteristics
  - Affects antibody properties
  - Induces estrus, uterine hypertrophy, vaginal cornification, potentiates and stimulates calcitonin secretion
9. **Deficiency Diseases, Disorders:** Menopause (natural deficiency) gonadal dysgenesis, delayed maturation
10. **Essentiality for Life:** Not for life of organism, but for reproduction of organism

## CHEMISTRY

### 1. Structure



Estradiol-17 $\beta$ , C<sub>18</sub>H<sub>24</sub>O<sub>2</sub>

### 2. Reactions

- |                      |   |
|----------------------|---|
| Heat—Stable          | Oxidation—Unstable. Forms<br>estriol or estrone |
| Acid—Stable (dilute) | Reduction—Unstable                              |
| Fluoresces (conc.)   | Light—No data                                   |
| Alkali—Sol., stable  |   |
| Water—Insol.         |   |

### 3. Properties

- |                             |                     |
|-----------------------------|---------------------|
| Appearance—colorless powder | MP—173-179°C        |
| MW—272.4                    | Crystal Form—Prisms |

**Salts, Esters—Acetate,  
benzoate, propionate,  
heptanoate, valerate**

#### **Important Groups for Activity**

**Aromatic Ring A  
—C(3)OH, —C(17)OH**

#### **Solubility**

**H<sub>2</sub>O—Insol.  
(Estriol—3 mg/100 cc H<sub>2</sub>O)**

**Acet., Alc.—Sol.**

**Benz., Chl., Eth.—Sol.**

**Absn. Max.—225, 280 m $\mu$**

**Chemical Nature—Alcohol,  
aromatic, phenolic**

$\alpha_D^{22} = 76.83$

### **4. Commercial Production**

**Extract pregnant mare's urine**

**Total synthesis**

### **5. Isolation**

**Sources—Pregnancy urine of mares, follicular liquor of sow ovaries**

**Method**

**Protein-bound or conjugated steroids: 15% HCl, 60 min 100° $C$ , or  
sephadex G-25 with H<sub>2</sub>O elution, or amberlite column LA-2,  
elution with ethyl acetate at pH = 2; saponification**

**Free steroids: ether extraction**

**Purification**

**Countercurrent distribution**

**Column chromatography**

**High-voltage electrophoresis**

### **6. Determination**

**Bioassay**

**Vaginal cornification**

**Increase in uterine weight in ovariectomized animals**

**Topical application in vagina; vaginal smear of exfoliated cells**

**Physicochemical**

**Fluorescence assay**

**Colorimetry—Kober reaction**

**Chromatography**

**Radioimmunoassay**

## **MEDICAL AND BIOLOGICAL ROLE**

### **1. Species Occurrence, Specificity, Antigenicity**

**Occurrence—All vertebrates, but different distribution of activities for  
three physiological forms. Some plants**

**Specificity**

$17\beta$ -Estradiol, estrone (human, dog, pig, rat)

Estrone, equilin, equilinin (horse)

$17\alpha$ -Estradiol (sheep, goat, beef)

$17\beta$ -Epiestradiol (mouse)

Species difference in sensitivity

Antigenicity—No antigenicity reported

**2. Units:** 1 mg = 10,000 I.U.

**3. Normal Blood Levels (Man):** Male .008  $\mu$ g/100 ml (estradiol and estrone).

Females 0.2  $\mu$ g/100 ml or less (estrone and estriol). Pregnant

Females (av.) 2.1  $\mu$ g/100 ml estradiol, 6.8  $\mu$ g/100 ml estrone,  
10.9  $\mu$ g/100 ml estriol (varies with stage of pregnancy)

**4. Administration:**

Injection—Subcutaneous, intramuscular

Topical—In creams and cosmetics

Oral—Inactive free form. Active as esters or synthetic analogs. Various  
synthetic estrogens used in small quantity with synthetic progesto-  
gens in contraceptive pills

**5. Factors Affecting Release**

Inhibitors—Feedback via blood to hypothalamus

Stimulators—FSH and LH (cyclic via hypothalamus)

**6. Deficiency Symptoms (Humans)**

Delayed maturation

Female accessory and reproductive organs regress

Decreased female behavioral pattern

Senescence

Menopause

**7. Effects of Overdose, Excess**

Tumors

Inhibition of gonads (decrease FSH, LH)  $\rightarrow$  permanent sterility

## METABOLIC ROLE

**1. Biosynthesis:** Acetate  $\rightarrow$  Mevalonate  $\rightarrow$  Squalene  $\rightarrow$  Cholesterol

$\rightarrow$  Pregnenolone  $\rightarrow$  Progesterone  $\rightarrow$   $17\alpha$ -Hydroxyprogesterone

$\rightarrow$  Androstenedione  $\rightarrow$  Testosterone  $\rightarrow$  19-Hydroxytestosterone

$\rightarrow$  Estradiol

Site(s) in cell—Mitochondria, microsomes

**2. Production Sites**

All vertebrates

Ovarian follicles (membrane granulosa, theca interna)

Testes (interstitial cells)

Corpus luteum, adrenal cortex (fasciculata reticularis)

Placenta, embryonic rest cells

**3. Storage Areas:** Unknown**4. Blood Carriers**

Plasma proteins—Estriol glucuronides, free estrone and estradiol

Plasma lipoprotein, estroprotein, serum albumin, red cell proteins

**5. Half-life:** 2-4 min**6. Target Tissues:** Systemic; uterus, mammary gland, vagina, ovary (corpus luteum), secondary female sex organs, skin, CNS, thyroid, thymus, long bones, anterior pituitary, hypothalamus**7. Reactions**

Reactive forms (Redox couple)

Estradiol  $\rightleftharpoons$  estrone  $\rightarrow$  estriol (oxidation product)

<i>Organ</i>	<i>Enzyme System</i>	<i>Effect</i>
Uterus	Lactic acid dehydrogenase Phosphorylase b $\rightarrow$ a RNA polymerase	Activated Activated Activated
Placenta Endometrium	{ Isocitric dehydrogenase Glucose-6-phosphate dehydrogenase	Activated Activated
Kidney	Kynurene aminotransferase	Inhibited
Liver	Kynureninase <i>N</i> <sup>1</sup> -Methylnicotinamide oxidase	Inhibited Inhibited

**8. Mode of Action**

Cellular

Anabolic

RNA and protein synthesis (uterus) increased

CHO synthesis (uterus) increased

Increased growth (uterus)

Catabolic—CHO glycolysis (uterus) increased

Other

Direct action on nucleus

- Increases mitosis (uterus)
- Transcription of RNA affected
- Hyperpolarization of cell membranes
- Organismal**
- Uterus
  - Increases glycolysis, respiration, H<sub>2</sub>O permeability, hyperemia
  - Releases histamine
  - Potentiates and stimulates TCT in calcium bone deposition
  - Development of female characteristics
  - Growth of female 1° and 2° sex organs
    - Estradiol, estrone—Act on corpus luteum
    - Estriol—Acts on sex organs
  - Regulates menstrual cycle and sex behavior
  - Maintains secondary sex characteristics
  - Affects antibody properties

## 9. Catabolism

Intermediates—Estriol

Excretion Products

Urine—Mainly conjugated  $\frac{\text{estrone glucuronide or SO}_4}{\text{estriol glucuronide or SO}_4} = 1/3$

Free—As estriol or 16-epiestriol

Pregnancy—Estrone + estradiol increases 100x. Estriol increases 1000x

Feces—Enterohepatic circulation of estrogens

## MISCELLANEOUS

### 1. Relationship to Vitamins

Folic acid—Involved in mitotic effect of estradiol

Niacin (TPN)(DPN)—Involved in increased respiration and in cholesterol precursor synthesis

Vitamin E—Involved in gonadotropin production or release

Vitamin B<sub>6</sub>—Competes as cofactor with estrogen sulfate in kynurenine aminotransferase activity

Vitamin D—Synergistic in calcium metabolism with estradiol

### 2. Relationship to Other Hormones

Progesterone, Cortisol, Testosterone—Antagonistic or synergistic to estradiol depending on relative concentrations of estradiol and other hormone

Prolactin, STH, Oxytocin, T4, Relaxin—Synergistic to estradiol  
TCT—Potentiated and stimulated by estradiol  
FSH, LH—Stimulate release or production of estradiol

### 3. Unusual Features

Estradiol- $17\beta$   $\rightleftharpoons$  estrone  $\rightarrow$  estriol (activity 1000:100:1)  
Aromatic ring—Carcinogenicity implicated  
Redox couple estradiol  $\rightleftharpoons$  estrone  
Derived from testosterone in biosynthesis  
Occurrence of estrogens in plants—Genistein, Coumestrol (active)  
Tumor formation enhanced by estradiol  
Enterohepatic circulation of estradiol  
Variable species forms  
Synthetic estrogens not steroids

### 4. Possible Relationships of Deficiency to Metabolic Action

Ovarian regression—Decrease of mitosis in sex tissues  
Regression of female sex organs and secondary sex characteristics—  
decrease of mitosis in sex tissues  
Decreased female sex behavior patterns—Decrease of estradiol in central  
nervous system.  
Senescence, menopause—Decrease in mitosis in sex organs

# 34 Progesterone

## GENERAL INFORMATION

1. **Synonyms:** Progestin, luteosterone, corpus luteum hormone

2. **History**

1903—Fraenkel demonstrated that removal of corpora lutea in pregnant rabbits terminates pregnancy, prevents attachment of ovum to uterus

1928—Corner and Allen restored progestational changes in above rabbits with extracts of corpora lutea

1930—Fels and Slotta

1932—Allen

1932—Fevold and Hisaw

1934—Butenandt *et al.*

Slotta *et al.*

Allen *et al.*

Hartmann *et al.*

Obtained crude crystalline concentrates containing progestational activity

Isolated pure crystalline corpus luteum hormone

1934—Slotta *et al.* proposed formula for corpus luteum hormone

1934—Butenandt, Fernholz synthesized progesterone from stigmasterol

3. **Physiological Forms:** Progesterone, 17 $\alpha$ -Hydroxyprogesterone

4. **Active Analogs and Related Compounds:** (Progestins, progestogens)  
Natural

20 $\alpha$ -Hydroxypregneneone

20 $\beta$ -Hydroxypregnene  
11-Dehydroprogesterone  
Cortexone  
17 $\alpha$ -Hydroxyprogesterone  
Synthetic  
A-Norprogesterone  
19-Norprogesterone  
21-Norprogesterone  
Ethisterone  
17 $\alpha$ -Methyltestosterone  
6 $\alpha$ -Methyl-17 $\alpha$ -acetoxyprogesterone  
 $\Delta^1$ -Dehydro-6 $\alpha$ -methyl-17 $\alpha$ -acetoxyprogesterone

#### 5. Inactive Analogs and Related Compounds

5 $\alpha$ -Pregnane-3 $\beta$ -ol-20-one, 21-ethylprogesterone  
11 $\beta$ -Hydroxyprogesterone, pregnanediol, pregnanetriol

#### 6. Antagonists: (Estradiol, testosterone, oxytocin, aldosterone) all concentration dependent

#### 7. Synergists: Estradiol, prolactin, testosterone, cortisol, STH, T4, relaxin, oxytocin

#### 8. Physiological Functions

##### Low concentrations

Prepare uterus for blastocyst implantation, promote ovulation and mammary gland development

Regulate female sex accessory organs, weak corticosteroid properties, precursor to sex hormones

##### Higher concentrations

Maintain pregnancy, repress ovulation and sex activity, inhibit vaginal cornification, and parturition, decrease myometrial excitation

#### 9. Deficiency Diseases, Disorders: Pseudopregnancy (laboratory animals), acne, dysfunctional uterine bleeding

#### 10. Essentiality for Life

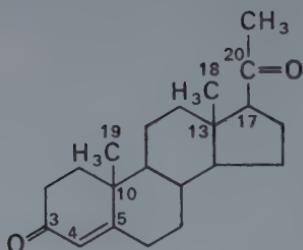
Indirectly essential for life via corticosteroid requirement

Essential for aldosterone and glucocorticoid formation

Essential for reproduction in female vertebrates

## CHEMISTRY

## Structure

Progesterone,  $C_{21}H_{30}O_2$ 

## 2. Reactions

Heat—Stable  
 Acid—Unstable; fluoresces  
     in  $H_2SO_4$   
 Alkali—Unstable  
 Water—Insol.

Oxidation—Unstable  
 Reduction—Unstable;  
     reduces to pregnanediol  
 Light—Unstable

## 3. Properties

Appearance—white powder  
 MW—314.5  
 MP— $\alpha = 128^\circ C$   
 $\beta = 121^\circ C$

Crystal Form  
 $\alpha$ -Orthorhombic prisms  
 $\beta$ -Orthorhombic needles  
 Salts, Esters-Acetate,  
 caproate

Important Groups for Activity  
 $-C(3)=O,$   
 $-C(4)=C(5)-$   
 $-C(20)-CH_3$   
 $\quad \quad \quad \parallel$   
 $\quad \quad \quad O$

Solubility  
 $H_2O$ —Insol.  
 Acet., Alc.—Sol.  
 Benz., Chl., Eth.—Sol.  
 Absn. Max.— $240 m\mu$   
 Chemical Nature  
 Ketone, steroid  
 $\alpha_D = 172-182$  (dioxane)

## 4. Commercial Production

Synthesis from cholesterol, stigmasterol, or diosgenin  
 Isolation from sow ovary corpora lutea

## 5. Isolation

Sources—Sow ovary corpora lutea

## Methods

Extract with alkali

Extract with ether or ether-ethanol (1:3) or methyl acetate-benzene

Partition between hexane (or petroleum ether) and 70% methyl alcohol

Purify by chromatography: celite column, thin layer, paper or counter current distribution

## 6. Determination

Bioassay

Decidual responses

Change of progesterone in endometrium

Physicochemical

Absorption at 240 m $\mu$  or at 290 m $\mu$  in H<sub>2</sub>SO<sub>4</sub>

Yellow fluorescence with SbCl<sub>3</sub>

Blue absorption with phosphomolybdic acid

Protein-binding assay

## MEDICAL AND BIOLOGICAL ROLE

### 1. Species Occurrence, Specificity, Antigenicity

Occurrence—Found in plants, all vertebrates

Specificity—Activity crosses species lines

Antigenicity—No antigenicity reported

### 2. Units: $\mu$ g or mg; rabbit unit = 0.6 mg progesterone

### 3. Normal Blood Levels

Normal males—0.03  $\mu$ g/100 ml plasma

Normal females—0.1-0.3  $\mu$ g/100 ml plasma

Pregnant females—10-28  $\mu$ g/100 ml plasma

### 4. Administration

Injection—Intramuscular

Topical—Not reported

Oral—As caproate or acetate of 17 $\alpha$ -hydroxyprogesterone; various synthetic progestogens used in contraceptive pills in combination with small amounts of estrogens

### 5. Factors Affecting Release

Inhibitors

Psychic phenomena

- Uterine factor
- Feedback mechanisms via hypothalamus
- Environmental factors
- Stimulators
  - Hypothalamic agent—LRH (human)—via pituitary and LH
    - Males—Continuous secretion (low levels)
    - Females—Continuous secretion in nonspontaneous ovulators (rabbit, ferret, cat); rhythmic in spontaneous ovulators (dog, human)
  - Psychic and environmental controls
  - Prolactin or LH, depending on species

## 6. Deficiency Symptoms (Humans)

- Termination of pregnancy
- Decreased production of steroids
- Decreased ovulation
- Loss of normal cyclic changes
- Decreased development for implantation and gestation

## 7. Effects of Overdose, Excess

- Progestational changes
- Pregnancy prolongation
- Inhibition of uterine growth
- Increased Na and K excretion

## METABOLIC ROLE

1. Biosynthesis: Acetate → Mevalonate → Squalene → Cholesterol  
→ Pregnenolone → Progesterone  
Cell Site: Microsomes
2. Production Sites
  - Ovary (follicles, corpus luteum)
  - Testicles (interstitial cells)
  - Adrenal cortex (reticularis fasciculata)
  - Placenta (syncytial trophoblast)
3. Storage Sites
  - Corpora lutea
  - Adrenal cortex

4. **Blood Carriers:** Plasma lipoproteins—albumin, transcortin
5. **Half-life:** About 5 min
6. **Target Tissues:** Uterus, vagina, cervix, pubic symphysis, ovary, hypothalamus, mammary gland, female sex accessory organs, kidney, adrenal cortex, adenohypophysis

### 7. Reactions: Reactive form—Unknown

<i>Organ</i>	<i>Enzyme System</i>	<i>Effect</i>
Uterus	Acid phosphatase Carbonic anhydrase	Activated Activated

### 8. Mode of Action

#### Cellular

Anabolic: Increases glycoprotein (uterus). Increases glycogen (uterus)  
 Catabolic: Increases protein catabolism. Increases galactose oxidation  
 Other: Increases membrane potential. Immediate precursor for other sex hormones. Thermogenic action

#### Organismal

Increases kidney filtration rate (glomerulus)  
 Promotes development and growth of uterus and mammary gland  
 Promotes ovulation and development of sex accessories (female)  
 Promotes excitation of uterus  
 Inhibits release of LH

### 9. Catabolism

Intermediates—Pregnanediol,  $17\alpha$ -hydroxyprogesterone

Excretion products

Urine—Mainly as glucuronates of pregnanediol, pregnanetriol

Feces—Androgens (cow, rat)

## MISCELLANEOUS

### 1. Relationship to Vitamins

Niacin—DPN involved in progesterone synthesis

Vitamin C—Depleted from adrenal cortex or ovary on progesterone formation

### 2. Relationship to Other Hormones

Estradiol—Antagonist or synergist to progesterone, depending on concentration; made from progesterone

Prolactin, LH—Stimulant for production of progesterone, depending on species  
Testosterone—Antagonist or synergist to progesterone, depending on concentration; made from progesterone  
Cortisol, Aldosterone—Made from progesterone  
STH, T4—Synergist in growth aspects of progesterone  
ACTH—Releaser of steroids from adrenal cortex; stimulator of progesterone production  
FSH—Synergist with LH in production of progesterone  
Relaxin, Oxytocin—Synergist with progesterone in parturition  
LRH—Hypothalamic agent stimulating release of LH

### 3. Unusual Features

Concentration dependence of effects  
Primitive type of hormone  
Causes maternal behavior in rabbit  
Causes pseudopregnancy in nonspontaneous ovulators  
Inhibits estrogenic tumors  
Anesthetic effects  
Androgenic or antiandrogenic, depending on species  
Cyclic release in certain species but not in others

### 4. Possible Relationships of Deficiency Symptoms to Metabolic Action

Loss of pregnancy—Lack of growth and developmental stimulus to uterus by progesterone  
Decreased steroid production—Serves as precursor to all other steroid hormones  
Decreased ovulation—No progesterone stimulus for development of follicle in ovary  
Loss of normal cyclic changes—Feedback mechanisms of progesterone on hypothalamus not controlling (?)  
Decreased development for implantation and gestation—Loss of growth and development stimulating action on uterus due to lack of progesterone

# 35 Testosterone

## GENERAL INFORMATION

**1. Synonyms:** 17 $\beta$ -Hydroxy-4-androsten-3-one,  $\Delta^4$ -androsten-17 $\beta$ -ol-3-one

**2. History**

1849—Berthold demonstrated effects of castration prevented by testis transplants

1889—Brown-Sequard claimed rejuvenative powers of testicular extracts

1911—Pezard showed comb growth in capons by injection of testicular extracts

1927—McGee found extracts of bull testis highly potent for male sex hormone activity

1931—Butenandt isolated androsterone from human urine

1935—Laqueur crystallized testosterone from testicular extracts

1935—Butenandt, Ruzicka determined structure and synthesized testosterone

**3. Physiological Forms:** Androstenedione, testosterone, 11 $\beta$ -hydroxyandrostenedione, adrenosterone

**4. Active Analogs and Related Compounds (Androgens)**

Natural

11-Hydroxyandrosterone, adrenosterone, 7-hydroxyprogesterone

11-Keto-androsterone

11 $\beta$ -Hydroxyandrostenedione

**Synthetic**

Ethylyn testosterone, methyltestosterone

$6\alpha$ -chlorotestosterone, 19-nortestosterone,  $17\alpha$ -ethyl-19-nortestosterone

**5. Inactive Analogs and Related Compounds (for Androgenic Activity)**

Cortisone, cortisol, 17-hydroxyprogesterone, lumiandrosterone

$17\alpha$ -hydroxy-11-desoxycorticosterone,  $17\beta$ -methyl epitestosterone, etiocholanolone

**6. Antagonists: Estrogens, (except in low concentrations), progesterone, norethandrolone,  $11\alpha$ -hydroxyprogesterone, methylcholanthrene, A-norprogesterone****7. Synergists: STH, insulin, other androgens, estrogens (in low concentrations)****8. Physiological Functions**

Controls secondary male sex characteristics

Maintains functional competence of male reproductive ducts and glands

Increases protein anabolism; maintains spermatogenesis; inhibits gonadotrophin

Increases male sex behavior; increases closure of epiphyseal plates

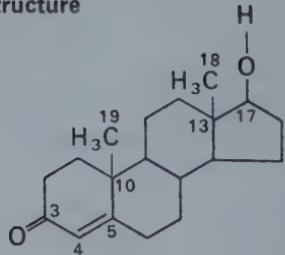
**9. Deficiency Diseases, Disorders**

Male hypogonadism, eunuchoidism

Feminizing testes, hyperplasias of adrenals and testes

**10. Essentiality for Life**

Not essential for life of the organism, but essential for reproduction in all (male) vertebrates

**CHEMISTRY****1. Structure**

Testosterone,  $C_{19}H_{28}O_2$

## 2. Reactions

Heat—Stable	Oxidation—Oxidizes to androstenedione
Acid—Esterifies	Reduction—Unstable
Alkali—Fluoresces (conc.)	Light—Stable
Water—Insol.	

## 3. Properties

Appearance—White powder	Solubility
MW—288.4	H <sub>2</sub> O—Insol.
MP—155° C	Acet., Alc.—Sol.
Crystal Form—Needles	Benz., Chl., Eth.—Sol.
Salts, Esters	Absn. Max.—238 m $\mu$
Propionate, acetate, Butyrate, palmitate, Stearate, Benzoate	Chemical Nature
Important Groups for Activity	Alcoholic ketone, steroid
—C(3)=O, -C(17)-OH	$\alpha_D^{24} = 109^\circ$
—C(4)=C(5)	

## 4. Commercial Production

Microbiological conversion of dehydroandrosterone  
Synthesis from cholesterol

## 5. Isolation

Sources—Urine, blood

Method: Urine

Hydrolyze with H<sub>2</sub>SO<sub>4</sub>, extract with organic solvents

Precipitate with digitonin or Girard's reagent T

Chromatography: MgSiO<sub>4</sub> column or paper or gas

Method: Blood

Complex with methyl green; transesterify with acetic acid

Chromatography on Florisil alumina columns

## 6. Determination

Bioassay

Growth of capon comb

Increase in various muscles

Increase in weight of prostate

Increase in fructose, citric acid in semen

Maintenance of spermatogenesis in hypophysectomized rat

Physicochemical—Zimmerman reaction-(17-oxosteroids); Pettenkofer reaction

## MEDICAL AND BIOLOGICAL ROLE

### 1. Species Occurrence, Specificity, and Antigenicity

Occurrence—Vertebrates (cyclostomes and higher forms), variable types of androgens

Specificity—Variable

Mammals and Birds—testosterone and androsterone active; pregnenolone inactive

Rat—pregnenolone active (not in mammals or birds)

Antigenicity—None reported

### 2. Units: 0.015 mg = I.U.

### 3. Normal Blood Levels (Man)

Males av. 0.60 µg/100 ml plasma—Androsterone and dehydroepiandrosterone; females av. 0.05 µg/100 ml plasma

### 4. Administration

Injection—Intramuscular preferred

Topical—Some cutaneous absorption

Oral—Active, but less than injected or implanted hormones. More active as esters or synthetic androgens

### 5. Factors Affecting Release

Inhibitors

Cortisol

Psychic effects

Androgens

Feedback to hypothalamus

Stimulators

Photoperiodicity

Temperature increase, within limits

Melatonin

FSH, ACTH, LH, LRH

Increased blood flow to testis

Decreased blood levels of androgens or estrogens

### 6. Deficiency Symptoms (Humans)

Involution of accessory organs (prostate, seminal vesicles)

Decreased male behavior patterns and libido

Decreased secondary sex traits

Poor muscle development and function

- Delayed closure of epiphyses
- Decreased excretion of 17-keto-steroids in urine

7. Effects of Overdose, Excess:  $LD_{100} = 325 \text{ mg/kg}$  in female rats
  - Increases libido
  - Virilization, acne
  - Increases fat catabolism
  - Increases androgen and estrogen excretion (17-keto-steroids)
  - Precocious sex development
  - Hypertrophy of accessory sex organs
  - Increases skeletal growth until epiphyses close
  - Increases muscle mass, hirsutism
  - Decreases scalp hair growth (?)
  - Decreases weight—chick, rat

## METABOLIC ROLE

1. Biosynthesis: Acetate  $\rightarrow$  Mevalonate  $\rightarrow$  Squalene  $\rightarrow$  Cholesterol
  - $\rightarrow$  Pregnenolone  $\rightarrow$  Progesterone  $\rightarrow$   $17\alpha$ -hydroxyprogesterone
  - $\rightarrow$  Androstenedione  $\rightarrow$  Testosterone

Cell Sites: Leydig cells in interstitial cells of testis: Agranular cytoplasm
2. Production Sites
  - Interstitial cells of ovary and testis: Agranular cytoplasm
  - Adrenal cortex (reticularis fasciculata), embryonic placenta
3. Storage Areas: No data
4. Blood Carriers: Albumin, and a specific  $\beta$ -globulin
5. Half-life: About 4 min
6. Target Tissues
  - Systemic, fat deposits, muscles, hypothalamus, kidney
  - Male sex organs, adenohypophysis, hair follicles
  - Epiphyses of long bones, vocal cords
7. Reactions: Reactive forms
  - Redox couples—Testosterone  $\rightleftharpoons$  androstenedione  $\rightleftharpoons$  androsterone

<i>Organ</i>	<i>Enzyme System</i>	<i>Effect</i>
Kidney	$\beta$ -Glucuronidase	Activated
	<i>d</i> -Aminooxidase	Activated
	Arginase	Activated
	Alkaline phosphatase	Inhibited
Prostate	Succinic dehydrogenase	Activated
Seminal vesicle	Amino acid activating enzymes	Activated

## 8. Mode of Action

### Cellular

Anabolic—Increases incorporation of amino acids and protein synthesis in muscles, liver, kidney

Catabolic—Increases fat catabolism. Decreases amino acid catabolism

Other

Redox couple regulation of oxidation

Increased mitosis in certain tissues

Increases creatine storage

Membrane effects

### Organismal

Increases development of male secondary sex organs and characteristics

Increases growth of muscles, liver, kidney

Androgenic, increases libido

Effects on CNS, male behavior

Increases folliculoid and luteoid activity in immature females

Increases basal metabolism

Maintains positive balances of N, K, Ca, P

Decreases creatinuria

Promotes closure of bone epiphyses

Stimulates red cell production

## 9. Catabolism

Intermediates—Androstanolone, androstanedione

Excretion Products—Androsterone, etiocholanolone, 17-keto-steroids, dehydroepiandrosterone. In urine, bile, feces-free or conjugated with sulfate or glucuronide. Enterohepatic circulation

## MISCELLANEOUS

### 1. Relationship to Vitamins

Vitamins A, E, C, Folic Acid—Synergists with testosterone for maturation of germ cells and increased anabolic activity

Vitamin B Complex—Male accessory gland maintenance in rat (involution on vit. B deficiency, similar to castration); synergistic in increased metabolic rate

Vitamin D—Synergist with testosterone in bone metabolism

## 2. Relationship to Other Hormones

Estradiol—Formed from testosterone

LH, LRH, FSH—Stimulators of testosterone formation or release

Estradiol, STH, Insulin—Synergists for action of testosterone (in proper concentrations)

ACTH—stimulates formation of adrenal androgens

Progesterone, Estrogens—Antagonists to testosterone (in proper concentrations)

Cortisol, Estrogens, Androgens—Act as release inhibitors in high concentrations

## 3. Unusual Features

Multiple sources of production

Fetal sex determination to male via hypothalamus by testosterone

Sensitivity of capon comb to testosterone

Insensitivity of certain muscles to testosterone

Female birds produce testosterone in ovary

Immediate precursor in estrogen synthesis

Two major synthetic routes, three minor ones in adrenals and testes

Social functions in seals affected by androgens

Species differences in effects of testosterone on sperm maturation rate

Dietary effect—Vitamin B deficiency or protein deficiency similar to castration

## 4. Possible Relationships of Deficiency Symptoms to Metabolic Action

Involution of male accessory organs, decreased secondary sex traits—withdrawal of anabolic effect of testosterone

Decreased male behavior and libido—decreased effect on CNS

Poor muscle development and function—withdrawal of anabolic effect of testosterone

Delayed closure of epiphyses—withdrawal of anabolic effect of testosterone

Decreased excretion of 17-keto-steroids in urine—decreased production of androgens

# 36

# Relaxin

## GENERAL INFORMATION

1. **Synonyms:** Releasin, Cervilaxin

2. **History**

1926—Hisaw cited evidence for a pregnancy hormone which causes relaxation of pelvic ligaments in preparation for parturition  
1930—Fevold *et al.* extracted relaxin from corpora lutea  
1942—Abramowitz isolated relaxin from pregnant rabbit serum  
1955—Lehrman *et al.* isolated and purified relaxin from ovaries of pregnant sows  
1966—Struck and Bhargava isolated first homogeneous preparations of relaxin

3. **Physiological Forms:**  $\beta$ -relaxin

4. **Active Analogs and Related Compounds:** Four similar peptides in relaxin family

5. **Inactive Analogs and Related Compounds:** Oxidized or reduced forms of relaxin

6. **Antagonists:** Androgens, corticosterone, high levels of estradiol and progesterone

7. **Synergists:** Low levels of estradiol and progesterone, oxytocin, T4

## 8. Physiological Functions

- Enlargement of birth canal in preparation for parturition
- Separation of symphysis pubis, loss of rigidity in pelvic bones
- Decreases uterine motility
- Maintenance of pregnancy (progesterone + estrogen sparing)
- Increases sensitivity to oxytocin
- Releases oxytocin
- Stimulates mammary gland
- Stimulates imbibition of water in uterus
- Inhibits uterine contraction

**9. Deficiency Diseases, Disorders:** None known

**10. Essentiality for Life:** Not essential for human female reproduction, but is essential for other mammalian reproduction. Otherwise not essential for life

CHEMISTRY

**1. Structure:** Polypeptide (4 peptides with activity have been isolated). Contains Ala, Asp, Cys, Glu, Gly, His, Lys, Ser, Tyr, Val, Arg, quanidine. About 30-40 amino acids in each peptide

## 2. Reactions

Heat-Stable to 100°C neut.  
soln.

Acid—Inactivates (in acidic methanol)

Alkali—Inactivates (in hot alkali)

#### Water-Sol. (acidic)

#### Oxidation—Inactivates

Reduction—Inactivates (SH agents)

### **Light—No data**

#### **Proteolytic enzymes—Inactivate**

### 3. Properties

**Appearance—**Amorphous powder.

MW-4000-5000

MP—No data

### Crystal Form–Amorphous

### **Salts—No data**

## Important Groups for Activity

### Guanidine S-S

Cys

## Solubility

### H<sub>2</sub>O-SI. sol.

### Acet., Alc.-Insol.

Benz., Chl., Eth.-Insol.

Absn. Max.—277.5 m $\mu$

## Chemical Activity—Acidic

**4. Commercial Production**

Isolation from pregnant sow ovaries

**5. Isolation**

Source—Pregnant sow ovaries

Method—Extraction with trichloroacetic acid, glacial acetic acid, acid-acetone; chromatography on columns of DEAE cellulose, IRC-50; gel filtration on sephadex G-50

**6. Determination of potency and concentration**

Bioassay—Measure length of interpubic ligament in mice

X-Ray photography of innominate bones in estrogen primed guinea pig

Inhibition of motility of mouse uterine segments in vitro

Physico-chemical—None

## MEDICAL AND BIOLOGICAL ROLE

**1. Species Occurrence, Specificity, and Antigenicity**

Occurrence—Found in mammals, birds, sharks. Relaxin-like substances have been isolated from elasmobranch ovaries and bird testes

Specificity—High; species differences pronounced

Antigenicity—Moderate; can be antigenic

**2. Units:** Guinea pig units. Minimal amount necessary to cause appreciable separation of symphysis in guinea pig

**3. Normal Blood Levels:** 200 GPU/100 ml (pregnant sow)

**4. Administration**

Injection—Usually used

Topical—Not active

Oral—Not active

**5. Factors Affecting Release**

Inhibitors

Androgens

Corticosterone

High progesterone level

High estradiol level

**Stimulators**

- Low estradiol level
- Low progesterone level
- Pregnenolone

**6. Deficiency Symptoms:** Humans—Unknown

**7. Effects of Overdose, Excess:** Unknown.

**METABOLIC ROLE****1. Biosynthesis****Precursors**

- 11 of 20 standard amino acids, progesterone (cofactor)
- Reducing sugars

Missing: Try, Asn, Gln, Met, Leu, Ile, Phe, Thr, Pro

Intermediates—Unknown

Site(s) in Cell—Unknown

**2. Production Sites:** Corpus luteum in pregnancy. Possibly placenta, uterus in some species

**3. Storage Areas:** None

**4. Blood Carriers:** Unknown

**5. Half-life:** Approx. 1 hr

**6. Target Tissues**

- Connective tissue of pubic symphysis
- Uterus (diminution of contractions and softening of cervix)
- Mammary gland
- Vagina

**7. Reactions:** Reactive Forms: Unknown

<i>Organ</i>	<i>Enzyme System</i>	<i>Effect</i>
Pubic symphysis	Collagen depolymerases	Activated
Liver	Cholesterol biosynthesis	Inhibited
Uterus	Alkaline phosphatase	Increased

**8. Mode of Action**

Cellular

Anabolic—Increases uterine glycogen synthesis

Catabolic—No data

Other—Decreases membrane potential of myometrium. Enzyme activator

Organismal

Increases vascularity of pubic symphysis

Imbibition of water; disaggregation and depolymerization of mucoproteins in ground structure of symphysis

Increases glycogen and water content of uterus, also dry weight and N content

Decreases uterine motility

Softens cervix of uterus

Increases uterine sensitivity to oxytocin

Stimulates release of oxytocin

Relaxes interpubic ligament

**9. Catabolism**

Intermediates—Peptides, amino acids

Excretion products—Ammonia, CO<sub>2</sub>, H<sub>2</sub>O, amino acids, 1-4% relaxin in urine

**MISCELLANEOUS**

**1. Relationship to Vitamins:** Vitamin C—Maintains mucoprotein ground substance in connective tissue, affected by relaxin

**2. Relationship to Other Hormones**

Estradiol—Relaxin works in conjunction with estrogens—synergistic or antagonistic depending on concentration (requires estrogen “priming”)

Oxytocin—Relaxin may initiate oxytocin release

STH—Relaxin may require growth hormone for relaxation of interpubic ligament

Progesterone—Synergistic or antagonistic depending on concentration

TSH—Increased biosynthesis of TSH stimulated by relaxin

Testosterone, Corticosterone—Act as release inhibitors

**3. Unusual Features**

Hormone of pregnancy only

Strictly female hormone, although general effects noted in body

Found in rooster testes—No known function  
Inhibits cholesterol biosynthesis, hypocholesteremic  
Increases hydrolysis of collagen

**4. Possible Relationships of Deficiency Symptoms to Metabolic Action:**  
**Unknown**

# 37

# Epinephrine

## GENERAL INFORMATION

1. **Synonyms:** Adrenaline, Adrenin, Suprarenin, Vasotonin, Vasoconstrictine, Adrenamine, Levorenine
2. **History**
  - 1895—Oliver and Shafer demonstrated pressor effect of suprarenal extracts
  - 1899—Abel named pressor agent epinephrine
  - 1901—Takamine, Aldrich isolated epinephrine from animal adrenal glands
  - 1904—Stolz }  
1905—Dakin } synthesized *d/l*-epinephrine
  - 1908—Flacher responsible for resolution of *d/l*-form of epinephrine
  - 1910—Barger and Dale defined sympathomimetic amines and their properties
  - 1958—Pratesi determined configuration of epinephrine
3. **Physiological Forms:** */l*-Epinephrine
4. **Active Analogs and Related Compounds**
  - d*-epinephrine (1/15 as active as */l*-isomers), norepinephrine, dopamine, ephedrin, benzedrine, paredrine, tyramine, isoproterenol
5. **Inactive Analogs and Related Compounds:** DOPA

**6. Antagonists:** Insulin, ergotamine, dibenamine, oxytocin, dibenzylidine, tetraethylammonium chloride

**7. Synergists:** Glucagon, T4, cortisol, ACTH

### 8. Physiological Functions

Blood Circulation—Increases blood pressure (pressor agent), peripheral vasodilator, increases heart output and rate, flow increase in brain, liver, and skeletal muscle

Kidney—Reduces glomerular filtration rate

Lung, intestine, genital system—Inhibited motility

Metabolic effects—Increases O<sub>2</sub> consumption, increases temperature, increases BMR, increases gluconeogenesis

CNS effects—Restlessness, anxiety

Pituitary effects—Stimulates production and release of ACTH and corticoids

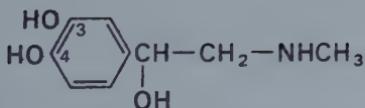
Emergency hormone—Stress reactions

**9. Deficiency Diseases, Disorders:** Pheochromocytoma (chromaffin cells)

**10. Essentiality for Life:** Not absolutely essential for life of organism; possible shortening of life span due to decreased response to emergencies

## CHEMISTRY

### 1. Structure



*L*-Epinephrine, C<sub>9</sub>H<sub>13</sub>NO<sub>3</sub>

### 2. Reactions

Heat—Decomposes at 215°C

Acid—Inactivates

Alkali—Unstable—Very sol. in dil. NaOH. Insol. in NH<sub>4</sub>OH

Water—Sol., basic

Oxidation—Oxidizes easily

Reduction—Stable

Light—Fluorescent in UV; darkens on exposure, forms adrenochrome

**3. Properties**

Appearance—white crystalline powder  
 MW—183.2  
 MP—211–212°C  
 Crystal Form—No data  
 Salts—HCl  
 Important Groups for Activity  
 Phenol, amine, alcohol  
 $-C(4)OH$ ,  $-NH-$ ,  $-CHOH$

Solubility  
 $H_2O$ —Sparingly  
 Acet., Alc.—Insol.  
 Benz., Chl., Eth.—Insol.  
 Absn. Max.—279 m $\mu$   
 Chemical Nature  
 Catecholamine  
 Secondary amine  
 $\alpha_D^{25} = -53.5^\circ$  (0.5 N HCl)

**4. Commercial Production**

Adrenal gland extractions  
 Synthetic production

**5. Isolation**

Sources—Adrenal medulla, urine, blood  
 Methods  
 Hydrolysis of conjugates, if any, boiling at pH 2, 20 min  
 Extraction with acidic ethanol or *n*-butanol  
 Purification via paper chromatography

**6. Determination**

Bioassay  
 Inhibition of movement of isolated rat uterus  
 Constrictor action on artery of denervated rabbit ear  
 Physicochemical  
 Iodochrome oxidation to distinguish norepinephrine from epinephrine  
 Fluorescence in alkali  
 Color reaction with ferric chloride

**MEDICAL AND BIOLOGICAL ROLE****1. Species Occurrence, Specificity, and Antigenicity**

Occurrence—Found in all vertebrates and some invertebrates  
 Specificity—None, full interspecific potency  
 Antigenicity—None

**2. Units:** None; by weight**3. Normal Blood Levels (Man):** Approximately 0.01  $\mu$ g/100 ml plasma (venous)

**4. Administration**

- Injection—Subcutaneous, intramuscular
- Topical—Active (electrophoretic application)
- Oral—Possible, but slow

**5. Factors Affecting Release**

- Inhibitors—Nerve controls, excess catecholamines
- Stimulators—Nicotine, histamine, reserpine, acetylcholine, morphine, ether, ACTH, glucocorticoids, low blood sugar, stress, insulin, psychic (hypothalamus) nerve controls, trauma, exercise

**6. Deficiency Symptoms** Not fatal, but organism cannot respond to emergency, hard work, temperature extreme, emotional disturbance**7. Effects of Overdose, Excess**

- Decreases oxygen consumption, BMR, clotting time,
- Tachycardia, restlessness, anxiety, fatigue, inhibited G.I. tract,
- Increases heart rate, respiration, pallor, blood sugar, sweat, blood flow (muscle)
- Ventricular fibrillation, paroxysmic or sustained hypertension

**METABOLIC ROLE**

- 1. Biosynthesis:** Phenylalanine → Tyrosine → 3,4-Dihydroxyphenylalanine (DOPA) → 3,4-Dihydroxyphenylethylamine (Dopamine) → Norepinephrine → Epinephrine  
Site(s) in cell: In golgi (osmiophilic granules)
- 2. Production Sites:** Chromaffin cells in gut and adrenal medulla
- 3. Storage Areas:** Chromaffin cells in liver and gut
- 4. Blood Carriers:** Free in blood or conjugated with sulfate or glucuronides, or combined with albumin
- 5. Half-life:** About 2 min
- 6. Target Tissues:** Systemic, vascular system, liver, muscles
- 7. Reactions**  
Reactive intermediate—Cyclic AMP—(secondary messenger)

<i>Organ</i>	<i>Enzyme System</i>	<i>Effect</i>
Muscle and liver	Phosphorylase b Adenyl cyclase Phosphorylase b kinase Synthetase I kinase Synthetase I	Activated Activated Activated Activated Inhibited
Adipose tissue	Lipase Adenyl cyclase	Activated Activated

## 8. Mode of Action

### Cellular

Anabolic—No data

Catabolic—Increases glycogenolysis in liver, increases fat catabolism  
Other

Decreases glucose entry into cells of skeletal muscle

Increases glucose entry into heart, brain and adipose tissue cells

Increases cyclic AMP

Suppresses mitosis

Calorigenic action

### Organismal

Increases—Systolic pressure; blood flow to skeletal muscles, liver; blood sugar; lipolysis; blood K<sup>+</sup>; O<sub>2</sub> consumption (BMR), glucose absorption from gut, mental alertness, sweating

Decreases—Glucose tolerance, eosinophils, blood flow to capillaries of skin and kidney, plasma volume

Lightens chromatophores

## 9. Catabolism

Intermediates—3,4-dihydroxymandelic acid

Excretion Products—Free (0.5 to 2%) or as metanephrine (3-methoxy, 4OH-mandelic acid)

## MISCELLANEOUS

1. Relationship to Vitamins: Vitamin C—Maintains reduced state of epinephrine. Vitamins C, B<sub>6</sub>, B<sub>12</sub>, folic acid—Cofactors in synthesis of epinephrine from phenylalanine

2. Relationship to Other Hormones

Norepinephrine—Immediate precursor to epinephrine

Insulin—Antagonist to epinephrine

Glucagon, T4, ACH—Synergists to epinephrine

TSH—Released by epinephrine

Prolactin—Blocking of milk ejection by epinephrine

Cortisol, Cortisone—Synergistic in stress response

Oxytocin—Epinephrine antagonistic in milk ejection

### 3. Unusual Features

Active at 1.4 parts per billion

Absent in developing fetus; Proportion of NOR/EP = 1:4 in adult human adrenal (reverse in chick); blocks milk ejection; rabbit most sensitive; behavioral effects

Proportion of NOR/EP varies in invertebrates

Increases mental alertness

Calorigenic action

### 4. Possible Relationships of Deficiency Symptoms to Metabolic Action

Decreased emergency response—Decreased lipolysis in adipose tissue results in decreased glucose energy (ATP) available for stress reaction

Decreased response to emotional disturbances, temperature extremes, hard work—as in the previous symptom

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# Norepinephrine

## GENERAL INFORMATION

1. **Synonyms:** Noradrenaline, arterenol, levarterenol

### 2. History

1898—Lewandowsky	}	Noted similarity of effects of adrenal gland extracts and stimulation of sympathetic nerves, on tissues
1901—Langley		
1904—Eliot proposed sympathetic nerve endings release epinephrine-like substance		
1910—Barger and Dale synthesized norepinephrine		
1927—Cannon and Uridil noted that liver releases epinephrine-like substance called sympathin on stimulation of sympathetic nerves		
1948—Tullar resolved <i>d</i> -form of norepinephrine		
1951—Euler demonstrated sympathin to be norepinephrine		
1959—Pratesi established configuration of norepinephrine		

3. **Physiological Forms:** *l*-Norepinephrine

4. **Active Analogs and Related Compounds:** Dopamine, ephedrine, *d*-norepinephrine, *d*-epinephrine (1/15 as active as *l*-isomers)

5. **Inactive Analogs and Related Compounds:** DOPA

6. **Antagonists:** Insulin, vasopressin

**7. Synergists:** Epinephrine, serotonin, cortisol, cortisone, glucagon

### 8. Physiological Functions

Blood circulation—Increases blood pressure, peripheral vasoconstrictor, without change or slight decrease in output and heart rate. No flow increase in brain, liver, or muscle

Kidney—Decreases glomerular filtration rate

Lung, intestine, genital system—Inhibited

Metabolic effects—Weak epinephrine effect.

CNS effects—Adrenergic transmitter agent at synapses, no brain excitation

Pituitary effects—None

Maintenance hormone—Diurnal regulation

Immediate precursor of epinephrine

### 9. Deficiency Diseases, Disorders

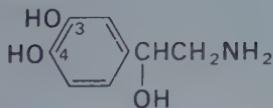
Neuroblastoma

Pheochromocytoma

**10. Essentiality for Life:** Not absolutely essential for life of organism, except if other neurotransmitters not available

## CHEMISTRY

### 1. Structure



/-Norepinephrine, C<sub>8</sub>H<sub>11</sub>NO<sub>3</sub>

### 2. Reactions

Heat—Unstable

Acid—Inactivates

Alkali—Very sol. dil. NaOH;

Insol. NH<sub>4</sub>OH

Water—Soluble, alkaline

Oxidation—Easily oxidizes to noradrenochrome

Reduction—Stable

Light—No fluorescence in UV

### 3. Properties

Appearance—Colorless crystals

MW—169.2

MP—145-146°C

Crystal Form—No data

Salts—HCl

Important Groups for Activity

Alcohol—CHOH, phenol,

—C(4)OH, amine, (—NH<sub>2</sub>)

Solubility	Chemical Nature—Catecholamine;
H <sub>2</sub> O sparingly	primary amine
Acet., Alc.—Sl. sol.	$\alpha_D^{25} = -37.3$ (HCl)
Benz., Chl., Eth.—Sl. sol.	Misc.—pK = 8.8, 9.98
Absn. Max.—279 m $\mu$	

#### 4. Commercial Production: Synthetic production

#### 5. Isolation

Sources—Adrenal medulla, blood, urine

Methods

Hydrolysis of conjugates, if any—Boil at pH 2, 20 min

Extraction with acidic ethanol or *n*-butanol

#### 6. Determination

Bioassay—Pressor effect in cat, rat

Physicochemical

Colorimetric—Ferric chloride complex

Fluorometric—Condense with ethylenediamine

### MEDICAL AND BIOLOGICAL ROLE

#### 1. Species, Occurrence, Specificity, and Antigenicity

Occurrence—Found in all vertebrates and some invertebrates

Specificity—None; full, interspecific potency

Antigenicity—None

#### 2. Units: None; by weight

#### 3. Normal Blood Levels (Man): Approx. 0.05 $\mu$ g/100 ml plasma (venous)

#### 4. Administration

Injection—Usual

Topical—By electrophoresis through skin

Oral—Inactive

#### 5. Factors Affecting Release

Inhibitors—Nerve controls, excess catecholamines

Stimulators—ACH, nicotine, histamine, Tyr, Phe, low blood sugar, low T4, nerve controls, stress, trauma, reserpine, morphine

## 6. Deficiency Symptoms

Poor nerve condition

Orthostatic hypotension—Fainting on standing up, dizziness, light-headedness

## 7. Effects of Overdose, Excess: Bradycardia, pheochromocytoma

### METABOLIC ROLE

- Biosynthesis:** Phenylalanine → Tyrosine → 3,4-Dihydroxyphenylalanine (DOPA) → 3,4-Dihydroxyphenylethylamine (Dopamine) = Norepinephrine  
Site(s) in cell—Osmophilic granules in golgi apparatus

## 2. Production Sites

Adrenal medulla

Adrenergic nerve endings

Chromaffin cells—sympathetic nerves and ganglia, gut

- Storage Areas:** Chromaffin cells in liver and gut, intraaxonal spaces, adrenal medulla

- Blood Carriers:** Free or sulfate, glucuronide esters

- Half-life:** 2 min or less

- Target Tissues:** Systemic, esp. vascular system, lung, eye

- Reactions:** Reactive intermediate: Cyclic AMP—secondary messenger

Organ	Enzyme Systems	Effect
Muscle and liver	Adenyl cyclase	Activated
	Phosphorylase b	Activated
	Phosphorylase b kinase	Activated
	Synthetase I kinase	Activated
Adipose tissue	Synthetase I	Inhibited
	Adenyl cyclase	Activated
	Lipase	Activated

## 8. Mode of Action

Cellular

Anabolic—No data

- Catabolic
  - Increased CHO catabolism
  - Increased glycogen to glucose conversion
  - Increased fat catabolism
- Other—No data
- Organismal
  - Decreases—Pulse, blood flow, G.I. and genital activity, respiration
  - Increases—Diastolic and systolic pressure, vasodilation of coronary arteries, lipid mobilization, glucose absorption from gut
  - Bradycardia
  - Vasoconstrictor

#### **9. Catabolism**

- Intermediates—3,4-dihydroxymandelic acid
- Excretion products—Free in urine (3-6%), normetanephrine, 3-methoxy, 4-hydroxymandelic acid

### **MISCELLANEOUS**

- 1. Relationship to Vitamins:** Vitamin C protects against oxidation of norepinephrine. Vitamins B<sub>6</sub>, C, folic acid—cofactors in synthesis of norepinephrine from phenylalanine
- 2. Relationship to Other Hormones**
  - Epinephrine—Derivative of norepinephrine; synergist also
  - Insulin—Antagonist to norepinephrine, secretion inhibited by norepinephrine
  - Serotonin, Cortisol, Cortisone—Synergists to norepinephrine
  - T4, ACH—Stimulators for release of norepinephrine
- 3. Unusual Features**
  - Neurohumor—Much carried intraaxonally
  - EP/NOR = 4/1 in medulla (man)
  - Diurnal (higher in day)
  - No behavioral effects
  - Increases pigment concentration in skin
  - Main amine in fetus
  - Anticipatory type, i.e., normal plasma maintenance

- 4. Possible Relationships of Deficiency Symptoms to Metabolic Action**

- Poor nerve conduction—Lack of transmitter agent
- Dizziness, light-headedness, fainting—Low blood pressure

# Summarizing Tables

TABLE 1. Characteristics of Vitamins

(+ = present in structure or function  $\pm$  = slightly)  
 (- = catabolic or inhibiting effect)

Structural Component or Function	A	B <sub>1</sub>	B <sub>2</sub>	B <sub>6</sub>	B <sub>1,2</sub>	C	D	E	K	Biotin	F.A. <sup>a</sup>	Niacin	P.A.
Amino Acid											+	+	+
Purine, pyrimidine (derivative)	+	+			+						+		
Benzene ring	+										+	+	
Pyridine ring					+						+		
Isoprene group (derivative)	+							+	+				
Sugar (derivative)	+							+	+				
Alcohol groups	+	+	+		+	+	+	+	+		+		
Double bonds (-C=C-)	+	+	+	+	+	+	+	+	+		+	+	
Elements other than CHON		S				Co			S				
Redox agent	+					+	+			+	+	+	
PO <sub>4</sub> complex <i>in vivo</i>	+	+	+	+	+			+		+	+	+	
Antioxidant		+				+	+			+			
Biosynthesis via Cholesterol pathway	+							+	+	+			

Anabolic functions	+	+	+	+	+	+	+	+	+	+
Catabolic functions	+	+	+	+	+	+	+	+	+	+
Stored in organism (man)	+	±	+	+	±	+	±	+	+	±
Available from intestinal bacteria (man)	-	±	±	+	+	+	+	+	+	+
Toxic in excess (man)	+	+	+	+	+	+	+	+	+	+
Mitosis effect	-	-	-	-	-	-	-	-	-	-
Mitochondrial sites	+	+	+	+	+	+	+	+	+	+
Chloroplast sites	+ <sup>g</sup>	+	+	+	+	+	+	+	+	+
Microsomal sites	-	-	-	-	-	-	-	-	-	-
Membrane sites	+	+	+	+	+	+	+	+	+	+
Protein synthesis	-	-	-	-	-	-	-	-	-	-
Amino acid synthesis	-	-	-	-	-	-	-	-	-	-
CHO synthesis	+	-	-	-	-	-	-	-	-	-

<sup>a</sup> Folic acid. <sup>b</sup> Pantothenic acid. <sup>g</sup> Carotenoids.

TABLE 1. Characteristics of Vitamins (cont.)

(+= stimulating effect or present in organelles)

Structural Component or Function	A	B <sub>1</sub>	B <sub>2</sub>	B <sub>6</sub>	B <sub>12</sub>	C	D	E	K	Biotin	F,A. <sup>a</sup>	Niacin	P,A. <sup>b</sup>
TCA Cycle effect		+	+								+		+
Lipid synthesis					+							±	
Fatty acid synthesis						+						±	
Nucleic acid synthesis							+						
Purine pyrimidine synthesis								+		+			
Mineral metabolism										Fe, Ca	Ca	Se	
H <sub>2</sub> O metabolism													+
Hormone Synthesis	Prog. <sup>c</sup>		ACH <sup>f</sup>			ACH <sup>f</sup>		Serot.				+	ACH <sup>f</sup>
	Cortic. <sup>c</sup>				Nor.			Gluc.					
	Andro. <sup>d</sup>					Serot.							
Sterol Synthesis		+				+		+				+	+

<sup>a</sup>Folic acid.<sup>b</sup>Pantothenic acid.<sup>c</sup>Corticosterone.<sup>d</sup>Androstenedione.<sup>e</sup>Progesterone.<sup>f</sup>Acetylcholine.

**TABLE 2.** Synergisms (+) and Antagonisms (-) Among the Vitamins

Vitamins	A	B <sub>1</sub>	B <sub>2</sub>	B <sub>6</sub>	B <sub>1,2</sub>	C	D	E	K	Biotin	F.A. <sup>a</sup>	Niacin	P.A. <sup>b</sup>
A		+		+	+					±			
B <sub>1</sub>			+	+	+							+	+
B <sub>2</sub>		+	+			+				+	+	+	+
B <sub>6</sub>			+	+		+	+	+		+	+	+	
B <sub>1,2</sub>		+	+	+		+	+	+		+	+	+	
C	+			+	+		+	+			+		+
D													+
E				+	+	+			+			+	
K	.					+	+						
Biotin		+	+	+							+		+
F.A. <sup>a</sup>		+	+	+	+	+	+	+		+	+	+	
Niacin	+	+	+	+	+					+			+
P.A. <sup>b</sup>	+	+		+	+					+	+	+	

<sup>a</sup>Folic acid. <sup>b</sup>Pantothenic acid.

TABLE 3. Characteristics of Hormones

Hormones <sup>a</sup>	Amino Acid Units (Proteins, Peptides)	CHO Component	S-S Bonds	Catecholamine	Elements Other Than CHO	Redox Couple In Vivo	Cyclic AMP	Mediated Via	CHO Anabolism +	Lipid Anabolism +	Protein Anabolism +	Nucleic Acid (Or Purine, Pyrim.)	Steroid Anabolism +	Anabolism +	Anabolism -	Catabolism -	Balancce Mineral and H <sub>2</sub> O	Mitotic Effect (Increase +, Decrease -)	Membrane Effect	Kidney Function	Blood Pressure	Nerve Function		
ACTH	+					+	+																	
Aldos.																								
Cort.		+																						
Epi.																								
Est.																								
FSH																								
Gluc.	+																							
GH (STH)	+	+																						
(HRH)	+	+																						

In.	+	+	S	±	+	+	+	+
LH	+	+	S	+	-	+	+	+
MSH	+		S	+		+		
Norepi.		+	S	+	-	-		
Oxy.	+	+	S			+	+	+
PTH	+		S	+	-	+	+	+
Prog.		+		±		+	+	+
Prol.	+	+	S	+	+	-	+	+
Relax.	+	+	S	±	±	+	+	+
Test.		+	S	+	-	+	+	+
TCT	+	+	S	+	+	+	+	+
T4	+		I	+	-	+	+	+
TSH	+	+	S	+	-	±	+	+
Vaso.	+	+	S	+	-	+	+	+

<sup>a</sup>See list of abbreviations for full name.    <sup>b</sup>Release.

TABLE 4. Synergisms (+) and Antagonisms (-)

Hormones <sup>a</sup>	ACTH	Aldos.	Cort.	Epi.	Est.	FSH.	Gluc.	GH (STH)	HRH	In.	LH
ACTH			±	+				±		-	
Aldos.			-		-			+			
Cort.	±	-		+	±		+	±		-	
Epi.	+			+			+			-	
Est.		-	±					+		+	
FSH								+			+
Gluc.				+	+			?		-	
GH (STH)	±	+	±		+	+				±	
HRH											
In.	-		-	-	+	-	-	±		±	
LH							+			±	
MSH			±	-				+			
Norepi.			+	+			+			-	
Oxy.	+	±	-	+				+			
PTH			±		± <sup>b</sup>			-			
Prog.	-	+			±			+			
Prol.			+		±			+			±
Relax.			-		±						
Test.			-		±			+		+	
TCT						+					
T4	±		+	+	+	+		+		-	+
TSH	+							+			
Vaso.		±	-	+				+			

<sup>a</sup> See list of abbreviations for full name.<sup>b</sup> Birds.

## Among the Hormones

	Hormones <sup>a</sup>	MSH	Norepi.	Oxy.	PTH	Prog.	Prol.	Relax.	Test.	TCT	T4	TSH	Vaso.
ACTH											±	+	
Aldos.			+		-							±	
Cort.	±	+	±	±	+	+	+	-	-		+	-	
Epi.	-	+	-	-							+	+	
Est.			+	± <sup>b</sup>	±	±	±	±	±	+	+		
FSH												+	
Gluc.		+											
GH (STH)	+		+	-	+	+			+		+	+	+
HRH													
In.		-								+		-	
LH					±							+	
MSH											+	+	
Norepi.												-	
Oxy.					±	+	+					+	
PTH						+			-	-	-	-	
Prog.			±			+	±	±				+	
Prol.		+	+	+					-		+		+
Relax.		+		±					-		+		
Test.			-	±	-	-	-						+
TCT				-									
T4	+	-	+	-	+	+	+	+			+	+	
TSH	+											+	
Vaso.		-				+			+		+		

<sup>a</sup>See list of abbreviations for full name. <sup>b</sup>Birds.

**TABLE 5. Synergisms (+) and Antagonisms (-) Between Vitamins and Hormones**

Hormones <sup>a</sup>	A	B <sub>1</sub>	B <sub>2</sub>	B <sub>6</sub>	B <sub>1,2</sub>	C	D	E	K	Biotin	F.A. <sup>b</sup>	Niacin	P.A. <sup>c</sup>
ACTH	+									+		+	+
Aldos.													
Cort.						±	-						
Epi.				+			+						
Est.	-	-					+	+			+		
FSH													
Gluc.				+							▼		
GH (STH)	+	+	+	+	+	+	+	+	+	+	+	+	+
All related to growth													
HRH													
In.		+	+				-						
LH								+					
MSH	+												
Norepi.				+			+						
Oxy.													
PTH						±							
Prog.													
Prol. <sup>e</sup>	+	+	+	+	+	+	+	+	+	+	+	+	+
Relax.													
Test.	+	+	+				+	+	+		+	+	
TCT								-					
T4	± <sup>d</sup>	+	+	-			+		-				+
TSH	- <sup>d</sup>			+									
Vaso.													

<sup>a</sup> See list of abbreviations for full name. <sup>b</sup> Folic acid. <sup>c</sup> Pantothenic acid. <sup>d</sup> Large Doses.<sup>e</sup> All synergistic when acting as a growth hormone.

**TABLE 6. Principal Functional Relationships of Vitamins and Hormones**  
 ( ) = indirect effect    \_\_\_\_\_ = Major Effect

Function	Vitamin(s) <sup>a</sup>	Hormone(s) <sup>a</sup>
Bone and Ca metabolism	A, C, <u>D</u>	Cort., (ACTH), Est., GH <u>PTH</u> , Test., <u>TCT</u> , T4, (TSH)
Circulation, blood cells	<u>B<sub>6</sub></u> , <u>B<sub>12</sub></u> , C, E, K, Bio., <u>F.A.</u> , P.A.	Cort., (ACTH), <u>Epi.</u> , Norepi., Vaso.
Digestion and absorption	<u>B<sub>1</sub></u> , <u>B<sub>12</sub></u> , D, E, F.A., Nia.	Cort., (ACTH), Gluc., <u>In.</u> , PTH, <u>T4</u> (TSH)
Epithelium, skin (membrane effect)	<u>A</u> , <u>B<sub>2</sub></u> , <u>B<sub>12</sub></u> , D, Bio., P.A.	<u>Aldos.</u> , Cort., (ACTH), Epi., Est., GH, In., Norepi., Oxy., Prog., Relax., Test., T4 (TSH), <u>Vaso.</u>
Fat and CHO metabolism	<u>B<sub>1</sub></u> , <u>B<sub>2</sub></u> , <u>B<sub>6</sub></u> , <u>B<sub>12</sub></u> , Bio., Nia., <u>P.A.</u>	(ACTH), Aldos., Cort., Epi., Est., Gluc., GH, <u>In.</u> , Norepi., T4 (TSH), Test.
Growth	All, by definition	All, by definition; Esp.: <u>Est.</u> , <u>GH</u> , <u>In.</u> , <u>T4</u> (TSH), <u>Test.</u>
Metabolic rate, tempera- ture (TCA Cycle)	<u>B<sub>1</sub></u> , <u>B<sub>2</sub></u> , C, E, K, Nia., <u>P.A.</u>	<u>Epi.</u> , Norepi., Prog., <u>T4</u> , (TSH), Test.
Nerve function, psyche	A, <u>B<sub>1</sub></u> , <u>B<sub>2</sub></u> , <u>B<sub>12</sub></u> , C, Bio., Nia., <u>F.A.</u> , P.A.	Cort., (ACTH), <u>Epi.</u> , Norepi., Prol., Test., <u>T4</u> , (TSH), Est.
Pigmentation	<u>B<sub>6</sub></u> , C, F.A., <u>Nia.</u>	(ACTH), Cort., <u>MSH</u>
Pregnancy, lactation	All required at higher levels	Cort., (ACTH), <u>Est.</u> (FSH), GH, In., (LH), <u>Oxy.</u> , <u>Prol.</u> , <u>Prog.</u> , <u>Relax.</u> , <u>T4</u> , (TSH)
Salt (Na) and H <sub>2</sub> O metabolism	<u>B<sub>6</sub></u> , <u>P.A.</u> , (A, C, E, Nia.)	<u>Aldos.</u> , Cort., (ACTH), Epi., Gluc., GH., (In.), Norepi., Oxy., Prog., T4, (TSH), <u>Vaso.</u>
Stress, immunity	<u>C</u> , P.A., <u>A</u> ( <u>B<sub>1</sub></u> , <u>B<sub>2</sub></u> , <u>B<sub>6</sub></u> , K, Bio., F.A.)	<u>Aldo.</u> , <u>Cort.</u> , (ACTH), Est.
Visual mechanisms	<u>A</u> , <u>B<sub>2</sub></u>	

<sup>a</sup> See list of abbreviations for full name.

**TABLE 7. Food and Nutrition Board, National Academy of Science—National Research Council Recommended Daily Dietary Allowances,<sup>1</sup> Revised 1968**  
Designed for the maintenance of good nutrition of practically all healthy people in the U.S.A.

								Fat Soluble Vitamins		
	Age <sup>2</sup> Years From Up to	Weight Kg (lb)	Height cm (in.)	Kcal	Protein g	Vit. A Activity I.U.	Vit. D I.U.	Vit. E Activity I.U.		
Infants	0-1/6	4 9	55 22	kg x 120	kg x 2.2 <sup>5</sup>	1500	400	5		
	1/6-1/2	7 15	63 25	kg x 110	kg x 2.0 <sup>5</sup>	1500	400	5		
	1/2-1	9 20	72 28	kg x 100	kg x 1.8 <sup>5</sup>	1500	400	5		
Children	1-2	12 26	81 32	1100	25	2000	400	10		
	2-3	14 31	91 36	1250	25	2000	400	10		
	3-4	16 35	100 39	1400	30	2500	400	10		
	4-6	19 42	110 43	1600	30	2500	400	10		
	6-8	23 51	121 48	2000	35	3500	400	15		
	8-10	28 62	131 52	2200	40	3500	400	15		
Males	10-12	35 77	140 55	2500	45	4500	400	20		
	12-14	43 95	151 59	2700	50	5000	400	20		
	14-18	59 130	170 67	3000	60	5000	400	25		
	18-22	67 147	175 69	2800	60	5000	400	30		
	22-35	70 154	175 69	2800	65	5000	—	30		
	35-55	70 154	173 68	2600	65	5000	—	30		
	55-75+	70 154	171 67	2400	65	5000	—	30		
Females	10-12	35 77	142 56	2250	50	4500	400	20		
	12-14	44 97	154 61	2300	50	5000	400	20		
	14-16	52 114	157 62	2400	55	5000	400	25		
	16-18	54 119	160 63	2300	55	5000	400	25		
	18-22	58 128	163 64	2000	55	5000	400	25		
	22-35	58 128	163 64	2000	55	5000	—	25		
	35-55	58 128	160 63	1850	55	5000	—	25		
Pregnancy				+200	65	6000	400	30		
Lactation				+1000	75	8000	400	30		

1. The allowance levels are intended to cover individual variations among most normal persons as they live in the United States under usual environmental stresses. The recommended allowances can be attained with a variety of common foods, providing other nutrients for which human requirements have been less well defined. See text [of Recommended Dietary Allowances, National Research Council Pub. # 1694] for more detailed discussion of allowances and of nutrients not tabulated.

2. Entries on lines for age range 22-35 years represent the reference man and woman at age 22. All other entries represent allowances for the midpoint of the specified age range.

corbic d. d.	Water Soluble Vitamins						Minerals				
	Folacin <sup>3</sup> mg	Niacin mg. equiv. <sup>4</sup>	Ribo- flavin mg	Thiamine mg	Vit. B <sub>6</sub> mg	Vit. B <sub>12</sub> μg	Calcium gm	Phos- phorus gm	Iodine μg	Iron mg	Magnesium mg
0.05	5	0.4	0.2		0.2	1.0	0.4	0.2	25	6	40
0.05	7	0.5	0.4		0.3	1.5	0.5	0.4	40	10	60
0.1	8	0.6	0.5		0.4	2.0	0.6	0.5	45	15	70
0.1	8	0.6	0.6		0.5	2.0	0.7	0.7	55	15	100
0.2	8	0.7	0.6		0.6	2.5	0.8	0.8	60	15	150
0.2	9	0.8	0.7		0.7	3	0.8	0.8	70	10	200
0.2	11	0.9	0.8		0.9	4	0.8	0.8	80	10	200
0.2	13	1.1	1.0		1.0	4	0.9	0.9	100	10	250
0.3	15	1.2	1.1		1.2	5	1.0	1.0	110	10	250
0.4	17	1.3	1.3		1.4	5	1.2	1.2	125	10	300
0.4	18	1.4	1.4		1.6	5	1.4	1.4	135	18	350
0.4	20	1.5	1.5		1.8	5	1.4	1.4	150	18	400
0.4	18	16	1.4		2.0	5	0.8	0.8	140	10	400
0.4	18	1.7	1.4		2.0	5	0.8	0.8	140	10	350
0.4	17	1.7	1.3		2.0	5	0.8	0.8	125	10	350
0.4	14	1.7	1.2		2.0	6	0.8	0.8	110	10	350
0.4	15	1.3	1.1		1.4	5	1.2	1.2	110	18	300
0.4	15	1.4	1.2		1.6	5	1.3	1.3	115	18	350
0.4	16	1.4	1.2		1.8	5	1.3	1.3	120	18	350
0.4	15	1.5	1.2		2.0	5	1.3	1.3	115	18	350
0.4	15	1.5	1.2		2.0	5	1.3	1.3	115	18	350
0.4	13	1.5	1.0		2.0	5	0.8	0.8	100	18	300
0.4	13	1.5	1.0		2.0	5	0.8	0.8	90	18	300
0.4	13	1.5	1.0		2.0	6	0.8	0.8	80	10	300
0.8	15	1.8	+0.1		2.5	8	+0.4	+0.4	125	18	450
0.5	20	2.0	+0.5		2.5	6	+0.5	+0.5	150	18	450

3. The folacin allowances refer to dietary sources as determined by Lactobacillus casei assay. Pure forms of folacin may be effective in doses less than 1/4 of the RDA.

4. Niacin equivalents include dietary sources of the vitamin itself plus 1 mg equivalent for each 60 mg of dietary tryptophan.

5. Assumes protein equivalent to human milk. For proteins not 100 percent utilized factors should be increased proportionately.

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# HANDBOOK OF VITAMINS AND HORMONES

Roman J. Kutsky, Ph.D.

Professor of Life Sciences, Bishop College, Dallas, Texas

This book makes available for the first time a "one-stop" reference source containing most of the known information about vitamins and hormones and their interrelationships. Emphasis is placed on the relation between the chemical reactions of vitamins and hormones in the test tube and their metabolic reactions in the human body.

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Here are a few of the many topics of special interest covered in this volume:

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This handbook will be welcomed by physicians, pharmacologists, nurses, and dietitians, as well as by researchers, teachers, and students in the various fields of life sciences. It will also guide the educated layman through the vitamin fads of the day, enable him to make rational meal and cooking selections, and aid him in understanding the many hormone-related articles in current newspapers and magazines.

## About the Author...

His background includes 15 years' research in cellular nutrition (tissue culture). In addition, he taught advanced courses in biochemistry, vitamins and hormones, endocrinology, molecular biology, cell physiology and metabolism for five years at Texas Woman's University.

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