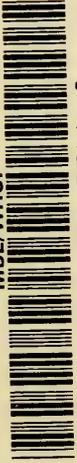




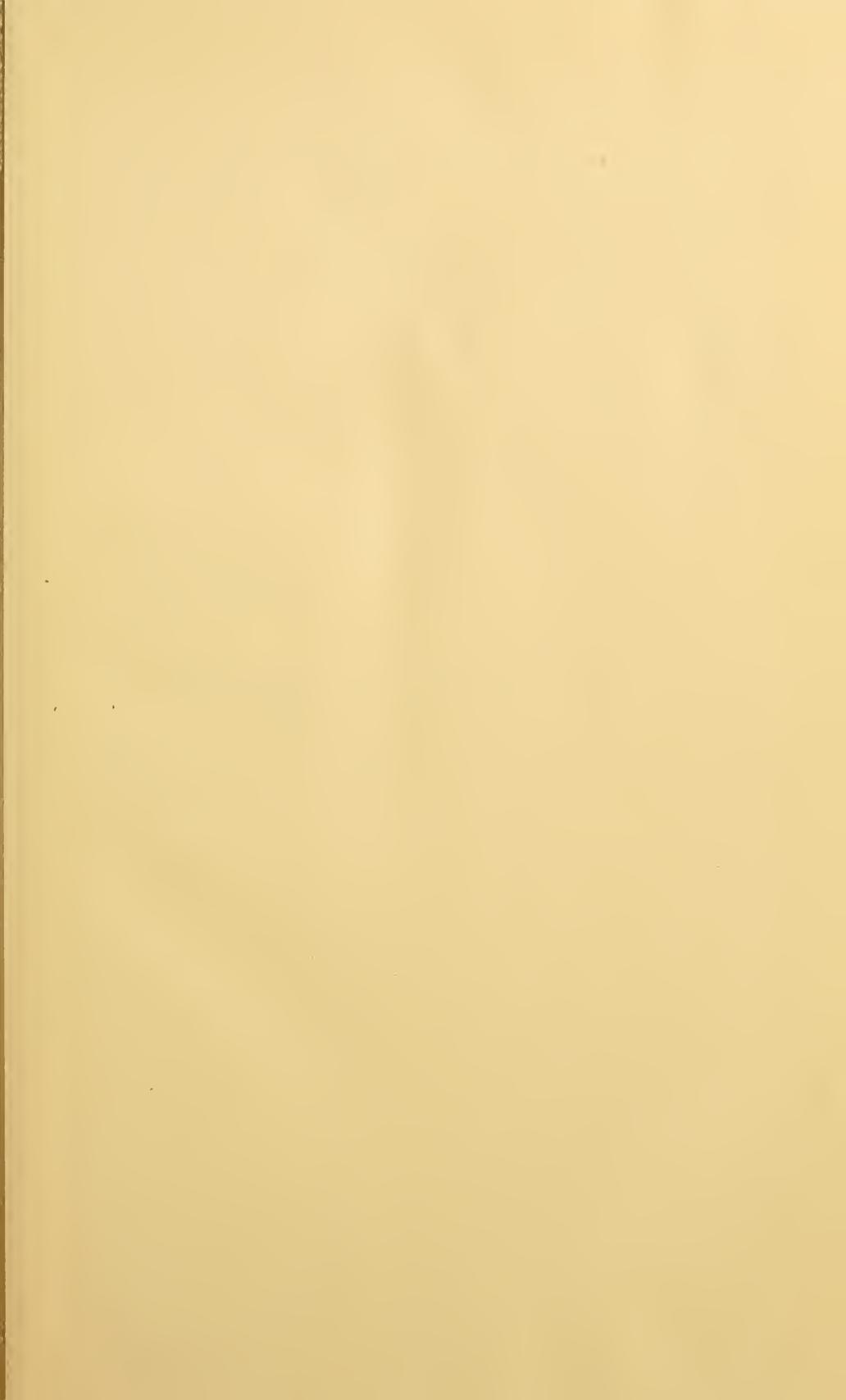


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THE EFFECTS OF  
INANITION AND MALNUTRITION  
UPON  
GROWTH AND STRUCTURE  

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JACKSON



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THE EFFECTS OF  
INANITION AND MALNUTRITION  
UPON  
GROWTH AND STRUCTURE

BY  
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117 ILLUSTRATIONS

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TO MY TEACHERS  
HOWARD AYERS  
AND  
HENRY H. DONALDSON



## PREFACE

The widespread occurrence of human famine during and since the world war has raised serious questions concerning both the immediate and the remote effects upon the human species. Even in the more fortunately situated countries, recent investigations have revealed, especially among children, a large amount of malnutrition, with possible consequences of great importance to society.

Inanition in animals and plants is likewise a subject of much interest, and presents a method of the utmost value in the study of the living organism. By withholding or decreasing the normal diet (total inanition) or merely one or more of the essential nutritional elements (partial inanition), we may observe effects which throw much light upon the process of nutrition from the standpoint of normal morphology, of physiology, or of pathology.

Inanition is therefore a subject of both theoretical and practical importance to scientific workers in various fields—to biologists (both zoologists and botanists), who are concerned with the fundamental characters of living organisms; to anatomists, who are interested in the problems of morphogenesis; to physiologists and biochemists, working in the various fields of human and animal nutrition; to pathologists, since inanition is one of the primary factors in pathogenesis; and to physicians, who recognize inanition, not merely as a therapeutic measure of occasional utility, but especially as a complication in most of the disorders with which they have to deal. Inanition and malnutrition have long been considered of importance in connection with the diseases of infancy, but only recently has their significance become more fully apparent likewise for adults, and above all in the so-called "deficiency diseases." The nature of these deficiency disorders as forms of partial inanition, and their relationship to each other and to inanition in general, constitute an outstanding problem in medicine.

On account of these varied and important relations, a systematic review of the subject of inanition seems desirable, especially from the viewpoint of morphology. The present work will therefore include not only the results published by the author and his coworkers during a decade of research in this field, together with a considerable amount of unpublished material, but also a comprehensive review of the widely scattered data in the literature concerning the morphological effects of inanition in all living organisms. While an adequate critique in so vast a field is impossible, it is hoped that even a brief survey of the literature will be of interest and service. Especial care has been taken to make the bibliography as complete and accurate as possible, although errors and omissions are unavoidable.

Grateful acknowledgment is due to several of my friends and colleagues, especially to Professors Donaldson, Scammon, Downey, Sigerfoos, McKnight, Bell and Litzenberg, who have read and criticised certain chapters; to the artist, Miss Jean Hirsch, and to various authors for the illustrations used; and to the Graduate School of the University of Minnesota for special support in the original investigations which are utilized in the present work.

C. M. JACKSON.

MINNEAPOLIS.

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## INTRODUCTION

It is desirable at the outset to define some of the terms used throughout the present work.

**Inanition** is defined by the Standard Dictionary as the state of being void or empty; specifically, in pathology, exhaustion from lack of nourishment, whether by absence of food or disorder of the nutritive system (from Latin *inanis*, empty). Accordingly the term inanition as used in the present work indicates in a broad sense the lack of food or of any foodstuff (including water) which is essential to the living organism. *Malnutrition* or *dystrophy* are often used as synonymous with inanition in general, but are wider in scope, including disturbances of nutrition from causes other than mere lack of nutriment. *Starvation*, in the broad meaning of the term, is synonymous with inanition; but is more frequently used to indicate the extreme stages of inanition, leading to death. *Famine* denotes inanition or starvation on a large scale, especially in the human species, with widespread scarcity of food, usually resulting from war, drought, floods, insects, etc. *Hunger* and *thirst* indicate the sensations arising from the lack of food or water, respectively; and to *famish* means to undergo extreme hunger or thirst.

Inanition as above defined includes many different conditions, which may be classified in various ways. As to the **character** of the inanition, we may distinguish (A) *total inanition*, with absence or insufficiency of all nutriment; or (B) *partial inanition*, with absence or insufficiency of merely one or more of the essential elements of food. As synonymous with "total" inanition, the terms "absolute," "general," or "quantitative" inanition are frequently used in the literature. As synonymous with partial inanition, the terms "relative," "special" or "qualitative" inanition are often employed. Some authors use the term "complete" inanition as synonymous with "total," and "incomplete" as synonymous with "partial;" but they are defined differently in the present work, as noted below.

As to the **degree** of either total or partial inanition, we may distinguish either (1) *complete inanition*, with entire absence of all food (in total inanition) or of the deficient elements (in partial inanition); or (2) *incomplete inanition*, with merely an insufficient amount of all food, or of the deficient elements. The terms "underfeeding," "subnutrition," or "caloric insufficiency" are frequently used to indicate incomplete total inanition.

As to the **duration** and **severity** of the inanition, we may distinguish (1) *acute inanition*, which is severe and of shorter duration; and (2) *chronic inanition*, which is milder and of longer duration.

Inanition may also be classified according to the **mode of occurrence** which results in the malnutrition of the cells of the living organism. Thus inanition may arise from *extrinsic* causes, which in some way prevent the necessary nutri-

ment from reaching the cells; or from *intrinsic* causes, affecting protoplasmic metabolism. The intrinsic causes may interfere with the proper assimilation (anabolism) of the food, even though it may reach the cells in adequate quantity and quality; or they may occasion an abnormally rapid consumption (katabolism) of the food, thereby creating a condition of relative inanition.

Thus among the **extrinsic** causes of inanition in the higher organisms, in addition to (a) *lack of adequate food*, there may exist (b) *faulty ingestion or mastication* of the food, due to oral defects, stenosis of the alimentary canal, etc.; (c) *faulty digestion*, due to glandular deficiency; (d) *faulty absorption* through the alimentary mucosa; or (e) *faulty transportation*, through defects in the blood or vascular system.

Similarly, various **intrinsic** conditions may prevent the normal metabolism of the food, even though it is brought to the cells in normal quantity and quality. Thus the faulty cell metabolism may arise from (a) hereditary, *inherent defects* in cell structure or composition; (b) *toxic influences* which prevent normal metabolism; or (c) lack or excess of the *hormones* normally concerned with cell metabolism. For example, a condition of inanition may arise either from lack of the pancreatic hormone (insulin) in diabetes mellitus, or from excess of the thyroid hormone (thyroxin) in hyperthyroidism (*cf.* Lubarsch '03; Watson '99; Barker '16).

The various types of inanition are summarized in the following table:

Inanition	{	A. Total	{	1. Complete (no food whatever)				
		(quantitative)		2. Incomplete (insufficient nutriment; general under-feeding)				
	{	B. Partial (qualitative)	{	1. Complete (entire absence)	{	of one or more of the neces- sary food- stuffs	{	proteins,
		2. Incomplete (insufficient amount)		fats,				
							carbohydrates,	
							salts,	
							vitamins,	
							water.	

# PART I

## PLANTS AND INVERTEBRATES

### CHAPTER I

#### EFFECTS OF INANITION ON PLANTS

While the present work is concerned chiefly with the effects of inanition upon animals, a brief (and necessarily incomplete) review of the effects upon plants also will be found of interest and value. The general observation that plants, as well as animals, thrive according to the quantity and quality of their nutriment was doubtless made even in prehistoric times. More exact knowledge has slowly accumulated, but apparently the process of starvation has been studied less extensively in plants than in animals. The metabolic processes are fundamentally similar in plants and animals, and some aspects of inanition (especially of partial inanition) are more clearly apparent in the simpler plant organism. The chief effects of inanition on plants will first be summarized briefly, followed by a more detailed account of the results of total or partial inanition upon the various species.

#### SUMMARY OF THE EFFECTS ON PLANTS

Plants in general, much more than animals, appear susceptible to modification by various external factors, including the food supply. It is difficult to summarize briefly the principal morphological effects of inanition upon plants, on account of the wide range in the character of these organisms and the great differences in their mode of nutrition. In general, however, it will appear that the effect of inanition is to restrict or inhibit their growth during the developmental period, often resulting in premature development with the production of marked abnormalities of form and structure. In the poppy (*Papaver*) an inheritance of some of the experimentally produced variations is claimed. In later stages of growth the plants are usually less susceptible, but sooner or later a deprivation of nutriment will usually produce protoplasmic atrophy, with progressively degenerative changes in the cells and tissues, finally resulting in the death of the organism. Of the cell constituents, the formed storage products (starch, oil, etc.) are usually consumed first; then the cytoplasmic structures are attacked; lastly the nucleus, which is the most resistant.

These effects are produced not only by general or total inanition (either complete or incomplete) but also often in a strikingly characteristic manner by partial inanition, when there is a marked deficiency of only one (or a few) of the

numerous essential factors in plant nutriment. Lack of any one of these factors—water, calcium, potassium, magnesium, iron, phosphorus, sulphur, manganese, nitrogen, carbohydrates and possibly vitamins—will cause stunting of growth with variable, degenerative cell-changes. These are expressed by morphological and physiological derangements, often resulting ultimately in the death of the organism. The effects are apparently most severe in the case of phosphorus or nitrogen deficiency.

In addition to the deleterious effects more or less common to all these partial deficiencies, there are in each case certain peculiarities due to the special functions which each of the food-elements normally performs. These peculiarities appear also to vary considerably in different classes of plants.

Thus water deficiency (aqueous inanition) is usually expressed promptly by characteristic changes in form and structure of plants, on account of its fundamental importance in morphogenesis and adult structure, as well as in transportation. Of the various salts, those of calcium, potassium and magnesium are especially essential for chlorophyll production and starch formation. Phosphorus appears to be more concerned with the transformation than with the origin of carbohydrates. Cellulose formation proceeds in the absence of phosphorus, but is impossible without calcium. Mitosis may occur in the absence of calcium or of magnesium, but not without potassium or phosphorus. The process of inflorescence and the development of the sexual organs in general appear to be unusually susceptible to the effects of malnutrition, and in some cases (especially in fern prothallia) a deficiency of calcium or nitrogen may influence sex by inhibiting the development of the female organs (archegonia). Numerous other instances of characteristic effects of the various types of partial inanition in plants will be cited in the following pages.

Some of these effects of inanition upon plants, especially with reference to cellulose, chlorophyll and starch production, are peculiar to the plant kingdom. Most of the effects, however, resemble those found in animals. A study of these effects is therefore of interest to the biologist, since the phenomena common to plants and animals indicate characters of fundamental importance. A knowledge of these fundamental characters is likewise useful in the analysis of conditions found in the higher animals, and is essential to the comprehension of many of the complex problems of human medicine, as will appear in later chapters.

The effects of inanition on plants will be considered in detail under (*A*) total inanition (or on water only), and (*B*) partial inanition. Although subsistence on water alone is, according to definition, a form of partial inanition, the results are similar to those of total inanition, and are grouped with them for convenience.

#### (*A*) EFFECTS OF TOTAL INANITION, OR ON WATER ONLY

According to Winkler ('13), the theory has recently been emphasized (by v. Göbel, Klebs and Sachs) that the morphogenesis of plants depends chiefly upon their metabolic activities, in which case the production of abnormal forms through inanition is to be expected. Palladin ('18) concluded that "each external condi-

tion—such as heat, light, atmospheric pressure, humidity, gravitation, and the supply of nutrient material—exerts an influence upon plant growth, and consequently upon both external form and internal structure.”

As to the **duration of starvation**, Coupin ('21) observed that seedlings, which after germination were kept in distilled water in the dark, lived the following number of days before death from inanition: nut-bearing pine, 60; pumpkin, 46; winter vetches, 44; lentils, 40; marvel of Peru, 39; peas, 33; beans, 32; sunflower, 30; buckwheat, 25; radish, 24; nasturtium, 23; spinach, 22; tomato, 21; beet, 20; common cress, 18; mustard, 18. Thus considerable variation occurs, which is ascribed by Coupin to variations in the resistance of the plant itself, and especially to the quantity and quality of the reserve material available. London ('97) found that active bacteria may survive without food for 49 to 88 days.

As to the **effect on size**, it is well known that a decrease in size (or a stunted growth) is the general effect of insufficient nutriment in plants; but the result is usually less obvious than in animals on account of the rigidity of the cell walls in plants. Quantitative studies on this topic in plants appear scarce. London ('97) used a centrifuge in measuring the volume of bacteria (*Bacillus anthracis*, *B. subtilis* and *Streptococcus pyogenes*), and found during inanition a progressive loss amounting to an average total of 51 per cent (range 27–72 per cent). Some measurements of retardation in weight of plants in the absence of certain growth-promoting substances (vitamins) were made by Bottomley ('14).

According to Winkler ('13), the dwarfing (nanism) due to inanition does not always reduce the plant organism proportionately in all parts, but **morphological peculiarities** may occur (Gauchery, Kraus). Such modifications are generally not hereditary, although de Vries ('00) obtained inheritance of experimentally produced variations in *Papaver somniferum polycephalum*. According to Thomson ('88) and Rignano ('11), Hoffmann's ('87) researches prove the inheritance of variations (such as relatively large number of atypical flowers) produced by insufficient nourishment in *Papaver*, *Migella* and *Argemone*. Inflorescence may also occur prematurely (Winkler) or in great profusion (Gagnespan '19) as a result of starvation.

Another effect of inanition upon the reproductive mechanism is possibly the **modification of sex** (extensive review of earlier literature by Strassburger '00, and O. Schultze '03). Various botanists have claimed that the prothallia of ferns grown under unfavorable nutritive conditions produce only antheridia (male organs), and no archegonia (female organs). A suppression of the development of female organs by malnutrition was observed in maize (*Zea mays*) by K. Müller ('64) and Cugini ('80); and in *Equisetum* by Buchtien ('87) and others. The relation of inanition to maleness is discussed by Hoffmann ('85). Heyer ('84) was skeptical as to the modification of sex in *Mercurialis* by environmental factors, though Klebs ('95, '96, '03) obtained positive results in some Algae and Fungi. According to Geddes and Thomson ('01): “The experiments of Klebs may perhaps be regarded without unfairness as marking the real beginning of a physiology of reproduction in plants. For he has set himself to show how definite environmental conditions of nutrition, temperature, etc., are definitely

associated with the occurrence of particular modes of reproduction in Algae and Fungi."

DeVries ('00) noted that the extent to which the stamens are metamorphosed into carpels in *Papaver somniferum polycephalum* is a highly variable character, and is determined by external (especially nutritional) factors at a *certain critical period*, about the seventh week of development. Influences at earlier or later periods are ineffective. This may perhaps explain some of the conflicting results which have been obtained in other forms.

There is also clearly a difference between the monocious and diecious forms, in respect to their susceptibility to sex-modification by environmental changes, as has been emphasized by Strassburger ('00) and O. Schultze ('03), who concluded that the sex (in diecious forms) is predetermined in the ovum, and apparently unmodified by environmental changes. Thus Strassburger could obtain no modification of sex in *Melandrium*. Noll, while getting positive results in the usually monocious *Equisetum Telmateja* (only male prothallia developing in cultures without phosphates), had negative results with the diecious *Marchantia polymorpha*.

Coulter, Barnes and Cowles ('11) cited numerous examples of the reproductive process as influenced by various unfavorable conditions, including desiccation and decreased food supply. The effects vary greatly in different species. In moulds generally the formation of asexual spores is favored by desiccation and starvation (and of zygospores by the opposite conditions), but the sexual mode of reproduction is induced by food scarcity in *Saprolegnia*. According to Morini ('85), a reduction of nutrition appears necessary for zygospore formation in the *Ustilagineae*. As to *sex determination*, Coulter, Barnes and Cowles stated that in diecious plants undernourishment and xerophytic (dry) conditions apparently facilitate the development of male (staminate) plants, but other factors must be considered. Recent evidence indicates that in diecious plants, as in animals, sex is determined at a much earlier period than was formerly supposed, being usually predetermined in the gametes, independently of external factors. Apparent change of sex seems best explained by assuming that such forms are at least potentially bisexual, and that external factors may either cause suppression of one of the sexes (as in *Zea*) or stimulate development of the sex commonly suppressed (in *Carica*).

Love ('09) found that in peas a decrease in the food supply decreases the **coefficient of variability** in yield and number of internodes, but increases the variability in height.

Data upon the **cytological effects** of starvation in plants appear relatively few, and have been described chiefly in connection with various forms of partial inanition (to be considered later). Cunningham ('80) found protoplasmic atrophy and fatty degeneration in the mycelium and fruiting organs of certain moulds (*Choanephora* and *Pilobolus crystallinus*) kept in distilled water. Bokorny ('92) likewise found cytoplasmic atrophy, as well as changes in fat content, cell-sap, etc. of *Spirogyra* cells (see also later under potassium deficiency). Kosinski ('02) found in fungus cells (*Aspergillus niger*) during starvation diminished respiration and a gradual consumption of the plastic formed material to

yield energy. Growth ceases, but returns on refeeding. Hottes observed that in developing beans, upon the removal of the cotyledons with their food supply, the meristematic tissue which would normally produce the lateral roots is transferred to the tip of the root and there used for growth. In 3 or 4 weeks all the cells in the upper part of the root have lost most of their cytoplasm, and the only actively functioning cells are those at the tip. Decrease in the size of the root is due to decrease in the number of cells, rather than to decrease in their size. Winkler ('13) also concluded that cell size is not greatly affected as a rule by environmental factors, the size of a plant in general being due to the number rather than to the size of the constituent cells. Maige ('23), however, found a relation between the size of the nucleus and nucleolus and the amount of nutrition in the bean seedling.

The effects of inanition upon the growth and differentiation (as noted above for sex) of plants also vary according to the age or stage of development of the organism. Thus Davidson and Le Clerc ('18) found that the greatest increase in the yield of wheat occurs when the soil fertilizer (sodium nitrate) is added during the first stage of growth, with a slighter effect in the second stage and none in the third. Hoagland ('19) similarly noted that the yield of barley is largely conditioned upon favorable supply and concentration of nutrients for the plant during the first eight or ten weeks of the cycle. Urbain ('20) observed that embryos deprived of their normal food (endosperm) at an early stage and placed in nutrient solutions are inhibited in their later development, being dwarfed and presenting various abnormalities (to be described later).

**Mode of Action.**—Reed ('07) pointed out that the essential elements in plant nutrition appear to act in two ways: (a) as component parts of the cell structures or fluids; and (b) as indirect agents in causing less understood physical or chemical conditions necessary for the proper functioning of the cell, whether as carriers of other ions, or as specific antidoting agents. Thus v. Liebig ('76) found that ammonia stimulates plant growth, provided the other necessary nutrients are present. Reed ('07) noted that algae thrive best in neutral or slightly acid cultures, while phanerogams thrive best in neutral or slightly alkaline solutions. Moore, Roaf, and Knowles ('08), in experiments on the hyacinth and onion, found that alkalinity in general apparently stimulates growth, producing increased nuclear division, changes in the chromosomes and obscure cell-outlines; while acidity causes decrease or absence of nuclear division, and thickening of cell-walls. Steinberg ('19) concluded that "Increased acidity of the Pfeffer nutrient solution within a certain range results in the exhibition in *Aspergillus niger* cultures of growth 'stimulation' like, but less in amount than, that observed by addition of salts of certain heavy metals." The mode of action in such cases is obscure and it is difficult to draw the line between growth stimulants (including the vitamins) and nutrients.

#### (B) EFFECTS OF PARTIAL INANITION

Heretofore we have been considering chiefly the effects of inanition in general—of *total* inanition (excepting water), the nutriment being either entirely absent (complete inanition) or reduced in amount (incomplete inanition). We have

now to consider the effects of *partial* inanition, only one or more of the essential food factors being deficient. Aside from the carbon dioxide used for starch formation in the green plants, the necessary factors include water and certain mineral salts, especially nitrates and phosphates of calcium and potassium. Magnesium, iron and sulphur also appear essential, at least in small amounts. Some plants (fungi and many algae) require also organic (protein) nutriment. The various factors are of unequal importance, however. Thus in the oat plant, Dickson ('18) found that a deficit of phosphorus or nitrogen is much more injurious than a deficit of calcium, potassium or magnesium, which is in general agreement with the earlier results of Reed ('07) in various plants. The effects of the various substances upon plant morphogenesis and structure may be designated as "Chemomorphoses" (Winkler).

#### AQUEOUS INANITION (WATER DEFICIENCY)

Water, as is well known, is a fundamental necessity for both plants and animals. Hygromorphosis is the primary factor in determining the form in many plants, both higher and lower. With reduction of the normal supply of water, many of the higher plants wilt through loss of turgescence due to osmotic pressure. Sagot noted that dryness has a marked effect upon the structure of plants. When growing plants are deprived of water, dwarfing and various abnormalities of form may occur. Some amphibious plants have a water form and a land form, apparently conditioned by the environment.

Coulter, Barnes and Cowles ('11) classified plants, with reference to their water requirements, as xerophytes, mesophytes and hydrophytes. "It would seem that the chief determining factors of leaf size and proportion are those that control the water supply." In the xerophytes (associated with water deficiency), there is high transpiration through the leaves and low absorption of water through the roots, resulting in leaves of small size and great thickness. The thickness is due to a relatively large amount of cell-division in planes parallel with the surface. They cite many variations experimentally produced in the leaves and stems, the latter being shortened and thickened by dessication. Upon the reproductive structures, dessication usually has an effect similar to that of other unfavorable external conditions, frequently stimulating reproduction, but often inducing modifications of the normal process.

Palladin ('18) likewise emphasized the marked differences in the dandelion (*Taraxacum officinale*) and broom (*Genistica anglica*) grown in moist and in dry air. "The difference is so great that they might be taken for distinct species." As Palladin pointed out, however, water deficiency may arise in either of two ways, diminished intake (through roots) or increased exit (transpiration through leaves). The two modes may result in different morphological effects, as shown by the experiments of Kohl ('86) on *Tropaeolum majus* (see accompanying table).

EFFECTS OF VARIOUS DEGREES OF MOISTURE UPON THE STRUCTURE OF *Tropaeolum majus*  
(KOHLE '86)

Culture No.	External conditions		Relative size of leaf-blade	Kind of cuticle	Anatomical characters	
	Soil	Air			Epidermis	Collenchyma
1	Moist	Moist	5	Thin	Cells tangentially elongated; thin outer walls	None
2	Moist	Dry	4	Thick	Cells radially elongated; thick outer walls	Two adjacent layers well developed
3	Dry	Moist	3	Thin	Cells almost cubical	Poorly developed
4	Dry	Dry	1	Thick	Cells very much elongated radially	Less developed than in 2

The general effects of the second type of water-deficiency (increased exit through transpiration) were summarized by Winkler ('13) as follows:

“Werden Pflanzen in trockener Luft erzogen, so ist im allgemeinen das Längenwachstum verzögert, auch werden die Internodien weniger lang, dafür aber dicker und ihre Zahl wird erhöht; die Festigkeit der Achsenorgane ist grösser; die Haarbildung an Blättern und Stengeln erscheint gefördert; die Wurzelbildung erfolgt reichlicher, der Blattfall, die Blute- und Fruchtbildung eher; die Epidermis-, Rinden- und Markzellen bleiben kleiner; die Bildung von Sekretionsorganen und Kristallzellen wird begünstigt, die Entstehung von Kork und Sclerenchym beschleunigt, die Gefässbildung gefördert. Kultur in feuchter Luft hat gerade den umgekehrten Erfolg (Kohl, Eberhardt).”

Dickson ('18) found that the water requirement in the oat plant varies considerably according to the proportions of the various salts found in the nutrient medium. The requirement is decreased by a deficiency of magnesium, slightly increased by a deficiency of calcium, and greatly decreased by a deficiency in potassium, phosphorus or nitrogen.

## CALCIUM DEFICIENCY

That calcium is essential for the normal growth of the higher plants has long been recognized (e.g. by Stohmann '62, in the maize plant), but its function is not yet entirely clear. Loew ('92) considered calcium as one of the important mineral bases entering into the constitution of the proteins in the cell-nucleus and chlorophyll-bodies. Reed ('07) pointed out that calcium differs from potassium and phosphorus in forming but a small proportion of the actual living protoplasm; but it has varied and important functions, influencing processes and products into which it does not itself seem to enter. True ('22) recently concludes:

“It appears that a certain quantity of Ca ions must be present in the medium for the maintenance of the chemical and functional integrity of the deeper lying living parts of the cells of absorbing roots of higher green plants . . . . When this necessary minimal supply of Ca ions is lacking . . . the function of absorption is upset and a more or less marked leaching of ions from the plant follows. In the absence of this necessary minimum of Ca, the soil solution or culture solution may be rich in all other required ions, but these are useless to the plant. They are unabsorbable.”

Von Liebig ('76) stated that calcium is doubtless necessary for cellulose formation. Boehm ('75) in *Phaseolus vulgaris*, v. Raumer ('83) in *Phaseolus multiflorus*, and Molisch ('95) in *Spirogyra* noted that a calcium deficit interferes with the formation of new cellulose walls after cell-division. Reed ('07) likewise noted that in *Spirogyra* and roots of *Zea mais* kept in solutions without calcium salts, although nuclei divide mitotically, new cell septa are formed imperfectly or not at all. After two months in Ca-free solutions, most of the *Spirogyra* cells were found dead and those alive markedly degenerated. He states, however, that some investigators (Bruch '02) have found calcium unnecessary for nutrition in fungi and lower algae, and even toxic in some cases; but all agree that seedlings in calcium-deficient solutions usually develop small leaves. Reed also found that in *Spirogyra*, *Zygnema* and *Vaucheria*, calcium appears necessary for the growth and activity of chlorophyll and chloroplasts (in agreement with Bokorny '95 and Loew '92); perhaps serving also as an antidote to the bad effects of magnesium, oxalic acid, etc. He further observed that spores of *Gymnogramme sulphurea*, cultivated in calcium-free solutions, developed prothallia in which antheridia were produced in large numbers, but archegonia were absent. Controls were normal. In certain mosses (*Atrichum*), he noted that the spores fail to germinate in calcium-free solutions, although a retarded development (with peculiar moniliform cells) occurs when the calcium is replaced by sodium. Palladin ('18) emphasized the importance of calcium for normal leaf development of plants. In the development of the oat plant, Dickson ('18) found that a deficiency of calcium *increased* the general vigor of growth, lengthened the period of development and increased the total dry weight of the plant. The grain production was lowered, however, the ratio of grain to straw and the weight of the individual kernels being decreased.

#### POTASSIUM DEFICIENCY

According to Reed ('07), de Saussure, in 1804, established the necessity of potassium for the growth of terrestrial plants, which has been confirmed by Nobbe ('71) and many later investigators. Dickson ('18) found that in the oat plant a deficiency of potassium in the nutrient solution causes a decrease in the general vigor of growth, a shortened period of development and a decrease in the total dry weight of the plant. The grain production is also lowered, although the ratio of grain to straw is increased and the weight of the individual kernels greater.

Cytological effects of potassium deficiency upon algae (chiefly *Spirogyra*) were noted by Bokorny ('92). He found the chains of cells broken up into small

segments or individual cells; cells shorter, and more turgid, with bulging ends. Atrophy of the cytoplasm and chlorophyll bands occurs, and changes in the fat content, cell-sap, etc. may appear. Molliard and Coupin ('03) found that when *Sterigmatocystis* (*Aspergillus*) *niger* is grown in the absence of potassium, the normal form of the conidial apparatus disappears, variable outgrowths replacing the normal conidiophores. Prothallia of *Gymnogramme sulphurea* are able to grow and form chloroplastids with only traces of potassium present, but no starch is formed. In cells of *Hydrodictyon* and *Basidiobolus ranarum* on K-free media, the cytoplasm becomes abnormally vacuolated and the nuclei indistinct. In *Zygnema* filaments the pyrenoids rapidly lose starch, the chloroplasts becoming vacuolated and the radiating strands of protoplasm disappearing. In *Spirogyra* cells kept in K-free solution, after 35 days no mitosis occurs, although both cells and nuclei undergo preliminary elongation. The inhibition of mitosis cannot be attributed to the lack of potassium in the nucleus, however, since Macallum ('05) has shown that potassium is normally absent from the nucleus in both plant and animal cells.

Reed, in agreement with previous investigators (see literature reviewed by him), found that in some cases the function of potassium can be partially accomplished by the substitution of sodium. For example, when a subminimal amount of potassium is present, some evidence indicates that certain moss-spores can germinate and utilize sodium during the embryonic stages of development. Dasonville ('98) found that the substitution of sodium for potassium in the wheat plant produces less growth but more lignification; in the secondary roots of the tomato certain characteristic histological changes result.

#### MAGNESIUM DEFICIENCY

Although von Liebig ('76) and earlier investigators recognized that magnesium is essential for the growth of the higher plants, its function long remained somewhat obscure. Loew ('92) thought it served as a carrier for phosphoric acid in the formation of nucleoproteins. Willstaetter ('06) has proved that magnesium is a constituent of the chlorophyll molecule. Numerous investigators have noted the antagonistic action of magnesium and calcium (literature reviewed by Reed), including possibilities of their substitution for each other in some cases.

Von Raumer ('83) noted in *Phaseolus multiflorus* deprived of magnesium a stunted growth of stem and leaves, with unhealthy chloroplasts. He concluded that magnesium is essential for starch transportation. Bokorny ('95) with magnesium deficiency in various algae likewise found modifications of the chloroplasts, with markedly decreased size of nuclei. Reed ('07) observed that the ratio of magnesium and phosphorus is an important factor in spore formation in *Aspergillus niger*, and in *Vaucheria* the oil droplets disappear in Mg-free cultures. In *Spirogyra*, the chloroplasts become variably disarranged and retracted into an irregular cytoplasmic mass near the center of the cell, although the pyrenoids and nuclei appear unaffected. Mitosis is still possible—though greatly retarded. According to Dickson ('18), a deficiency of magne,

sium in the medium apparently increases the general vigor of growth, lengthens the period of development and increases the total dry weight of the oat plant. The grain production is lowered, however, the ratio of grain to straw and the weight of the individual kernels being decreased. Thus the results are closely similar to those of a calcium deficit. In general, the results of magnesium deficiency also resemble those of etiolation, when plants are grown in darkness (to be discussed later). This is probably because of the interference with chlorophyll formation or function in both cases, a conclusion which is supported by recent studies on the effects of magnesium deficiency in tobacco and maize by Garner, McMurtrey and Moss ('22).

#### DEFICIENCY IN IRON, SULPHUR OR MANGANESE

Von Liebig ('76) recognized the necessity for a certain amount of sulphur in the formation of proteins in plants, and of iron for chlorophyll-formation in green plants. He stated that although only a very slight amount of iron is necessary, in its complete absence the plants become yellow and stunted in growth, a condition known as *chlorosis*. Knop ('64) had found iron necessary for the growth of buckwheat and grasses in general, though apparently not for maize and peas. Gile and Carrero ('16) concluded that in the absence of special precautions it is often possible that the rice plant may be inhibited in its growth by an insufficient supply of available iron; a view also in accordance with the experience of Hoagland ('19) for the barley plant. The exact rôle of iron in plant growth is not clear, for it does not enter into the chemical composition of chlorophyll (Willstaetter). McHargue ('22) found that in sand cultures manganese is necessary for plant growth and development to maturity. In cultures without manganese, growth ceased in about six weeks; the plants became chlorotic, with death of the young leaves and buds.

#### PHOSPHORUS DEFICIENCY

Ville ('61) was one of the first to demonstrate (in sand cultures) the indispensability of phosphates for all plant growth. This view has been universally adopted, the possible substitution of arsenic (Bouilhac '94) having been refuted. Loew ('91) found that when phosphorus is withheld the cells of *Spirogyra* cease to grow and the chloroplasts turn yellow. Starch formation continues for some time, however, and fats and proteins accumulate in the cells. Becquerel ('04) and Schoene ('06) found it possible to germinate moss spores in solutions lacking phosphorus; but the development of the protonema is inhibited, and the rhizoid system is abnormally extensive.

Reed ('07) found that of all the elements the lack of phosphorus seems to be the most injurious, its influence predominating in normal cell metabolism. In the spores of moss (*Atrichum*) no germination occurs without phosphorus. The thickness of the cellulose cell walls is increased in *Basidiobolus*, and in *Spirogyra* may even be doubled. In the latter, a few cells elongate, as in the K-free cultures, but no cell division occurs. (On adding a few drops of potassium

phosphate, mitosis appeared in one hour.) The cells show progressively degenerative changes in three stages: (1) the cells become cloudy, due to the accumulation of fat droplets (ascribed to lack of transformation into lecithin in the absence of P); (2) the chlorophyll bands become disarranged; (3) chlorophyll disappears from the chloroplasts and the cell contents become completely disorganized. Reed believed that phosphorus is more closely connected with the transformation than with the origin of carbohydrates; and that in its absence abnormal transformations occur. No especial susceptibility of the nucleus to phosphorus deficiency has been observed, which is surprising since this element is an essential component of the nucleoproteins (chromatin).

Moore, Roaf and Knowles ('08) observed that in hyacinth and onion the phosphatic ions have a peculiar effect on inflorescence. In the oat plant, Dickson ('18) found the general development of the plant severely affected by deficiency of phosphates. The vigor of growth is greatly decreased, the developmental period shortened, and stooling prevented; the total dry weight of the plant is diminished, and grain production lowered, although the weight of the individual kernels and the ratio of grain to straw are increased.

#### DEFICIENCY IN NITROGEN AND ORGANIC NUTRIENTS

Nitrogen ranks with phosphorus as of primary importance, being an essential constituent of protoplasm in both plants and animals. Aside from those cases where atmospheric nitrogen is fixed by the aid of the nitrifying bacteria, plants require nitrates or higher organic compounds of nitrogen. In spite of the fundamental importance of nitrogen in plant nutrition, however, comparatively few data appear as to the morphological effects of its absence. In germinating moss spores, Schoene ('06) found: "Bei Stickstoffhunger schreitet *Funaria* zu einer mächtigen Ueberlängung des Rhizoidsystems unter vollständiger Unterdrückung des Chloronemas, die übrigen Moossporen entwickeln sich zu chlorophyllosen Hemmungsbildungen." Winkler ('13) cited several examples to illustrate the dependence of form upon the *quality* of food in plants which require organic nutriment (fungi and many algae). No descriptions of cytological changes as a result of nitrogen deficiencies in plants have been found in the literature. Prantl ('81) noted that fern prothallia cultivated in nitrogen-free solutions produce antheridia only (archegonia also appearing in controls on complete nutrient solutions). Dickson ('18) found that in the oat plant the effects of a nitrogen deficit resemble those of a phosphorus deficit, either one severely crippling the development and preventing stooling. The developmental period is thereby lengthened and the total dry weight of the plant as well as the grain production is lowered, although the weight of the individual kernels and the ratio of grain to straw appear increased.

Urbain ('20) obtained some interesting results in numerous plants, including wheat, oats, barley, *Mirabilis jalapa*, *Spinacea cleracea* and *Pinus pinea*. The grains were soaked in water, and at successive intervals of time the embryos were removed from the endosperm (thereby depriving them of their normal organic nutriment, vitamins, etc.), and placed in artificial nutrient solutions.

It was found that the endosperm is not absolutely essential, since without it the embryos develop, though at a retarded rate and with marked changes appearing later. The roots are less branched; stems simpler; leaves fewer, simpler and smaller; inflorescence precocious and less well developed, showing various abnormalities; fruits often aborted; all parts dwarfed. Comparison of sections with those of normal controls in *Nigella*, *Papaver*, *Solanum*, *Torilis*, and *Zea* showed that the internal structure also is much simpler in plants deprived of their endosperm. In the stem, the cells are fewer and simpler; the cortex shows fewer layers; the tissues of the central cylinder are less differentiated, the vascular bundles being relatively undeveloped; the pith is relatively large. Similar modifications occur in the root and petiole. In the leaf the epidermis appears nearly normal, but the other tissues show a reduction in the number and size of their elements. The greater the dwarfing, the more pronounced are these modifications. The modification in the growth of beans observed by Hottes upon the removal of the cotyledons was mentioned previously. These are most striking examples of the profound morphological changes resulting from an early partial inanition in the higher plants.

#### ETIOLATION

It has long been known that a green plant deprived of light undergoes a series of striking changes, designated as "etiolation." These changes are associated with, and at least partly dependent upon, the lack of carbohydrate food normally produced through the chlorophyll. The plant is thus thrown upon its stored food material for nutrition, much like an animal during starvation. In producing etiolation, Sachs ('87) believed that this interference with nutrition is the primary factor. MacDougal ('03) while recognizing this factor, was inclined to lay greater emphasis upon other factors, such as the withdrawal of the direct effect of sunlight upon the living organism. Palladin ('18) similarly considered etiolation as due only partly to deficiency of the organic assimilation products, partly to lack of direct effects of sunlight, and partly to results of diminished transpiration, with disturbance of the water balance.

While the relative importance of the carbohydrate inanition factor in producing etiolation is thus somewhat uncertain, the changes in the plant as a result of etiolation are very marked. In addition to the yellow leaves and white stems (green chlorophyll lacking in the absence of sunlight), von Sachs ('87) noted that phanerogam seedlings develop longer shoot-axes and smaller leaves; and that after a variable length of time growth ceases and death results in the malformed, diseased plant. Further details in the process have been added by later investigators, notably MacDougal ('03), who made extensive observations upon the effects of etiolation in a large number of plants. He found that the form and structure of the plant are usually much altered, but the results are widely divergent in various types. There is an abnormal differentiation of tissues, "some being suppressed, others accentuated and in some instances new tissues arising. Variations occur in the form, size and number of the elements, the structure and characteristics of the walls being materially different from the

normal, while the protoplasts differ chiefly in the character of the inclusions and the composition of the vacuolar fluids." For further details, MacDougal's monograph may be consulted; also Palladin ('18). The results of etiolation, where there is a carbohydrate deficiency, may be contrasted with the converse experiments of Urbain (previously mentioned), in which the reserve food material (protein, fats, etc. of the endosperm) was removed and other nutrients fully supplied.

#### VITAMINS

The vitamins, or accessory food factors (of unknown composition) so essential in animal nutrition are, as is well known, derived directly or indirectly from plants. Funk ('22) and Sherman and Smith ('22) have recently reviewed at length the literature covering numerous researches which indicate the necessity, or at least the advantage, of the vitamins or apparently similar growth-promoting substances in the development of plants themselves, including yeast, bacteria, fungi and higher plants. It is quite possible, for instance, that the remarkable changes which Urbain ('20) effected by removal of the endosperm are at least partly due to the loss of vitamins stored to supply the needs of the plant during development. The fully-grown plants are apparently able to synthesize these vitamins (whatever they may be), possibly in some cases by the symbiotic aid of nitrifying bacteria. Possibly some of the growth-promoting effects of minute quantities of certain substances may belong in a similar category, as shown, for example, in the experiments of Bottomley ('14) on wheat seedlings. It remains for the future to reveal the chemical nature and mode of action of these obscure substances. Thjötta and Avery ('21) concluded that two distinct vitamin-like substances are required for the growth of the hemophilic bacteria. Ellis and Macleod ('22) have recently reviewed the literature on the relation of vitamins to the growth of yeast.

#### LIEBIG'S LAW OF THE MINIMUM

In connection with the inanition of plants, it seems desirable to consider what is generally referred to as Liebig's "law of the minimum" or the "limiting factor," because of its fundamental importance in animal as well as plant nutrition under conditions of partial inanition. Since this doctrine has occasioned much controversy, it is advisable to examine somewhat carefully Liebig's original ideas, which have been frequently misunderstood and greatly modified by subsequent investigators.

In the edition which I have consulted (*Die Chemie in ihrer Anwendung auf Agricultur and Physiologie*, 9. Aufl. Braunschweig, 1876), v. Liebig approaches the question from the point of view of fertilizers and their application to obtain the maximum harvest of crops. Under "Lehre (Gesetz) des Minimums" (p. 330 ff.) he explains how soils vary in composition and how successive crops may exhaust the soil by removing certain of its constituents which form the essential nutrients for plants. In the application of manures or fertilizers to enrich an impoverished soil, he emphasizes the importance of a knowledge of its content in the various essential plant nutrients, all of which are indispensable

(in variable amounts) and none of which can be substituted for each other. As v. Liebig puts it:

“Ein jedes Feld enthält ein Maximum von einem oder mehreren und ein Minimum von einem oder mehreren Nährstoffen. Mit diesem Minimum, sei es Kalk, Kali, Stickstoff, Phosphorsäure, Bittererde, oder ein anderer Nährstoff, stehen die Erträge im Verhältniss, es regelt und bestimmt die Höhe oder Dauer der Erträge. Ist dieses Minimum z.B. Kalk oder Bittererde, so werden die Ernten an Korn and Stroh, an Rüben, Kartoffeln oder Klee dieselben bleiben und nicht höher ausfallen, auch wenn man die bereits in Boden vorhandenen Kalis, der Kieselsäure, Phosphorsäure, etc., um das hundertfache vermehrt.”

Furthermore, field experiments are cited to prove that when enough of the minimum constituent is added to bring up its proportion to that of the next lowest constituent, further addition of the first constituent has no further favorable effect upon the yield.

While it is impracticable to follow in detail the controversy which has followed as to the validity of this law in plants (and later as extended to animals), the result may be summed up briefly in the statement that, as formulated and applied by v. Liebig, the law in general remains well established. This does *not* mean, however (as some have claimed), that *no growth whatever* will occur in the absence of any factor essential for normal nutrition, or that growth under restricted nutriment must always result in normally proportioned dwarfs, growth remaining normal until the limit is reached. Numerous examples of pathological development under such conditions have been cited in the foregoing pages, and some instances of such were recognized by v. Liebig.

Furthermore, this law (as strictly interpreted) must be modified by the recognition that growth may be limited or affected by many factors other than the amount of the minimum nutrient. The proportions of the other nutrients present, conditions of acidity or alkalinity, and other factors (some of which were elsewhere cited by v. Liebig) certainly have more or less influence in determining the amount, character and outcome of growth.

Thus the question becomes largely a matter of definition. In the sense intended by v. Liebig, the law still holds good in its general application to fertilizers and farm crop yields. If more strictly interpreted and extended, however, it certainly requires modifications. From this point of view, one must agree with the critics, such as Mitscherlich ('20), to take a recent example, who formulates a law of physiological relation of growth factors. He properly insists that, strictly speaking, there can be no such thing as any one minimum factor alone determining the amount of growth production, since the influence of all growth factors together must be considered. The significance of this question for animal growth will be considered in later chapters.

## CHAPTER II

### EFFECTS ON THE PROTOZOA

The effects of inanition on the protozoa are of especial importance, since the changes can be directly observed under the microscope in these unicellular forms. These changes are of extreme importance in interpreting the effects of inanition in the higher organisms, including man. In the present chapter, some of the more important results of inanition among the protozoa will first be indicated briefly in relation to duration of starvation, changes in cell size and form, endoplasm and ectoplasm, nucleus, reproduction, and recovery upon refeeding. The changes will then be explained more in detail in the various species of protozoa.

#### SUMMARY OF THE EFFECTS ON THE PROTOZOA

**Period of Survival.**—The period of survival during inanition among protozoa in general is usually quite limited, being only a few (four or five) days in *Stentor* and Rhizopoda without symbiotic algae. *Amoeba terricola* may survive ten to twenty days; *Amoeba proteus* and *Trichosphaerium*, two or three weeks. *Paramecia* may survive from three to twenty-one days. The minimum represents Lipska's observation for the (exhausted?) individuals immediately after conjugation. Her research indicates that five to seven days more nearly represents the average for complete inanition. The prolonged period is for exceptional individuals or (usually) represents incomplete inanition, where some food is available. Allescher's observations on *Dileptus* indicate that temperature is an important factor, the duration period increasing from four or five days at 6°C. to a maximum of seven to twelve days at 15°, then decreasing to five or six days at 25–30°. Death in starving *Paramecium* sometimes occurs suddenly, by rupture of the cell-membrane, but as a rule slowly, by gradual atrophy and degeneration. Death from starvation may be escaped by encystment (in *Didinium*) or by conjugation or encystment (in *Dileptus*).

**Change in Size and Form of the Cell.**—All the evidence shows a marked reduction in the size of protozoa during inanition. The maintenance of the original size of *Noctiluca* is merely apparent, the increase in peripheral vacuoles masking the decrease in cytoplasm. The recorded data indicate a decrease in length to about one-half of the original in *Paramecium*, one-fifth in *Stentor* and one-tenth in *Dileptus* and *Pleurotrichia*. Thus in these extreme cases the volume may be reduced to less than 1 per cent of the original. There are also more or less marked and variable changes in form accompanying the diminution in the size of the body.

**Changes in the Endoplasm.**—The cytoplasmic changes at first appear chiefly in the endoplasm, which becomes progressively reduced in amount and

transparent, on account of the disappearance of the food-vacuoles and similar inclusions. In the later stages of inanition, a progressive vacuolation of the endoplasm has been described in *Trichosphaerium*, *Didinium* and *Colpidium*; and in *Paramecium* by all recent observers except Lipska. Such vacuolation of the endoplasm apparently does not occur in *Noctiluca* and *Pleurotrichia*, however, and Lipska's results indicate that even in *Paramecium* it is probably only an indirect effect of inanition, being due primarily to other environmental factors.

**Changes in the Ectoplasm.**—In all cases the cell-membrane and associated ectoplasmic structures (cilia, trichocysts, cytopharynx, etc.) appear more resistant than the endoplasm, but in the later stages of inanition they also may be attacked and partially resorbed (in *Noctiluca*, *Didinium* and *Paramecium*). Associated with these regressive changes, there is a progressive decrease in motility and in other vital phenomena.

**Nuclear Changes.**—The nucleus in general is much more resistant than the cytoplasm, but may show changes in form with loss of chromatin content (in *Amoeba*, *Gregarina*, *Didinium*, *Stentor*, *Dileptus*). In forms such as *Paramecium*, with macronucleus and micronucleus, the former shows more distinct changes. In the earlier stages of inanition it frequently elongates and enlarges. Later it usually divides, and may show degenerative changes, with granulation, vacuolation, fragmentation and variable extent of resorption. The micronucleus usually persists practically unchanged, although rarely it may divide with reunion of the daughter nuclei. This persistence of the nucleus is a factor of great importance for the survival of the organism during periods of inanition. The less important constituents of the organism are usually consumed first, the most essential apparently survive longest. The persistence of the nucleus during starvation recalls a similar behavior when living cells are engulfed and digested (e.g., by *Trichosphaerium*, according to Schaudinn) and in trypsin digestion experiments. This may be of significance as indicating the presence of similar enzymes during the autolysis of cells in starvation.

**Effects on Reproduction.**—The relations of inanition to reproduction in Protozoa have attracted much attention. Many observers have noted an apparent stimulus to division resulting from a brief period of starvation (in *Stentor*, *Didinium* and *Paramecium*). R. Hertwig ('99, '03, '03a), however, observed that while under certain conditions fasting protozoa may divide more readily than well-nourished, as claimed by Jickili ('02) and others, this does not occur as a general rule. In *Paramecium*, which has been most extensively studied, divisions occur to a variable degree in the early stages of inanition, but rarely or never in the later stages. According to Hertwig's theory, inanition upsets the cell-equilibrium as expressed by the nucleus-plasma ratio; but the relative increase in the nucleus may be equalized later by a reduction in chromatin, associated with the process of conjugation. The literature on the nucleus-plasma ratio is reviewed by Erdmann ('12).

Rolph ('84), who proposed a nutritive theory of sex, claimed that conjugation occurs in protozoa when conditions result in an interference with their nutrition. Thus sex is considered as primitively a form of hunger, which drives the organism to engulf its neighbor ("isophagy"). A similar theory of sex was elaborated

by Geddes and Thompson ('01). The studies of Maupas ('88, '89) and of numerous more recent investigators, however, have shown that the life cycle of the protozoa, with its phases of sexual and asexual reproduction, is apparently a very complicated process, involving both internal and external factors. Among the latter, inanition is doubtless an important factor, which under certain conditions may induce conjugation. This was observed by Maupas and others in numerous species of Infusoria. Hertwig discovered that when low temperature cultures (which have a relatively large nucleus) are placed at a high temperature and kept without food, an artificial "depression" is produced, which leads to conjugation. This was confirmed by Prandtl ('06) for *Didinium*, and by Popoff ('07) for *Epistylis*. Conjugation has been observed in the earlier stages of ordinary inanition in *Paramecium* by Kasanzeff ('01), Wallengren ('02) and Chainsky ('06); but Calkins ('02) and Lipska ('10) found inanition very unfavorable to conjugation. It is evident that further research is necessary in order to clear up this fundamental problem.

**Recovery upon Refeeding.**—The protozoa show an astonishing capacity for recuperation upon careful refeeding after inanition. Maupas ('88) found that an atrophic *Stentor* regained its original size in two days of abundant realimentation, which evidently involved an increase of over 100 times its reduced volume. Joukowsky ('98) observed a similar remarkable capacity for recuperation in *Pleurotrichia*. In *Paramecium*, Wallengren ('02) found a normal recovery possible, even in the greatly vacuolated condition after fifteen days of inanition. Lipska ('10), however, found recovery in general possible only up to four or five days of inanition. The process of recovery is the inverse of that during inanition, and cell-divisions begin after three to five days of refeeding. Nirenstein ('10) observed regeneration of endoplasmic fatty granules in *Paramecium* within a few hours of refeeding. Jennings ('08) noted that variability in size is increased during refeeding, some individuals recuperating more rapidly than others; but the normal condition is eventually restored.

#### EFFECTS ON THE VARIOUS SPECIES OF PROTOZOA

**Protozoa Other Than Infusoria.**—Among the unicellular animals constituting the phylum Protozoa, only a few observations as to the effects of inanition have been made upon forms outside of the class Infusoria. Brass ('83) noted that in starving Amebae and Gregarinae, as well as in Infusoria, the chromatic nuclear substance becomes resorbed, serving (according to his interpretation) as a reserve nutritive material. Schaudinn ('99) observed that in *Trichosphaerium Sieboldii* (a species of Foraminifera) during starvation the first change is a retraction of the pseudopodia in two or three days, and a resorption of the nutritive granules. "Zugleich mit diesen Vorgängen beginnen die Zellkerne sich an einzelnen Stellen zu kleinen Gruppen zusammenzulagern. Nachdem das Plasma rein geworden ist, wird dasselbe grob *vakuolisiert*, und zwar scheint diese Vakuolisierung von der Peripherie gegen das Zentrum vorzuschreiten. Im weiteren Verlaufe vereinigen sich die einzelnen Kerngruppen zu einer einzigen grossen Gruppe, und die Zelle rundet sich kugelig ab. Die Vakuolisierung

nimmt immer mehr zu, und zwar werdern jetzt umgekehrt wie zu Anfang die zentralen Vakuolen immer grösser . . . Schliesslich zerfällt das Plasma (nach etwa 3 Wochen) in eigenthümlicher Weise, indem es sich zunächst in wenige grosse Kugeln zerteilt, die wieder in kleinere sich auflösen, welche dann ganz verschwinden. Der Kernhaufen bleibt schliesslich allein in der zusammengefalteten Gallerthülle übrig, und leistet noch lange Widerstand."

In *Actinosphaerium* (a Heliozoan), and also in certain Infusoria, Hertwig ('03a, '04) obtained by prolonged inanition a marked change in the nucleus-plasma ratio, the nucleus becoming relatively enlarged. The significance of this change will be mentioned later. Pearl ('06) found that poorly-nourished individuals of the flagellate *Chilomonas* are reduced in size and slenderer in form. Borowsky ('10) observed that *Actinosphaerium eichhorni* resists inanition 14-18 days. The nuclei become fewer (apparently by fusion), and in advanced stages the cytoplasm undergoes marked vacuolation.

Penard ('05) noted that *Amoeba terricola* may endure starvation for ten to twenty days; but that other Amebae and Rhizopoda, free from "zoochlorelles," perish in four or five days. Stolc ('06) observed that in *Amoeba proteus* by withdrawal of food for four days (as well as by overfeeding and other environmental changes) binuclear cells are obtained, which return to the usual mononuclear form upon restoring normal conditions. Gruber ('11) found that *Amoeba proteus* after six or seven days of starvation becomes sluggish, the plasma becoming denser and darker. The cell becomes decreased in size, although the nucleus gradually increases. After two or three weeks, the animal becomes rounded up, degenerates and dies. During starvation in *Amoeba diploidea*, Erdmann ('10) noted vacuolation and pigmentary degeneration.

As an example of the effects of partial (calcium) inanition, Maas ('12) noted a reduction of the calcareous skeleton in the Foraminifera *Bilocularia* and *Quinquelocularia* in Ca-free sea water. Thompson ('17) stated (p. 415) that "when *Foraminifera* are kept for generations in water from which they gradually exhaust the lime, their shells grow hyaline and transparent, and seem to consist only of chitinous material."

Pratje ('21) has recently made an extensive and careful study of the changes found in *Noctiluca miliaris* kept without food and observed alive. The normal fat-droplets disappear gradually (in eight to fourteen days), so that the cytoplasm becomes transparent. The central cytoplasmic mass is greatly reduced in amount, with fewer and thinner radial extensions to the periphery. There is a corresponding increase in the peripheral vacuolar fluid, however, so there is no appreciable decrease in the size of the whole cell. The nucleus becomes more distinctly visible and more transparent. The nucleoli often become visible. Thus far only the more fluid endoplasm has been affected, but as inanition progresses, the firmer, peripheral protoplasmic structures (cell membrane and organs) are attacked and consumed. In about three weeks, all available sources of energy are exhausted. Recovery by refeeding is now impossible, and death soon occurs. "Fassen wir unsere Ergebnisse der Hungerversuche bei *Noctiluca* zusammen, so finden wir, das im Hungerzustande zuerst die vorhandenen Nahrungsstoffe und Reservesubstanzen aufgebraucht werden und erst dann

das Protoplasma im Innern der Zelle in Angriff genommen wird. Auch der Kern zeigt geringe Veränderungen. Nach dem flüssigeren Innenplasma, wird das festere periphere Plasma als Energiequelle für den Stoffwechsel benutzt, sowohl Bestandteile der Zellmembran wie auch der Organellen, Staborgan, Tentakel, Zahn und Lippe."

**Infusoria.**—Among the Infusoria, the *Paramecium* has been studied most extensively, but some observations have also been made upon other species. Gruber ('86) noted cell-divisions with decreased size in malnourished *Stentor coeruleus*. The phenomena were more carefully described by Maupas ('88), who experimented at temperatures of 23–26°C. with the following results: "Lorsqu'on prend un *Stentor* bien nourri et arrivé à son maximum d'accroissement, et qu'on l'isole en le privant complètement d'aliments, il n'en continue pas moins à se multiplier. Mais chaque bipartition n'étant plus suivie d'accroissement, la taille diminue rapidement et après trois ou quatre divisions, on arrive à ne plus avoir que de petits avortons mesurant 235 $\mu$  en longueur et 105 $\mu$  en largeur (Pl. XII, Fig. 14). Si on continue à laisser ces avortons sans nourriture, ils s'étiolent de plus en plus et finissent par périr après deux ou trois jours. Mais en leur donnant une abondante nourriture, je les ai vus en deux jours, par une température de 24 à 25 degrés, s'accroître rapidement et reprendre leur taille normale de 1176 $\mu$  en longueur et 270 $\mu$  en largeur (Pl. XII, Fig. 15)."

Further observations were made by Sosnowsky ('99), who noted, in *Stentor coeruleus* fasting in distilled water, the appearance of nuclear vacuoles, often collapsing at the periphery so as to give an irregular nuclear contour. Allescher ('12) in the same species found the rate of loss during starvation to vary greatly according to temperature. Thus the loss in volume after three days at 6°C. averages 18.53 per cent; at 15°, 41.21 per cent; at 25°, 60.03 per cent. Frequency curves of distribution in size were made. "Pure line" cultures show no reduction in size variations. The nuclear substance shows no decrease in the cold (6°) cultures, but at higher temperatures there is a reduction in the size and number of the nuclear masses, and sometimes the nuclear chain is broken.

In *Colpidium*, Miyoshi ('96) and Jensen ('99) observed during inanition a diminution in size and a disappearance of the cytoplasmic granules, with resultant increase of transparency. Wallengren ('02) also noted vacuolation of the endoplasm during the later stages of starvation in *Colpidium*, together with other changes similar to those found in *Paramecium* (to be mentioned later). Peters ('20, '21) observed that in cultures of *Colpidium colpoda* in synthetic nutrient mixtures the structure is not easily modified by chemical changes in the medium. The size of the organism may be reduced by inadequate nutrition, but is regained by new subcultures on adequate diet. Experiments indicate that ammonium phosphate and chloride, and also magnesium salts, cannot be omitted from the medium without stopping growth. Phosphate deficiency causes apparent disintegration, and potassium deficiency results in loss of movement, with final death. However, sodium, calcium or sulphates may apparently be separately omitted (excepting traces) without injurious effects.

In *Pleurotrichia*, Joukowsky ('98) described a remarkable reduction in length from 200 $\mu$  to 30 $\mu$ , or even 15 $\mu$ , during inanition, with no visible degenerative changes; the body becoming enlarged again upon careful refeeding. In *Dileptus gigas*, Hertwig ('03) likewise observed a great decrease in size during starvation. Death may be escaped by conjugation or encystment, a result confirmed by Prandtl ('06). Hertwig's pupil, Allescher ('12) studied the changes in *Dileptus* in more detail. In "hunger cultures" at 6°C., the animals lived four or five days with estimated average loss of 56 per cent in volume; at 15°, seven to twelve days with loss of 97 per cent; at 25°, five days with loss of 98 per cent; at 30°, six days with loss of 99 per cent in volume (length reduced to less than one-tenth, and breadth to one-third of the initial). The *Dileptus* has normally a very large number of minute nuclear particles, probably over 1,000, which become reduced to 50 or 60 somewhat larger particles during starvation. The plasma is consumed more rapidly than the nuclear material, and becomes darker in color, due to formation of brownish pigment.

In *Didinium nasutum*, Thon ('05) noted two stages of inanition similar to those found in *Paramecium* by Wallengren ('02). "Die Hapterscheinung der ersten Periode ist das Verdauen der Einschlüsse und Kondensation des Plasmas, in der zweiten wird das Plasma vakuolisiert und die Tiere encystieren sich." In the first stage nearly all the individuals divide, and the contractile vacuoles become enlarged (especially also in *Spirostomum ambiguum*). In the later stages the organs associated with the cytopharynx may become disintegrated and absorbed. The changes in the nucleus appear early and are quite variable. Its horseshoe form may be preserved or distorted. The nuclear membrane is persistent, but wrinkled; and the nucleoli lose their chromatin content. Cell-division becomes impossible and encystment follows.

Encystment following inanition was likewise found by Root ('14) in *Podophryae*, and Mast ('17) usually obtained similar results in *Didinium nasutum*. Recently, however, Mast and Ibara ('23) conclude that inanition does not facilitate encystment in *Didinium*.

**Paramecium.**—The effects of inanition upon *Paramecium* have been observed by several investigators. Verworn ('00) noted remarkable changes in starving paramecia. "Ihr Zellkörper war durch ein Anzahl grosser kugelig Vakuolen nicht nur vollkommen deformiert, sondern auch in seiner Struktur in tiefgehendster Weise verändert."

The first extensive study of starving paramecia was by Kasanzeff ('01), a pupil of R. Hertwig. He found that *Paramecium caudatum* survives six to nine days, with marked decrease in size. In five days, the average length decreases from 0.232 mm. to 0.147 mm., and the breadth from 0.084 mm. to 0.042 mm. The endoplasm becomes transparent and the food-vacuoles disappear; but abnormal vacuolation occurs later. The macronucleus at first elongates, increasing in volume and in chromatin content; but in later stages it decreases greatly in size, extruding small yellowish masses into the endoplasm, and may finally become fragmented. Normal cell-division and conjugation usually occur only in the earlier stages of inanition. The micronucleus shows increase rather than decrease in size; it may divide with the later reunion of the

daughter nuclei (as in conjugation), a process interpreted as "self-fertilization." Kasanzeff distinguishes two phases of inanition, the second phase beginning with the disintegration of the macronucleus.

Wallengren ('02), a pupil of Verworn, studied "hunger cultures" of *Paramecium caudatum* (also of *Colpidium colopoda*). He also divided the inanition period of about 15 days into two phases. In the first phase of 8 or 9 days, the reserve food material becomes exhausted. Through the disappearance of the food-granules and food-vacuoles, the endoplasm becomes transparent and is greatly reduced in volume. In the second phase, the endoplasm is attacked and numerous vacuoles of variable size arise, "die wahrscheinlich durch osmotisch wirkende Zellprodukte entstanden sind" (see Fig. 6). The contractile vacuoles are reduced, and the ectoplasmic organs (trichocysts, cilia) become smaller and sometimes partially consumed. In the macronucleus appear granules which fuse to form a mulberry-like mass (nucleolus), which persists while the remainder of the macronucleus becomes progressively vacuolated, deformed, and often finally fragmented and largely resorbed. Of all the cell-organs, the micronucleus alone resists the destructive effects of inanition, although it may show changes preliminary to a normal division. Normal conjugation may occur during the early stages of inanition. "So schreiten also bei der einzelnen Zelle die Inanitionserscheinungen von den unwichtigeren Teilen zu der wichtigeren fort, die unentbehrlichsten halten am längsten stand."

In size, Wallengren's paramecia were reduced in ten days from 0.25-0.3 mm. to 0.16-0.17 mm. in length, and from 0.07-0.08 mm. to 0.028-0.042 mm. in breadth. (The loss in *Colpidium* was relatively even greater.) In the later stages, the breadth may be increased by enormous vacuolation. Death may occur either suddenly, by rupture of the cell-membrane; or more slowly, with gradual decrease of the cell until death from exhaustion. On refeeding, the paramecia may gradually regain their normal size and structure, even when markedly vacuolated by fifteen days of inanition.

Most of the observations of Wallengren upon *Paramecium caudatum* were verified by Calkins ('02, '04), who found that inanition is unfavorable to conjugation. He also studied the somewhat similar periodic "depression" phenomena, and found them to occur independent of nutrition.

Another extensive investigation was made by Chajinski (Chainsky) ('03, '06), who made over 15,000 observations on starving *Paramecium caudatum*. His results in general are very similar to those of Kasanzeff and Wallengren. In the earlier period, he found disappearance of the food-vacuoles, with successive vacuolation of the endoplasm, and vacuolation (sometimes division) of the macronucleus. In the later stages, the ectoplasm also becomes vacuolated, the macronucleus greatly vacuolated and fragmented, and the entire cell markedly deformed. The micronucleus persists unchanged. Conjugations may occur in the earlier stage of inanition.

Jennings ('08) made a careful and extensive statistical study of size, including the effects of varied nutrition, in *Paramecium caudatum* and *Paramecium aurelia*. "Pure line" cultures were utilized. A large number of *P. caudatum* were taken from a 24 hour hay-infusion culture, and were kept in a small

quantity of the same fluid. At the end of eleven days, "They had evidently begun to starve; they were small and thin, and almost half of them had died." In a similar test with *P. aurelia*, at the end of twenty-one days only 37 specimens out of many hundreds survived, and these were in the extremes of starvation. The numerical data (in microns) for 100 individuals in each group (except the starved *P. aurelia*) are summarized in the accompanying table.

EFFECTS OF INANITION ON PARAMECIUM. (JENNINGS '08)

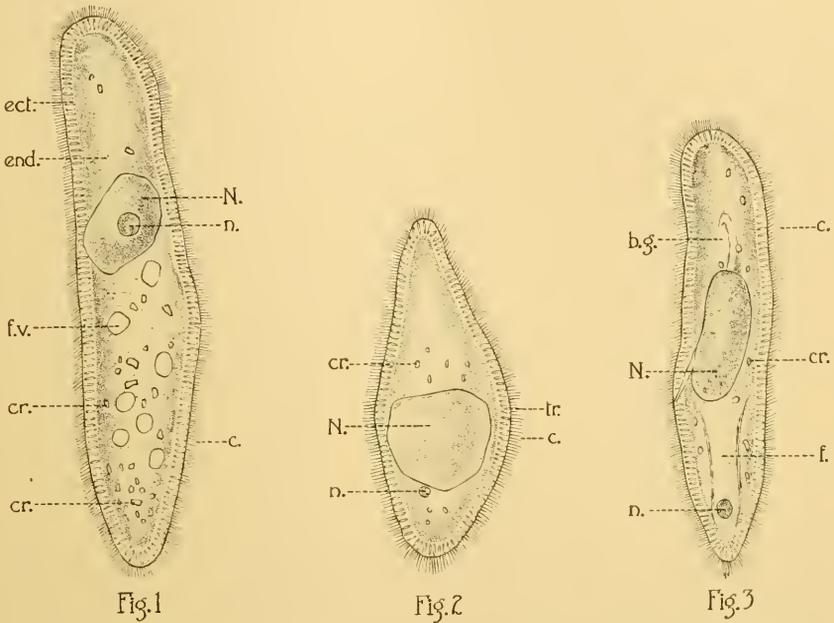
	Mean	Range	Standard deviation	Coefficient of variation
Normal <i>paramecium caudatum</i>				
Length.....	184.680 ± 0.848	156-224	12.596 ± 0.600	6.821 ± 0.327
Breadth.....	64.880 ± 0.580	44-88	8.624 ± 0.412	13.292 ± 0.645
<i>Paramecium caudatum</i> starved 11 days				
Length.....	149.360 ± 0.736	128-188	10.896 ± 0.520	7.296 ± 0.350
Breadth.....	38.080 ± 0.356	28-52	5.288 ± 0.252	13.881 ± 0.675
Normal <i>paramecium aurelia</i>				
Length.....	144.880 ± 1.097	100-176	16.264 ± 0.776	11.224 ± 0.542
Breadth.....	54.160 ± 0.765	32-84	11.346 ± 0.541	20.948 ± 1.042
<i>Paramecium aurelia</i> starved 21 days				
Length.....	102.594 ± 1.161	76-128	10.467 ± 0.821	10.202 ± 0.808
Breadth.....	23.892 ± 0.644	16-40	5.804 ± 0.455	24.291 ± 2.014

Thus during inanition the breadth of *Paramecium* is decreased more than the length, and is more variable. On refeeding, the variability is increased, since some individuals recover more rapidly than others; but eventually a normal equilibrium is restored.

Nirenstein ('10) proved that fatty granules are normally abundant in the endoplasm of *Paramecium*, but that they disappear more or less completely during the earlier days of inanition. Emaciated fasting individuals may be completely deprived of fat without the appearance of vacuoles or other degenerative phenomena. The characteristic fatty granules reappear within a few hours after refeeding with fatty emulsions, carbohydrates (starch) or even protein (Merck's egg-albumin). The possibility of fat formation from ingested bacteria was excluded.

The most recent extensive study of *Paramecium caudatum* during inanition is that by Lipska ('10), a pupil of Yung in Geneva. Lipska claimed that the "hunger cultures" of previous observers do not represent complete inanition. In such cultures, it is impossible to avoid bacterial contamination. Moreover, in the hundreds or thousands of individuals hitherto used in such cultures, many

die during the experiment and their disintegrated corpses, or more likely the bacteria which thrive thereupon, serve as food to prolong the life of the survivors. Lipska sought to avoid these difficulties by improvements in the experimental technique: (1) by repeated washings of the paramecia in boiled water at the beginning; and (2) by isolation of *individuals*, each in sterile water in a capillary glass tube two or three cm. in length, kept horizontally in a moist chamber. About 3,500 individuals were so observed, and in 350 cases the para-



FIGS. 1 to 6.—*Paramecium* in various stages of inanition. Figs. 1 to 5 from Lipska ('10); Fig. 6 from Wallengren ('02). Magnification about  $\times 400$ . *b.g.*, buccal groove; *c.*, cilia; *cr.*, excretion crystals; *d.v.*, degeneration vacuoles; *ect.*, ectoplasm; *end.*, endoplasm; *f.*, fold in body; *f.v.*, food vacuoles; *N*, macronucleus; *n*, micronucleus.

FIG. 1.—Normal *Paramecium caudatum* of average dimensions.

FIG. 2.—*Paramecium* after six days of inanition. The macronucleus (*N*) is greatly enlarged, occupying the posterior half of the pear-shaped body.

FIG. 3.—*Paramecium* after seven days of inanition. The macronucleus (*N*) is elongated; micronucleus (*n*) emigrated to posterior end of body. Two depressions are visible on the body, separated by a thick ridge or fold (*f*).

mezia were finally fixed, stained and mounted for more detailed microscopic study. The results, in comparison with those of her predecessors, will be summarized briefly (Figs. 1 to 5).

The average duration of life under such conditions was found by Lipska to be only five to seven days. The time varies according to circumstances, however. The (exhausted?) individuals starved immediately after conjugation survive only about three days. A few individuals, especially those containing symbiotic green algae, may survive ten or twelve days; and those previously hypernourished may survive even fifteen to twenty days. The higher averages of previous observers represent merely the few survivors of an incomplete inanition.

The body of *Paramecium* (as observed by Lipska) becomes progressively smaller, with no change of form until the fourth day of inanition. In later stages, it may become variously deformed—flattened dorsoventrally (Fig. 3), later often crescent-shaped (Fig. 4) or pyriform (Fig. 2). The average data for length and breadth in microns are as follows: normal *Paramecium*, 238 (length)—54 (breadth); starved and flattened, 124–28.5; starved and crescent-shaped, 136.8–28.8; starved and pyriform, 118–46. Thus there is a decrease of nearly

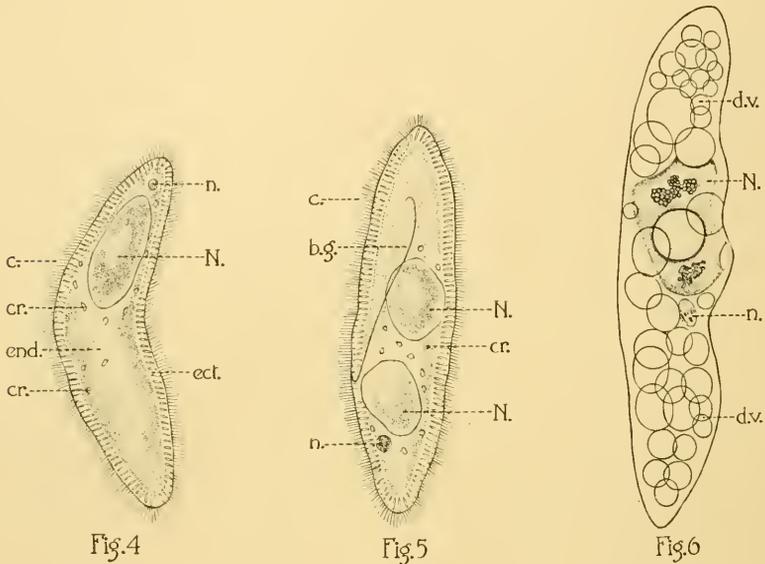


FIG. 4.—*Paramecium* after eight days of inanition. The characteristic crescent-shaped curvature of the body appears in this case. The macronucleus (*N*) and micronucleus (*n*) have emigrated to the anterior end of the body.

FIG. 5.—*Paramecium* after nine days of inanition. The macronucleus has divided into two spheroidal bodies (*N, N*), the micronucleus (*n*) remaining undivided.

FIG. 6.—*Paramecium* after twelve days of inanition, showing the degeneration vacuoles (*d.v.*), considered characteristic by Wallengren ('02) but not by Lipska ('10).

one-half in the various dimensions, which is somewhat greater than the average decrease obtained by Jennings, but not very different from that of Kasanzeff and Wallengren. A decrease of one-half in dimensions would correspond to a loss of seven-eighths ( $87\frac{1}{2}$  per cent) in volume. By a curious error, Lipska confuses dimensions and volume, concluding that "Il meurt lorsqu'il a perdu à peu près la moitié de son volume initial."

In the endoplasm of the starving *Paramecium*, Lipska found, in agreement with all previous investigators, a progressive disappearance of the food-vacuoles, with corresponding increasing transparency of the cytoplasm. The "excretion crystals" become more clearly visible, but decreased in size and number (as previously noted in *P. caudatum* by Schewiakoff '94). While apparently all previous observers (including Kölsch '02) have described a marked and progressive vacuolation of the endoplasm (*cf.* Fig. 6), Lipska could not find even a single case of such vacuolation during inanition. She found the vacuolation well marked in old cultures with the ordinary technique, however, and concluded

that it is due primarily, not to inanition, but to the toxic action of the *bacterial products* in such cultures.

In the ectoplasm, Lipska found no vacuolation (versus Chainsky) and rarely any involvement of the trichocysts and cilia (versus Wallengren). The movements become sluggish, however, and there is "un ralentissement général des phénomènes vitaux."

The macronucleus in the early stages of inanition becomes elongated and slightly enlarged (Fig. 2) confirming Kasanzeff and Chainsky, staining more deeply and often moving toward one end of the body. Toward the third or fourth day it frequently divides into two nearly equal spheroidal masses (Fig. 5), which separate later, but do not undergo the granular degeneration and fragmentation described by Kasanzeff, Wallengren and Chainsky (*cf.* Fig. 6).

The micronucleus may leave the vicinity of the macronucleus, but (in agreement with previous observers) usually undergoes no appreciable change in size, form or structure. Although the *Paramecium* in normal cultures averaged one division per day, only eleven cases of division were observed by Lipska in the thousands of individuals during inanition. Even these few divisions may have begun before inanition, as they occurred shortly after isolation. No cases of conjugation were found by Lipska during inanition, special tests for this purpose being made by placing five to ten paramecia together in a capillary tube. These tests are admittedly inconclusive, however.

Death of the paramecia from inanition was found to occur (as described by Wallengren) either (1) slowly, by a process of gradual granular degeneration and ultimate disintegration or (2) rapidly, an infrequent form due usually to a mechanical injury of the (probably weakened) cell-membrane. Granular masses of chromatic (nuclear) origin are frequently long recognizable in the disintegrating dead cells.

Recovery of the starving paramecia was found possible by careful refeeding, if begun not later than the third to fifth day of inanition. Division recommences three to five days later. The process of recovery is exactly inverse to the process of degeneration during inanition (confirming Wallengren).

## CHAPTER III

### EFFECTS ON THE HIGHER INVERTEBRATES

The striking effects of inanition on the invertebrates are very illuminating in comparison with the more complicated phenomena met in starvation and in the various deficiency disorders of the higher vertebrates, including man. It is difficult to summarize satisfactorily the effects of inanition upon the large and varied group of organisms included under the metazoan invertebrates. Nevertheless it will be profitable to review briefly some of the outstanding results as to duration of inanition, effects on weight, size and form of the body, changes in various organs and tissues, effects on the gonads and sex, effects on cell structure, effects on development, regeneration during inanition, and recovery upon refeeding. The data for the various groups of invertebrates will then be given in detail.

#### SUMMARY OF EFFECTS ON THE HIGHER INVERTEBRATES

**Duration of Inanition.**—The period of endurance naturally varies not only with the species, age, and individual, but also with the type of inanition, temperature and other external conditions. Hibernation or similar dormant periods are not comparable with ordinary inanition, because in the former case special stores of food are accumulated in the body for this purpose, and also because the metabolism is decreased so as to lessen greatly the need for nutriment. Some of the longer periods (years) of starvation reported for the leech, snail, spider and various insects are probably to be accounted for by unusually extensive periods of dormancy.

For complete starvation (total inanition) of adults, the periods reported for different species range from one or two days up to several years. In the Coelenterata, the period ranges from six weeks or less in the jellyfish *Cassiopea* to four months for *Hydra*; but newly hatched *Hydra* may survive only four or five days. The Platyhelminthes (flatworms) may endure six to fourteen months. The parasitic roundworm *Ascaris* can endure only seven to ten days, whereas the blood-leech *Hirudo* after engorgement may last one to three years. Among Echinoderms, the adult starfish can endure for months, while the larvae usually perish within a few weeks (maximum 60–70 days). Of the Mollusca, the mussel *Mya* endures only 18 days, the snail *Helix* four months (or in some cases possibly for years). Of the Arthropoda, the waterflea *Daphnia* endures only 11 days, the crayfish *Astacus* and spider *Epeira* a few months, the crab *Cancer* and the scorpion 18 months. The insects show enormous variation in different species, varying from only one or two days in the flies, bees and ants, dragon-flies, etc. to possibly several years for the bedbug. Among the beetles (Coleoptera) alone, the endurance in different species varies from two days to over six years.

The Orthoptera (grasshoppers) and Lepidoptera (butterflies and moths) endure starvation generally only a few days. The time varies inversely with the temperature and (in general) directly with the age; but in some cases (certain flies and beetles) the normal larval period may be prolonged by underfeeding. In the grasshoppers, the period of endurance is doubled if water is allowed. In all species there are also great individual variations.

**Effects on Body Weight and Size.**—As pointed out by Pütter ('11) the possible decrease in dimensions during inanition is much less in those forms having a firm skeleton (*e.g.* Arthropoda). The maximum possible reduction in body weight and size varies greatly among the higher invertebrates, ranging from 15 or 20 per cent in some Arthropoda to over 90 per cent in some coelenterates and planarians. Among coelenterates, *Hydra* is reduced to  $\frac{1}{7}$  or less in length; the jellyfish *Aurelia* to  $\frac{1}{4}$  and *Cassiopea* to  $\frac{1}{25}$  of the original volume. Planarians (flatworms) may be reduced to  $\frac{1}{12}$  in length and to  $\frac{1}{300}$  in volume. In the snail *Helix*, the loss in weight apparently varies from 11 to 50 per cent or more, according to species and conditions, with much individual variation. Among the Arthropods, a loss of 75 per cent in weight is recorded for the water-flea *Daphnia*, and of 15 per cent for the crayfish *Astacus*. Great variation has been found among the insects.

There are relatively few data on the loss during inanition in larval stages. The larvae of the sea-urchin *Strongylocentrotus lividus* may decrease to half the diameter of the original ovum. *Chortophaga* nymphs lose 20–25 per cent, and the tent-caterpillar (*Clisiacampa*) 35 per cent. The remarkable reduction (to  $\frac{1}{600}$ ) in the larva of the beetle *Trogoderma* is apparently exceptional. The loss during the pupal stage in general appears relatively slight.

Hall ('22) found marked differences in the limits of exsiccation in various invertebrates and vertebrates (see table on p. 116).

**Effects on the Form of the Body.**—During inanition the body is not only reduced in size, but also frequently more or less changed in form. *Hydra* for example, becomes at first abnormally elongated, later greatly contracted and relatively broader. The water-flea *Daphnia* presents a peculiar modification of body form attributed to malnutrition, and said to be hereditary (Woltereck). In the sponges, the coelenterates (*Hydra* and *Cassiopea*) and the planarians the changes are remarkably great, not only in external form, but also in corresponding internal structure. The so-called "reduction" process in these forms more or less resembles a reversal of the developmental process, which will be discussed later. In planarians, the involution frequently involves the posterior portion of the body to a greater extent, resulting in a relative enlargement of the head region. This is also true of the nemertin worm *Lineus lacteus*, but not of *Lineus ruber*, which illustrates the differences which may occur between species.

**Changes in Various Organs and Tissues.**—It is a remarkable fact that the various organs and tissues of the body differ very greatly in their resistance to inanition. Some undergo changes very quickly, others only after longer periods, and still others show a remarkable resistance. There are also differences in the extent of atrophy, as well as the order of sequence. The gonads will be discussed separately later, and also the changes in the developing organism.

In the medusa *Cassiopea*, the loss is almost entirely at the expense of the gelatinous ground substance; while in sponges, on the contrary, this substance is increased in amount. The ectodermal structures are more resistant, but they atrophy to a variable extent in different regions. In planarians, the intestinal epithelium, eyes, and pigment tissue and sexual duct system are affected relatively early; the muscles atrophy later, while the gonads and nervous system persist with great tenacity. In *Lineus*, the relative resistance of the various tissues is somewhat similar to that in planarians. Although among the higher invertebrates the skeleton is usually unaffected by starvation, in the snail *Helix* the calcareous shell is attacked as well as the soft tissues; while in sponges the results appear variable. Calcium deficiency usually causes involution of the invertebrate calcareous skeleton, both in larval and adult stages. In the reproductive passages of *Helix*, the non-glandular parts appear more resistant than the accessory albuminous gland, which undergoes an enormous involution. While the gland cells are greatly reduced, however, the associated "parenchyma" (stroma) nuclei persist and proliferate by amitosis.

**Effects on the Gonads and Sex.**—The effects of inanition upon the reproductive system and process have aroused much interest and have been carefully observed in various invertebrates as well as in other organisms. In forms where the process of reproduction may be either asexual by budding, fission or parthenogenesis) or sexual, the tendency of abundant nutrition is to favor asexual reproduction; while inanition or other unfavorable environment usually occasions a change to the sexual form, in many cases especially favoring the development of males. The gonads themselves are usually very resistant to starvation, being (like the nervous system) as a rule among the last of the organs to undergo involution. There are, however, evident variations in different species and individuals.

Among sponges, the process of involution during inanition frequently results in the formation of numerous small bodies ("gemmules"), from which new individuals may be reproduced later. In *Hydra*, budding is inhibited but the gonads (especially the testes) may mature in spite of the atrophy of the body as a whole. The predominating development of males in *Hydra* during inanition was emphasized by Nussbaum ('93), Schultz ('06) and Berninger ('10), but was denied by Hertwig ('06), Whitney ('07), Hänel ('08), Krapfenbauer ('08) and Frischholz ('09).

In planarians (flatworms), asexual reproduction is inhibited by inanition and there is a return to sexual reproduction, but the "cocoon" are reduced in size and the number of enclosed young markedly diminished. In the nemertean worm *Lineus*, the gonads undergo partial involution, but some areas (likewise the ducts) are very persistent.

In the rotifers (wheel-animalcules), Leydig noted that inanition causes prompt atrophy of the ovary and a tendency to production of males. Nussbaum ('97) concluded that in the rotifer *Hydatina* underfeeding in the *phase preceding the ripening of the ovum* tends to produce male offspring. This was confirmed by Lennsen ('98) but opposed by Whitney ('08). Shull ('10, '11) concluded that sex in *Hydatina* is determined by both internal and external

factors, but that the production of males during inanition is probably only an indirect effect.

The relation of nutrition to sex has also been studied extensively in the crustacean water-fleas by Leydig and others. The change from parthenogenetic to sexual mode of reproduction under unfavorable conditions (especially inanition) in this group was noted by Kerhervé ('92), Cuénot ('94) and Issakowitsch ('05). More recently, the internal factors have been emphasized, although it is admitted that the hereditary tendency may be influenced by external factors, such as malnutrition, especially during labile period of the ovum (McClendon '10; Woltereck '11). Green ('19) recently concluded that in *Simocephalus* the sex is probably predetermined in the ovary; but is also subject to environmental influence, though probably not through starvation.

Among insects the relations of nutrition to sex have been noted especially in the aphids (plant-lice), the Lepidoptera and the Hymenoptera. The appearance of winged male forms in aphids as a result of underfeeding was noted by Kyber (1813), Leydig, and others. The same phenomenon in the grape-louse *Phylloxera* was found by Keller ('87) and Behr ('92). Thus apparently all observers admit the effect of unfavorable environment, especially underfeeding, in causing the cessation of parthenogenesis and the appearance of males and sexual reproduction among the aphids. The conditions in this group therefore form strong evidence supporting the theory of nutritional sex-determination.

In the Lepidoptera, Treat ('73) observed a preponderance of males as a result of underfeeding the larvae of certain butterflies. This was not confirmed by Poulton ('93), although he admitted that a lesser resistance to inanition in the female larvae might result in a selective mortality with survival of a relatively larger number of males. This, of course, is not strictly a process of sex-determination, but rather of sex-survival. In the underfeeding experiments by Kellogg and Bell ('03, '04) on the silkworm *Bombyx*, and by Holmes ('10), Guyénot ('13) and Loeb and Northrop ('16) on the fruitfly *Drosophila*, no effect on the sex-ratio was observed.

Among the termites and Hymenoptera, the sex is known to be determined by fertilization (the unfertilized eggs producing the males). The diet, however, determines the development of the female reproductive tract, which in the few larvae well-fed (with "royal diet") becomes functionally developed, producing the queens; while in the less richly nourished larvae the reproductive tract remains rudimentary, producing the "workers," of which there may be different varieties, according to the amount of food available. There is some evidence indicating that in wasps (and possibly other Hymenoptera) the sex-ratio may be affected by nutrition, but this is somewhat uncertain.

*Among the invertebrates in general, we may therefore conclude from the available evidence that malnutrition tends to favor the sexual, rather than the asexual, mode of reproduction. Furthermore, especially in Hydra, rotifers, daphnids and aphids, the sex-ratio is at least to some extent subject to environmental influence, inanition tending to produce a preponderance of males.* Wilson ('00) concluded that nutrition is one factor which may determine sex. Schultze ('03) reached this conclusion for *Hydra* and *Hydatina*, but felt less certain regarding the

daphnids and aphids. How this influence becomes effective, however, is still a matter of uncertainty. In view of the conclusion by some investigators that temperature, rather than nutrition, is the decisive factor in sex-determination, we may recall the dictum of Cuénot ('94) that "la plupart des influences de milieu se ramènent en somme à des différences de nutrition." The whole question requires further investigation, especially in the light of the recent theory of sex-determination by the accessory chromosome.

**Effects on Cell Structure.**—We have noted that the effect of inanition is to produce a variable decrease in the size of the body as a whole, which is found to involve a variable reduction in the various parts, organs and tissues. This, of course, depends ultimately upon the changes in the underlying units, the component cells of the organism. Some cells are destroyed and absorbed, others persist more or less changed. From his study of the histological changes in *Hydra* and planarians during the involution process of inanition, Schultz inclined to attribute the marked decrease in size of the body to a decrease in the *number* of cells, those persisting being practically unchanged in size. The preponderance of evidence is against this view, however. Especially in the adult organism, all the cells of the body during inanition tend to undergo more or less atrophy. The extent and character of this atrophy vary in the different tissues, and in different cells of the same tissue. The decrease in the size of the body is therefore due partly to the complete disappearance of cells and partly to an atrophy of those persisting.

During the process of atrophy, the cytoplasm of the starving cells undergoes in general a series of characteristic changes, first losing its stored food material, pigment, mitochondria, and various inclusions. Later the cytoplasm of the cells often fuses into a syncytium. Vacuolation usually appears, with progressive decrease in amount of the cytoplasm, and terminal disintegration and complete absorption in the case of some of the cells. There is usually an earlier stage of reduction in size (simple atrophy) and a later stage of degeneration.

The nucleus is usually more resistant than the cytoplasm, giving a higher nucleus-plasma ratio. At first the nucleus may even enlarge, but later it tends to shrink (pynosis) with perhaps ultimate fragmentation, karyolysis, and final absorption. The reduction in cytoplasm and relative increase in nuclear size frequently gives the atrophic tissue an embryonal appearance.

Some further special features in the atrophic cell changes may be reviewed briefly. As noted by Terroine ('20) from the chemical viewpoint, the fat changes show great variation among species and individuals. While fat in general is quickly absorbed during inanition, in the vitelline gland cells of planarians it is tenaciously retained, disappearing only when the cells undergo final necrosis. In planarians and molluscs, the nerve cells may show certain degenerative changes, although the nervous tissue as a whole is remarkably resistant. It may be noted that apparently the final absorption of the degenerated cells in the various tissues is usually accomplished by simple solution in the interstitial tissue fluids; although phagocytosis has been noted in sponges, sea-urchin larvae, and especially in the case of the nemertin worm *Lineus*. The process of phagocytosis is said to occur also in the metamorphosis of insects.

Some specific changes in cell-structure are noted during various forms of partial inanition. Thus calcium deficiency may loosen the intercellular attachments, but it does not affect the ciliary mechanism, and apparently permits mitosis to continue in the embryonic tissues of various invertebrates. Phosphorus and potassium, however, are evidently necessary for mitosis, as in plants. In addition to the mineral salts, certain proteins, fats or carbohydrates, water, etc. are doubtless essential to life, but we have as yet few data upon the morphological effects of their deficiencies among the higher invertebrates.

**Effects on the Developing Organism.**—The effects of inanition upon the developing invertebrate organism, especially during the earlier embryonal stages, in many respects often differ markedly from those previously described for the adult. The embryonal cells have a characteristic tendency to growth and differentiation, which may enable certain organs and tissues not only to persist but even to develop at the expense of the remainder of the starving organism. This is true for general inanition, and is also especially evident during various forms of partial inanition; for example, in the case of specific salt deficiencies in the sponges, coelenterates, etc. Thus in many cases it is evident that deficiency in one limiting factor does not necessarily altogether inhibit the development of the invertebrate organism when that factor is exhausted, but occasions instead a disproportionate, abnormal growth, the extent and character of which will vary according to circumstances. Liebig's law does not apply in these forms.

On the other hand, in many cases the developing embryo or larva (in some species even the adult organism) tends to undergo during inanition a series of retrogressive stages more or less exactly reversing the normal order of development. This process (technically called "reduction") is often well-marked in sponges, coelenterates and planarians, though apparently rare in the more highly organized invertebrates. Even in the lower invertebrates, however, there is some question as to whether the (often remarkable) resemblance of the atrophic organism to the earlier embryonic stages may not be more apparent than real. But in some cases these atrophic remnants are actually able, under proper conditions of nutrition, to regenerate the normal structure of the organism. Child concludes that starvation results in morphological rejuvenation, followed by physiological regeneration upon refeeding.

The relatively great resistance to inanition usually offered by the gonads has already been mentioned for adults. This applies also in some cases to the developing organism, so that sexual maturity may occur in undersized bodies as a result of underfeeding (*e.g.*, silkworm and certain bees). But in others (starfish) sexual maturity is reached only upon the attainment of a certain body size, or the development of the gonads may even be entirely inhibited by inanition (fruitfly).

The sex of the offspring (as already mentioned) may also be influenced through the effect of inanition upon the germ cells in the larval stages, particularly at certain critical periods (rotifers, daphnids, aphids, etc.). In some insects, sexual maturity appears to be determined entirely by larval nutrition, in others chiefly

by the adult nutrition. Cuénot ('99) doubts whether the sex-ratio is notably affected by nutrition in species reproducing by fertilization only.

Underfeeding during the larval period may also result in undersized adults (various insects), and also sometimes in marked structural modifications (pigmentation, etc.). In some cases, these acquired characters appear hereditary, at least for a few generations; although ultimately upon adequate diet there is an evident tendency to return to the original condition.

The experiments with media or diets variously deficient have shown that compounds of P, K, Na, Ca, Mg, Fe, S and Cl appear necessary for development, growth being inhibited or variously perverted when the amount stored in the ovum is exhausted, unless a supply from without is available. The remarkable results (especially of Herbst, Loeb and Maas) in this field have been summarized by Driesch ('06). The marvelous effect of fat upon the development of the reproductive tract in the female Hymenoptera illustrates the morphogenetic potency of a single dietary factor. As to other forms of partial inanition, Baumberger holds that protein is in general the limiting factor in the growth of insects. The fruitfly *Drosophila* apparently requires yeast as well as sugar for growth, and other insects living on fermenting substrata of low protein content usually feed on the microorganisms present. Little or nothing is known concerning the possible requirement of vitamins by the invertebrates in general.

**Regeneration during Inanition.**—In many of the invertebrates, indications of regenerative activity may be observed in certain cells or regions during the general degenerative process of involution. Driesch ('01) observed that the reserve materials of the body which are consumed during starvation may be used to build up other parts of the organism. Thus in daphnids, crustacea and insects, repeated ecdysis (moulting), with regeneration of a new exoskeleton and appendages, may occur during starvation. This regenerative process occurs notably in the lower invertebrates, such as the sponges and coelenterates, and has been studied especially in planarians. Here the starving organism exhibits the remarkable capacity to regenerate large portions of the body, such as the head, with all its parts, pharynx, nerve ganglia, musculature and excretory system. Thus even during starvation, regeneration may restore a complete normal individual of much smaller size. In this process there is an extensive involution of the older tissues to furnish material for the regenerated parts.

**Recovery upon Refeeding.**—In general, it is possible for the starving invertebrates to recover their normal size and structure upon appropriate refeeding, if the process of involution has not proceeded too far in degeneration. This applies also to partial inanition. In sponges, for example, the skeleton is reformed upon restoring calcium carbonate to the medium. In planarians, regeneration of the gonads is possible even when they have nearly disappeared after three or four months of inanition. In the gland cells of the snail *Helix* starved five months, evidences of recuperation were found even after only two days of refeeding. *Drosophila* (fruitfly) larvae are capable of normal development after long periods of retardation on inadequate diet; and in this form, as likewise in the larvae of the beetles *Trogoderma* and *Tribolium*, the normal period of life may be greatly extended by retarding the developmental process

through alternate periods of fasting and refeeding. Underfed larvae of the moths *Acronyeta* and *Bombyx* produce smaller pupae and adults, the effect in the case of *Bombyx* being often carried over to the second and third generations.

#### EFFECTS ON THE VARIOUS PHYLA

Among the metazoan invertebrates, the effects of inanition upon growth and structure have been studied most extensively in the phyla Coelenterata, Platyhelminthes and Arthropoda. Some investigations, however, have been made also upon the Porifera, Nemathelminthes, Trochelminthes, Echinodermata, Annulata, and Mollusca. A few observations upon the Urochorda (Tunicata) are also included.

#### PORIFERA

The effects of inanition upon sponges have been studied chiefly by Maas. His first work ('04, '04a) was on the effects of a partial inanition upon the development of *Sycandra setosa* in  $\text{CaCO}_3$ -free sea-water. "Die Larven im künstlichen, karbonatfreiem Seewasser machten ebenfalls ihre Metamorphose durch, indem sie ungefähr in der gleichen Zeit festsetzten und ihre dermalen Zellen nach aussen, die gastralen nach innen kehrten; sie zeigten aber nach 24 Stunden und noch später *keine Spur von Nadeln* oder sonstigen Kalkkonkrementen." The skeleton is normally formed if the  $\text{CaCO}_3$  is merely reduced in amount, but  $\text{CaSO}_4$  cannot be substituted. In the  $\text{CaCO}_3$ -free sea-water, the body form is abnormally flattened, and various developmental irregularities occur. Usually the cells finally spread out into a flattened mass, which ultimately disintegrates.

In 1906, similar experiments by Maas on *Sycandra raphanus* were extended to include various larval and adult stages. When placed in artificial sea-water without  $\text{CaCO}_3$ , larval metamorphosis occurs. "Es kommt zum Ansetzen, zur sog. Umkehr der Schichten, Kalknadeln werden nicht gebildet; trotzdem zeigt sich ein Hohlraum, ja mitunter auch ein Osculum." These organisms without skeleton soon collapse unless  $\text{CaCO}_3$  is supplied, in which case they may recover normal structure if the cells have not been too greatly injured.

When placed in *entirely Ca-free* solutions (both carbonate and sulphate absent), the development is arrested earlier, in the amphiblastula stage. The ciliary mechanism is unaffected. On the fifth day, the granular ectoderm cells of the posterior half of the body become loosened and detached. The anterior mass of ciliated endoderm cells may persist for a week. Upon replacing the larvae in normal sea-water, recovery of more or less normal structure is possible, unless the granular ectoderm cells have been lost previously.

When the larvae, after normal metamorphosis, are transferred to  $\text{CaCO}_3$ -free solution, the previously formed calcareous spicules are gradually dissolved. The gastral cells form a rudimentary cavity and the dermal cells continue differentiation, but development gradually ceases in a variable time. In totally  $\text{Ca}$ -free solution (containing only  $\text{Na}$  and  $\text{Mg}$  salts) the skeletal spicules begin to disappear in a few hours. In one day, the soft parts also are degenerating; dermal

cells markedly loosened and dissociated; inner mass of cells usually compact, may show rudimentary gastrula cavity. "Die Zwischensubstanz ist auffallend schwach entwickelt."

When adult sponges (*Sycandra*) are placed in the  $\text{CaCO}_3$ -free solution, the skeleton shows little or no obvious change, although the soft parts are affected. The histological changes are somewhat similar to those seen in the experiments with larvae. "Im Innern des Tubar-Hohlraums zeigt sich Detritus mit Porenzellen; die Gastralzellen geben ihre histologische Ausprägung auf, ballen sich zusammen." In the gastral cells, karyokinesis may continue long in the  $\text{CaCO}_3$ -free solution. In completely Ca-free solution, the skeleton of the adult sponge *Sycandra* is but slightly affected. The soft parts, however, degenerate in a manner resembling the normal process of gemmulation.

Maas later ('07, '10) studied the effects of ordinary inanition upon sponges (and other organisms with calcareous skeleton). In *Ascandra Lieberkühnii* and *Sycon raphanus*, while in Ca-free medium the skeletal spicules disappear and the soft parts persist, during ordinary inanition (deprivation of food) the converse occurs. During hunger involution the organism is reduced in size, with involution of the old osculum, degeneration of part of the sponge and formation of a new osculum (sometimes two). The body becomes irregularly lobulated externally, with syncytial structure and excessive gelatinous ground substance internally. A similar reduction of the calcareous skeleton with persistence of the soft parts was observed in certain molluscs, the tube-worm *Spirorbis*, and Foraminifera (*Bilocularia* and *Quinquelocularia*).

The involution changes produced in sponges by unfavorable conditions (Ca-deficit, general inanition, etc.), according to Maas ('10), all involve loss of cellular differentiation (dedifferentiation). Through phagocytosis, syncytia arise which are considered equivalent to "gemmules." The body is reduced to a 2-layered condition, but these layers are not comparable to the normal germ layers. Wilson ('07), Urban ('10), and Müller ('11), likewise obtained experimentally a reduction or degeneration of sponges, with the ultimate formation of gemmule-like bodies. It is not clear, however, to what extent inanition was a factor in these cases.

#### COELENTERATA

Among the Coelenterata, observations upon the effects of inanition, aside from a few studies on Scyphozoa, and a single observation on Ctenophora, have apparently been confined to the class Hydrozoa. Of the Hydrozoa by far the greater number of investigations have concerned the fresh-water polyp, *Hydra*, which will be considered first.

**Hydrozoa.**—The earliest recorded inanition experiments on *Hydra* were those of Trembley (1744), who noted that both *Hydra viridis* and *Hydra fusca* required four months for death from starvation. Retrogression and premature detachments of buds during inanition were also observed. "Quand la nourriture manque, les jeunes polypes se séparent plutot. Il est apparent que, pressés par la faim, ils se detachent pour aller chercher ailleurs de quoi la satisfaire" (*l.c.*, p. 159). This was confirmed by Marshall ('82) and Berninger ('10).

Baudelot ('69), Kleinenberg ('72), Marshall ('82), and Schultz ('06) found that in underfed *Hydra*, well-formed buds, instead of becoming detached, may undergo reduction, retrogression and final disappearance.

Greenwood ('88) described the changes in the entoderm cells of *Hydra* during the earlier stages of inanition. The nutritive vacuoles (containing protein and fat) persist for two or three days, but become fewer and smaller or disappear entirely in more protracted fasting. The smaller "gland cells" of the entoderm become progressively more conspicuous, but in prolonged starvation their secretory granules may become smaller and partly dissolved. The pigment, though abundant during inanition, may also be slowly discharged.

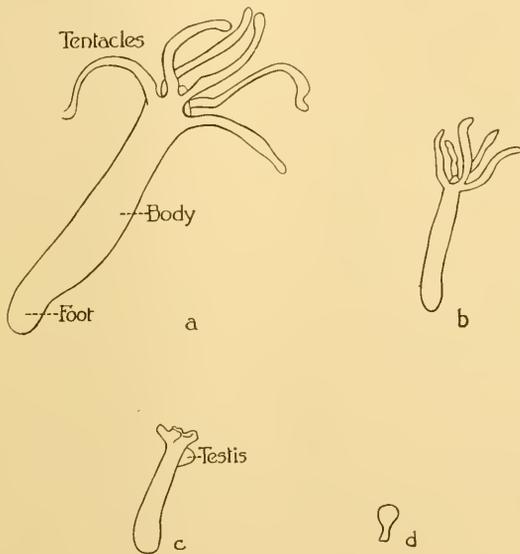


Fig 7

FIG. 7, a to d.—To illustrate the changes in size and external form of the fresh-water polyp, *Hydra fusca*, during starvation. All  $\times 10$ . (After Schultz '06.) a, Normal *Hydra*; b, *Hydra* starved  $1\frac{1}{2}$  weeks; size reduced, but form still nearly normal; c, later stage of reduction; tentacles have become rudimentary; the testis has matured, in spite of the atrophy of the body as a whole; d, terminal stage of reduction (cf. Figs. 8-11).

Nussbaum ('87, '93) was the first to study the effect of inanition upon sexual development in *Hydra*. He concluded that the (normally hermaphroditic) *Hydra* when abundantly fed will produce ovaries only; when moderately fed, both ovaries and testes; while those scantily fed produce testes only. This question is of fundamental importance in the theory of sex-determination, and has occasioned much controversy.

Hertwig ('06) opposed Nussbaum's view, and maintained that the conditions for sexual differentiation in *Hydra* are more complicated, temperature being a more important factor than nutrition. In his colony, sex-organs (always male) appeared only at lower temperature, whether starved or well-fed. The testes were better developed in the well-fed.

Schultz ('06) noted that although the process of asexual budding in *Hydra fusca* is inhibited by inanition, the differentiation of the testes proceeds, they being among the organs most resistant to starvation. Even in extreme stages the sex-cells (spermatogonia) persist and ripen into spermatozoa (Figs. 7c, 10).

Whitney ('07), on the basis of very careful and extensive experiments with *Hydra viridis*, concluded that temperature rather than food supply is the primary factor in sex-production. Low temperature followed by higher temperature causes budding and also formation of sex-organs, irrespective of food conditions.

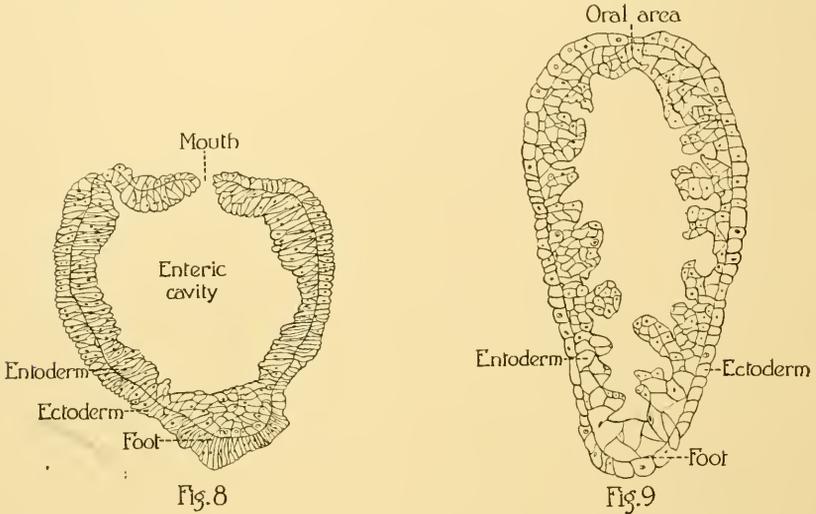


FIG. 8.—A longitudinal section of *Hydra fusca* after eight weeks of starvation. Body contracted; mouth aperture still open. (After Berninger '10.)

FIG. 9.—A longitudinal section of *Hydra fusca* after twelve weeks of starvation. Body oval in form; mouth aperture has closed. (After Berninger '10.)

Hänel ('08) found that neither inanition nor low temperature causes sex-production in *Hydra grisea*. Krapfenbauer ('08) obtained positive results by lowered temperature, but not by inanition. Frischholz ('09) found that within certain limits of temperature, sex-production in *Hydra* tends to appear in definite cycles of 20 to 40 days, depending upon the nutritional conditions. Even in extended inanition, however, sexual forms appear, either male or female (the strains used being always monosexual, never hermaphroditic). A change of temperature is unnecessary, but may accelerate sex-production. However, permanent exposure to high temperatures in *Hydra grisea* or to low temperatures in *Hydra fusca*, permanently inhibits sex-production, irrespective of the degree of nutrition. Finally, Berninger ('10) again found that in *Hydra fusca* (also in *Dendrocoelum lacteum*) inanition stimulates the development of the testes, with abundant ripening of the spermatozoa during starvation.

In summary, it is evident that Hertwig was correct in concluding that sexual differentiation in *Hydra* is a complicated phenomenon, various factors being involved. Besides temperature and nutrition, there is probably a cyclic or seasonal variation, and other hereditary characteristics, apparently varying in different species or strains of *Hydra*.

In addition to the effect upon the reproductive system, the general process of reduction in *Hydra fusca* during inanition has been described in detail by Schultz ('06). During the first week there is noted (except at low temperatures) a remarkable elongation, both body and tentacles forming thread-like extensions often reaching ten times the normal length. In the following weeks (Fig. 7, a-d) the animals gradually retract and become smaller, resulting in very small hydras (reduced to  $\frac{1}{7}$  normal length or less), but of normal body form. The tentacles become shortened, with swollen extremities; finally they disappear. The body, deprived of tentacles, gradually becomes pear-shaped and later spherical, the oral aperture closed and obliterated. Finally there results a spherical planula of ectoderm and endoderm, resembling the embryonal form (Figs. 8 to 11). Thus involution apparently reverses the processes of embryonic development in *Hydra*.

The **histological changes** in the tentacles of *Hydra* during reduction are not very striking. Apparently the loss of cells is chiefly at the tips, where degenerating cells are frequently seen.

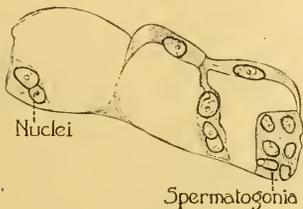


Fig. 10

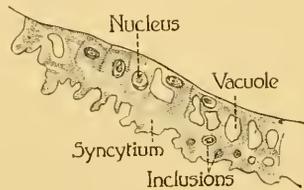


Fig. 11

FIG. 10.—Ectoderm cells from starving *Hydra fusca*. Highly magnified. The cells are separated by large interstitial spaces. The cytoplasm is scanty; the nuclei relatively large. A group of the persistent sex-cells (spermatogonia) is shown. (After Schultz '06.)

FIG. 11.—Entoderm cells from starving *Hydra fusca*. (After Schultz '06.) Highly magnified. The cells have fused into an irregular syncytium, containing vacuoles, pigment granules and inclusions. The free surfaces of the cells show irregular processes.

In the body ectoderm (Fig. 10), there is great variation in the resistance of different cells. The epithelium-muscle cells remain flatly extended, with progressive loss of plasma until the nucleus is barely covered. The cytoplasm usually becomes vacuolated. The nematoblasts disappear entirely. Other cells, however, may retain much cytoplasm, sometimes with gigantic nuclei. The gland cells of the foot remain apparently unchanged. The development of the testes (as above mentioned, Fig. 10) proceeds in spite of inanition, "Oder richtiger gerade infolge des Hungers." "Je mehr das betreffende Tier reduziert war, desto weiter war meistens die Reife der Testikel geschritten. Auch wimmelten meine Aquarien, wo ich die hungernde Tiere hielt, bald von Spermatozoen. Doch wachsen die Testikel nie zu jenen mammaförmigen Gebilden, wie sie gewöhnlich bei *Hydra fusca* erscheinen. Sie blieben weit kleiner und bildeten nur geringere Anhäufung unter dem Ectoderm. Eine Reifung der Ovarien beobachtete ich nie."

Of the entoderm in *Hydra*, the so-called gland cells show no morphological changes, although they decrease in number. The intestinal epithelium, how-

ever undergoes marked changes, the earlier stages of which were described by Greenwood ('88), as above mentioned. In contrast with the ectoderm, these entodermal cells become less vacuolated by disappearance of the food-vacuoles. Later the cells fuse into a syncytium, containing pigment, vacuoles and other inclusions (Fig. 11). The entoderm cells of the foot become indistinguishable from the intestinal epithelium. The entodermal nuclei at first become somewhat swollen, with indistinct nuclear membranes, later frequently undergoing chromatolysis. The intestinal cavity contains extruded masses of cytoplasm, intermingled with desquamated epithelial cells containing nuclei in various stages of degeneration. "Der Tod des Tieres wurde durch die volle Degeneration des Entoderms eingeleitet, während Ectoderm und Genitalanlage noch am Leben bleiben."

Schultz claimed that the tremendous reduction in the size of *Hydra* (as in Planarians) during inanition is accomplished chiefly through decrease in the number of cells, the size of those persisting being not very different from the normal. He opposed Roux's theory that those cells persist which require less food in the struggle for existence, stating that in the disappearance of organs during inanition the sequence is in general the opposite to that by which the organism developed, ontogenetically and phylogenetically. This order of loss is not always that most advantageous to the individual organism, however.

Berninger ('10) obtained results very similar to those of Schultz. He considered *Hydra viridis* unsuitable for inanition experiments, on account of the symbiotic algae, and studied chiefly *Hydra fusca*. In ordinary filtered tap water they all died within three weeks, but in spring water they lived twelve to fourteen weeks. As an age difference, Frischholz ('09) noted that newly hatched *Hydra fusca* die of starvation in four or five days. There is notable elongation in the first week, as observed by Schultz and by Krapfenbauer. The involution changes are not marked until the fifth or sixth week, when the body is reduced to about half its original length (Fig. 7, a to d). In fourteen weeks of starvation the *Hydra* is reduced from 7-8 mm. length and  $1\frac{1}{2}$ -2 mm. width to 0.2 mm. length and 0.13 mm. width. This is estimated to be about  $\frac{1}{30}$  of the original size, corresponding to a *Hydra* embryo a few hours old. Structurally the reduced *Hydra* differs from the embryo only in the higher differentiation of the cells, and the absence of yolk granules. "Also kann man wohl sagen, dass die Hunger bewirkte Reduktion die *Hydra* ungefähr auf ein embryonales Stadium zurückbrachte, wobei der umgekehrte Weg eingeschlagen wurde, welchen die Entwicklung durchlief."

Child and Hyman ('19) observed that in *Hydra* "The differences in diameter, general appearance and opacity between body and stalk become less marked with lack of food and in advanced starvation may almost or entirely disappear." In starved animals, the entoderm becomes much less susceptible to the disintegrative effect of cyanide, dyes, etc.

A few observations have been recorded as to the effects of inanition upon other Hydrozoa. Semper ('81) states that "The observations made on Hydroid Polyps by Hincks, Allman and Schneider are highly interesting. According to these, in the first place a Medusa of the group of the Hydroidea can be

induced by lack of nourishment to assume the polyp-form, *i.e.*, the larva form of the species." Linko ('00) noted a disappearance of pigment in the ocelli of the medusa *Margellium retropunctatum* which had been in an aquarium without food for a long time. Citron ('02) found that in *Syncoryne Sarsii* the ectodermal cells become flattened, the cytoplasm greatly reduced in amount, and the cells fusing into a syncytial condition.

In connection with his pioneer work on physiological morphology, J. Loeb ('92) found that potassium must be present in small quantity in the surrounding water to permit regeneration of polyps in *Tubularia mesembryanthemum*, and magnesium in addition to permit normal growth. Although at this time he considered the salts of these two elements, in addition to NaCl, as sufficient for regeneration and growth in *Tubularia*, he later (1905) admitted that traces of calcium salts were also present in the water used. Herbst ('97) observed that decapitated *Tubularia mesembryanthemum* are able to regenerate their heads in media free from calcium phosphate, perhaps because a sufficient supply was already stored in the body. The further work of Loeb and Herbst will be considered later in connection with the Echinodermata.

**Scyphozoa.**—Among the Scyphozoa, deVarigny ('87) observed three medusae of the jellyfish *Aurelia aurita*, weighing 98, 82 and 57 g., respectively. After 150 days in the laboratory, two survivors weighed 82 and 75 g., representing a loss of  $\frac{2}{3}$  or  $\frac{3}{4}$  of the original weight. Since protozoa and bacteria were not excluded from the sea-water, however, this probably represents an incomplete inanition.

Hadzi ('09) studied the effects of inanition upon larvae, probably of the Scyphomedusa *Chrysaora mediterranea*, in various advanced stages of development. Upon placing the hydriform scyphulae in sea-water without food (excepting the Ciliata present), the process of strobilization begins at once and many free-swimming ephyrae appear. On account of lack of food, the ephyrae are unable to develop further into Scyphomedusae, but undergo instead a series of characteristic retrogressive changes. The umbrella becomes smaller, later spherical, the marginal lobules and sense-organs (tentaculocysts) becoming detached. The gut lumen becomes constricted; the gastric diverticula retract and disappear. The body surface becomes ciliated. The reduced body later assumes an ellipsoidal form (Gastrea type) with a simple mouth opening, which finally becomes closed, resulting ultimately in a planula form, with distinct boundaries between ectoderm and endoderm. "Von einem über 1 mm. grossen, schon ziemlich hoch differenzierten Tiere, der Medusenlarve Ephyra, ist unter allmählicher Rückbildung eine möglichst einfach gebaute, oft nur 80 $\mu$  grossen, Planula entstanden." This reversal of the developmental process is completed within three weeks. The planulae may live fourteen days longer, but finally lose their cilia and disintegrate. Certain modifications of the process may occur, and the parent scyphula also undergoes similar regressive changes.

Stockard ('10) noted that vigorous regeneration occurs in experiments upon starving jellyfish, *Cassiopea xamachana*, but the corresponding decrease in body size is greater than usual in starvation, since regeneration proceeds at the expense of the older tissues.

Mayer ('14) made a more extensive and detailed study of the inanition changes in the same species of *Cassiopea*. The body weight decreases according to the formula:

$$Y = W(1 - a)^x$$

$W$  representing the initial body weight,  $Y$  the body weight after  $X$  days of starvation, and  $a$  (the "index of katabolism") being the fairly constant fraction of the existing body weight which is lost in any single day.

The rate of starvation varies according to circumstances. If the rate for the normal medusa in large aquaria of filtered stagnant sea-water is taken as 1.0, the rate in small aquaria (400 cc.) is 1.7; in running water, 2.4. For starving medusae regenerating their bell-rims, the rate is 0.96; if starving with stomachs removed, 1.27. In general the starving medusae regenerate as rapidly as the well-fed.

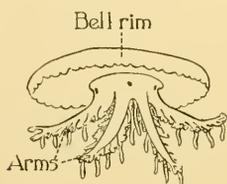


Fig. 12



Fig. 13

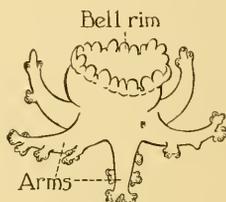


Fig. 14

FIG. 12.—Normal medusa of the jellyfish, *Cassiopea xamachana*. Lateral view, natural size. (After Mayer '14.)

FIG. 13.—Medusa of the jellyfish, *Cassiopea xamachana*, starved 41 days in darkness, with loss of about 96 per cent in weight. Lateral view, natural size. (After Mayer '14.)

FIG. 14.—Same as Fig. 13, but magnified to original size, for comparison with Fig. 12, to show more clearly the change in form undergone by the jellyfish *Cassiopea* during inanition. Note the relatively small bell (umbrella) with upturned rim, and the relatively large arms with rudimentary tentacles.

In six weeks of inanition, with final loss of over 96 per cent in body weight, there are likewise progressive changes in body form (Figs. 12, 13, 14). The bell-rim becomes shrunken and bent upward, and the arms atrophic. The mouths become closed by coalescence in about three weeks, so that subsequent recovery by refeeding is impossible. The cells are reduced in size; many become fused into a syncytial condition or degenerate and disappear. The gelatinous substance, which forms about 95 per cent of the organism, is greatly reduced in amount and becomes vacuolated. The commensal green algae become crowded in the diminutive starving *Cassiopea*, and ordinarily most of them escape from the body; but if the experiment is conducted in darkness most of the algae degenerate, and die, although a few may persist and regenerate a new supply upon refeeding.

Hatai ('17) confirmed Mayer's formula for the loss in weight of starving *Cassiopea* (after the first day), but found little change in the relative weights of the mouth organs, umbrella and velar lobes.

In connection with his experiments on partial inanition with various salt deficiencies, Herbst ('97) made a few incidental observations on *Cotylorhiza tuberculata*. Phosphorus was found necessary to enable the planulae to develop

into normal scyphostomata, the larvae disintegrating in P-free solutions. Similarly in potassium-free mixtures, the planulae developed no further, but gradually died off within seven days; while controls developed normally.

**Ctenophora.**—In connection with his experiments on partial inanition with various salt deficiencies, Herbst ('97) incidentally noted that when segmenting ova of *Beroe ovata* are placed in mixtures free from calcium phosphate, they soon perish; while the controls continue development.

#### PLATYHELMINTHES

Of the Platyhelminthes or flatworms, the class Turbellaria or planarians have been studied most extensively during inanition. Some observations have also been made upon the Nemerteans, a related group of somewhat doubtful classification.

**Turbellaria.**—F. F. Schultze ('36) was apparently the pioneer in observing the marked reduction in the size of planarians during protracted inanition. The first recorded measurements, however, are those of Voigt ('94), who noted that in ten or eleven months of fasting the length of *Planaria alpina* is reduced from 12 mm. to 1½ or 2 mm. The sexual reproduction is also affected, the "cocoon" being reduced to less than half their normal length, and the number of young from each being reduced from 55 in the well-fed to four in the starving individuals. Cuénot mentions that asexual division in some Turbellaria (*Microstoma*, *Planaria subtenaculata*) "trés prospère dans les moments d'abondance, s'arrête lorsque la nourriture devient rare." According to Rywosch and Zacharias ('86), however, the advent of unfavorable conditions may lead to the development of sex-organs, with return to sexual reproduction.

Lillie ('00) observed that in 43 days of starvation a *Planaria maculata* was reduced from 9 mm. (length) and 0.75 mm. (breadth) to 0.6 mm. and 0.25 mm. Assuming a decrease of one-half in the third (dorsoventral) dimension, this involves a reduction to 1/90 of the initial volume. The sex-organs appear immature. The pigment cells near the surface seem greatly reduced in number, but not in size. Although no detailed histological examination was made, the reduction process apparently reverses the steps of normal development. "Certain it is that specimens reduced by starvation to a smaller size than just hatched specimens of the same species resemble these in their general proportions, the relatively greater breadth in proportion to their length, as compared with mature specimens, the smallness of the cephalic lobes, and in the small number of intestinal diverticula and branches of the longitudinal nerves." During regeneration, Lillie also noted considerable loss, owing to the destructive metabolism in working over the old tissues into new form.

Morgan ('01) observed that if regenerating *Planaria lugubris* are fed, the old tissue loses but little and the new tissue grows faster; if the worms are unfed, the old tissue loses more and the new part grows less, forming a smaller worm. The decrease in the old part appears to be due, not to cell-migration, but to loss of substance, which is transported to the regions of active regeneration.

Stevens ('01) found a remarkable resistance of the nervous tissues to inanition in *Planaria lugubris*. "The nerve fibres are more easily traced in speci-

mens that have not been fed for several weeks before cutting; the other tissues degenerate somewhat while the nervous tissue does not to nearly the same extent. A specimen starved for 18 weeks showed the head ganglion nearly as large as those in corresponding specimens fed during the same time, while other tissues were much reduced; everything in the shape of fat or yolk material having entirely disappeared, and the actual size of the animal having been reduced from  $11 \times 3$  mm. to  $3 \times \frac{3}{4}$  mm."

More detailed investigation of the histological changes in planarians during inanition was made by Schultz ('02, '04, '04a, '08, '08a). In his first paper, Schultz ('02) noted a marked decrease in the body-size of *Dendrocoelum lacteum*. "Bei hungernden *Dendrocoelum lacteum* konnte ich beobachten, dass die Seitenverzweigungen des Darmes allmählich immer ärmer wurden. Auf Schnitten erwies es sich, dass das Darmepithel in den Seitenzweigen von den feinsten Endverzweigungen angefangen und weiter zum Centralstamme fortschreitend sich aus seinem Verbands löst. So sieht man auf Durchschnitten oft das Darm-lumen schwinden und die einzelnen Epithelzellen frei im Mesenchym liegen."

The histological changes during inanition in *Planaria lactea* were described by Schultz ('04) in greater detail. In six months the body length is reduced to  $\frac{1}{10}$  or  $\frac{1}{12}$ , and the worms begin to die after seven months. Some cells undergo degeneration, terminating in necrosis; others undergo reduction, *i.e.*, a "dedifferentiation" with return to embryonal condition; while some cells (body epithelium) remain unchanged in size and structure. The nuclei are very resistant and never decrease in size.

The **alimentary canal** in general decreases in proportion to the entire body, the form of the gut and branches being usually well preserved. The lining epithelial cells early begin to show changes, with loss of granules and fat, followed by progressive cytoplasmic atrophy. In some cases the cells degenerate, the nuclei often undergoing hypertrophy and karyolysis. In other cases the cells fuse into a syncytium with scanty cytoplasm, which may obliterate the gut lumen. The **eyes** likewise degenerate relatively early, by the fourth or fifth month, the optic cup breaking up. The pigment cells become disintegrated, leaving intercellular masses of pigment granules which are later resorbed. The **parenchyma**<sup>1</sup> (interstitial "Grundgewebe") is largely resorbed by the sixth month of fasting, although some cells remain unchanged. The **muscles** persist, even in extreme stages of inanition, but are reduced in size proportional to the whole body. The muscle-cells become shorter, but retain the same thickness. The **nervous system** is very resistant, although degeneration of nerve-cells occurs. "Das Gehirn und die Nervenstämmen mit ihren Quercommissuren sind noch zuletzt, wenn das Tier schon dem Hungertode ganz nahe ist, gut entwickelt." The **reproductive system** varies in its different parts. Reduction begins relatively early in the penis, which ultimately disappears. The fate of the ovaries is uncertain. The vasa deferentia, oviducts and associated genital

<sup>1</sup> It should be noted that many writers on the histology of invertebrates unfortunately use the term "Parenchyma" in a sense quite opposite to that generally used for vertebrates, where the corresponding interstitial tissue is designated as the "stroma."

passages later undergo progressive reduction. The testes are quite resistant, but in six months of fasting are reduced greatly in size and consist of small groups of three to five cells each, scattered through the "parenchyma." Even the spermatogonia may finally undergo necrosis and chromatolysis. Schultz (like Lillie) compared the reduction process to a reversal of the normal development, so that inanition may lead to a rejuvenation of the organism. He also considered the order of sequence in the loss of organs as a useful adaptation, the less important organs being sacrificed first, the most essential (and least differentiated) cells persisting longest.

Stoppenbrink ('05) made a most careful and thorough study of the changes during inanition, chiefly in *Planaria gonocephala*, but also in *Planaria alpina*, *Dendrocoelum lacteum* and *Polycelis nigra*. The extreme limit of duration found was fourteen months in *Planaria gonocephala* and ten months in *Planaria alpina*. The marked reduction in body size corresponds in general to that noted by previous investigators. There is also a marked change in the body form, the relatively large head and short postpharyngeal portion of the body resulting from unequal reduction in the different regions.

The reduction process in the various organs was found in general somewhat similar to that described by Schultz in *Planaria lactea*, but certain differences or additional features were noted. In the reduction of the intestine, no scattering of the epithelium in the mesenchyme was found (*P. gonocephala*, *D. lacteum*). The **vitelline glands** ("Dotterstöcke"), in which the fat deposits of the body are concentrated, do not lose this fat quickly during starvation, as might be expected, but retain it tenaciously, until the organ has undergone extensive retrogressive changes, with cellular necrobiosis and syncytial degeneration. The sexual duct system degenerates much later than the vitelline glands. The ovary and testes are the most resistant of all, although the sex-cells undergo regressive changes. Stoppenbrink summarizes his results as follows:

"Während die Grössenreduktion in einem gleichmässigen Kleinerwerden sämtlicher Zellen eine ausreichende und einfache Erklärung finden würde, deutet die Veränderung der Körperform auf anderweitige, gleichzeitig mitwirkende Ursachen hin. Diese Ursachen sind darin zu erblicken, dass eine ungleiche Beeinflussung der verschiedenen Gewebe stattgefunden hat, indem die *entbehrlicheren Organe zugrunde gingen*, um mit ihrem Stoffmaterial die Organe vor dem Untergang zu bewahren, die für das Tier unumgänglich notwendig sind. Eine stattfindende Nekrobiose lässt sich nur dort feststellen, wo untergehende Zellen in grösserer Menge beieinander angetroffen werden.

"Im *Nervensystem, Darm, Exkretionsgefässsystem, Parenchym, Hautmuskelschlauch* und *Körperepithel* trat ein gleichzeitig stattfindender Zerfall von Zellen in grösserem Umfange nicht ein. Dagegen liessen sich Degenerationsprozesse deutlich im Bereiche der Geschlechtsorgane beobachten, die zu einer totalen Rückbildung dieses Organsystems führten.

"Dieses Prozess erfolgte in der Weise, dass zuerst die *Dotterstöcke* angegriffen wurden, im späteren Verlauf der Begattungsapparat und zuletzt die *Hoden* und *Ovarien*. Dabei trat eine *Phagocytose* nicht ein, die Elemente zerfielen an Ort und Stelle und wurden resorbiert.

“Beachtet man, dass die postembryonale Entwicklung der Geschlechtsorgane in der Reihenfolge vor sich geht, dass zuerst die Bildung der Ovarien und Hoden, viel später erst die Entwicklung des Begattungsapparates und am Schluss die Anlage der Dotterstöcke erfolgt, so findet man, dass die *Involution der Geschlechtsorgane in der umgekehrte Reihenfolge stattfindet, wie ihre Entstehung.*”

Berninger ('11) likewise studied the effects of inanition in various species of planarians (*Planaria alpina*, *gonocephala*, *torva*; *Polycelis nigra*; *Dendrocoelum lacteum*), with results in general agreement with those of Stoppenbrink, Schultz and other earlier investigators. Death from starvation occurs in six to twelve months, with length reduced to about  $\frac{1}{12}$ ; volume to  $\frac{1}{300}$ . The nervous and muscular systems suffer no actual degeneration; the gut and “parenchyma” (stroma) but little. In darkness, the eyes degenerate and are entirely resorbed in seven or eight months. Of the reproductive system, the vitelline glands and penis are resorbed first, then the genital passages, later the ovaries and lastly (just before death) the testes. The “cocoon” are dwarfed and the enclosed embryos reduced in size and number. Regeneration of the sex-organs is possible upon refeeding, even when they have almost disappeared after three or four months of fasting.

Lang ('12) in connection with a study of regeneration in planarians, was able to confirm in general the results of previous investigators as to the effects of inanition. “Exkretionsgefäßsystem, Muskulatur und Nervensystem bleiben nicht nur vor dem Zerfall verschont, sondern regenerieren auch noch abgeschnittene Teile. Insbesondere regeneriert sich im Verlauf der Längsnerven stamme an Querschnitten ein neues Gehirn. Bei den gesamten Reduktionen und Regenerationen werden diejenigen Organe verschont bezw. gefördert die entweder zum Leben des Individuums unbedingt nötig sind oder die eine Vorbedingung für Beseitigung des Hungerzustandes bedeuten, insbesondere Pharynx und Nervensystem.”

In connection with a series of physiological studies, based upon experiments with planarians (chiefly *Planaria dorocephala*), Child ('11, '15, '19, '20) has made incidental observations as to the morphological effects of inanition. According to his conception, age is characterized physiologically by decreased metabolism, expressed morphologically by accumulation of structures which hinder cell-metabolism. “Starvation removes the structural obstacles to a greater or less extent, but without increasing the rate of metabolism, except perhaps at first; by means of food the rate of metabolism is increased and rejuvenation is accomplished. Starvation brings about morphological rejuvenation, the following feeding, physiological regeneration.”

In connection with his experiments on partial inanition with various salt deficiencies, Herbst ('97) made some incidental observations upon the marine polyclad worms, *Stylochus neapolitanus*, *Discocoelis tigrina* and *Thysanozoon Brochii*. In solutions without calcium phosphate, they died and disintegrated within about eighteen hours (controls unaffected), thus indicating the necessity for this salt in the medium for adult polyclads.

**Nemertinea.**—Aside from the observations by Giard ('05) on *Lineus bilineatus*, the effects of inanition upon the nemertine worms have been studied by Nus-

baum and Oxner. Oxner ('11) reported briefly the results in *Lineus ruber* and *Lineus lacteus*. On decapitation of young fasting individuals (or of older ones just after extrusion of the sexual products), the body undergoes a process of reduction and involution, without sexual maturation. If the sexual system has reached a certain stage of maturity, however, it will continue independent development to maturity in spite of the decapitation with consequent inanition, which prevents further growth of the body in general.

The changes in *Lineus ruber* and *Lineus lacteus* were studied in detail by Nusbaum and Oxner ('12). The starvation was in sea-water for various periods, six to thirteen and one-half months. The external dimensions of *Lineus ruber* reduced to  $\frac{1}{5}$  or  $\frac{1}{6}$ , all parts being nearly proportionately reduced (thus differ-

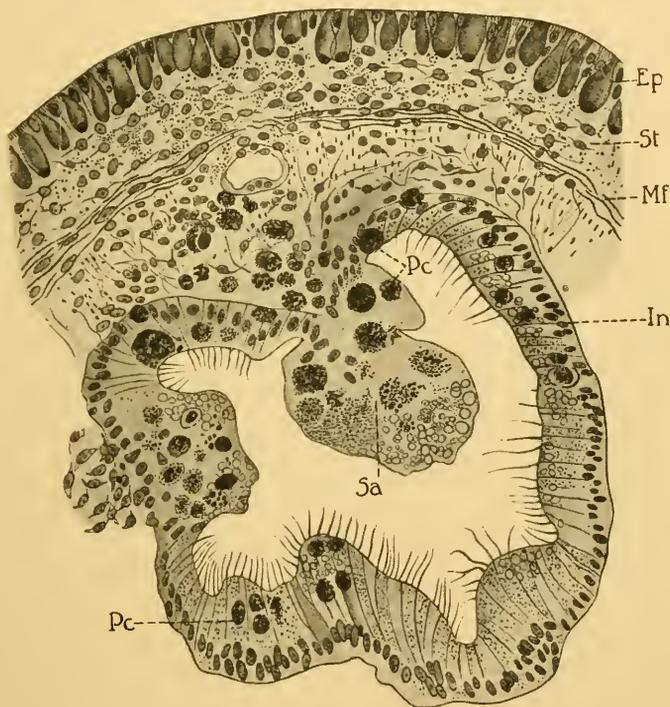


Fig. 15

FIG. 15.—A magnified portion of a cross section of the nemertean worm, *Lineus ruber*, after starvation for 12½ months. (From Nusbaum and Oxner '12.) Surface epithelial cells (*ep*) are markedly reduced in size. Stroma ("parenchyma") cells (*St*) of the underlying connective tissue are more closely packed, due to loss of the interstitial gelatinous substance. Muscle fibers (*Mf*) are greatly atrophied. Pigmented tissue (originally abundant) has largely disappeared from the body wall, being transported by phagocytic wandering cells (*Pc*) to the intestinal wall (*In*) serving as food for the starving organism. Areas of intestinal epithelium also undergo pigmentary degeneration into syncytial areas (*Sa*) which are finally absorbed.

ing from the planarians). In *Lineus lacteus*, however, the posterior portion is more reduced. The body wall is normally 0.06 to 0.09 mm. thick; including 0.02 mm. for cutaneous epithelium, 0.025 mm. for the "parenchyma" (stroma) and outer muscle layer, the remainder being the middle and inner muscle with

corresponding "parenchyma." In starvation, the body wall is reduced to about 0.04 mm. in thickness; including 0.02 mm. for the epithelium, 0.01 for the "parenchyma" and outer muscle, and 0.01 mm. for the remainder.

The cutaneous epithelial cells become lower, but the gland-cells may retain their original height. The reduction in size of the muscular and "parenchyma" layers is chiefly at the expense of the interstitial gelatinous substance, but most of the "Parenchymzellen und Bindegewebeselemente" also disappear. The muscles are also greatly atrophied; the individual fibers may be reduced to one-half in length and diameter. The **depigmentation** of the body is striking, the pigment cells undergoing degeneration and resorption in various parts of the body (including intestine, brain and eyes). Resorption is accomplished through phagocytosis by the wandering cells, which transport the material chiefly in pigment form to regions where most needed (Fig. 15).

The **intestine** in *Lineus* is decreased about one-third in thickness and two-thirds in number of epithelial cells counted in a cross section. In many places, especially in the hindgut, a degenerative involution occurs, particularly involving the folds projecting into the lumen (Fig. 15). The epithelial cells form extensive degenerative syncytial areas, within which occur occasional islets with cells of embryonal appearance. These may be able to regenerate the epithelium upon refeeding. The **eyes** degenerate and disintegrate, as described for the planarians. The **reproductive system** undergoes a partial reduction. "Sowohl in den Hoden wie auch in den Ovarien unterliegen gewisse Abschnitte des Keimepithels einem vollständigen Zerfalle unter Mitwirkung von Wanderzellen . . . Gewisse Abschnitte der Gonaden bleiben aber bestehen und hier bilden sich die Geschlechtsprodukte aus . . . Die Gonodukte unterliegen keiner Reduction, sogar in sehr späten Inanitionsstadien." The *nervous system* is very resistant; an apparent shrinkage in volume is due to atrophy of the connective tissue, the nervous elements remaining intact. There is likewise little or no change in the proboscis, nephridia, vessels, etc.

In general, therefore, there is in *Lineus* a remarkable difference among the various tissues and organs as to the time and extent of their reduction. A decrease in both number and size of cells is involved. In some cases the nucleus is more resistant than the cytoplasm, but in general the "Kernplasmarelation" is not much changed. In certain regions progressive, regenerative changes may occur among regressive, degenerative changes. The changes in *Lineus* during inanition and in regeneration of the body are naturally similar, since the regenerating organism takes no food and structures are regenerated at the expense of the remainder of the organism.

#### NEMATELMINTHES

Among the roundworms, but few observations on the effects of inanition are available. Maupas ('00) noted that in the hermaphroditic nematodes malnutrition reduces the number of ova, but does not affect the sex. In *Ascaris*, Weinland observed that the duration of starvation is greatest (seven to nine days) in fluid saturated with carbon dioxide. There is a marked decrease in the (normally very high) glycogen content. Ono ('20) studied the effect of starva-

tion upon the mitochondria in *Ascaris megalcephala*. The normal muscle cells of the body contain mitochondria, chiefly of filamentous form, but granular in the perinuclear region. "When starvation begins, however, the filamentous forms become granular ones, some by diminution, others seemingly by segmentation, while still others by the fusion of two or more of them may form globules, clumps, etc., usually connected by supporting fibrils; in short the whole number and quantity of mitochondria gradually diminish to a very small minimum at the end of about 10 days starvation." Similar results were observed also in the epithelial cells of the intestine.

#### ANNULATA

Relatively little attention has been paid to the effects of inanition upon the annelid worms. Apparently only the Hirudinea (leeches) have been studied in this respect, aside from a single reference to the Chaetopoda.

**Chaetopoda.**—In connection with the previously mentioned study of the effects of calcium-inanition on sponges, Maas ('12) noted that in calcium-free water a reduction of the calcareous substance without injury to the soft parts may likewise occur in the tubeworm, *Spirorbis*.

**Hirudinea.**—Only a few data, chiefly physiological, are available concerning the effects of inanition upon the leeches. Valisnieri is cited as authority for the statement that *Hirudo medicinalis* requires three years for death from starvation. Some observations by Cajal ('04a) and Dustin ('06) on the nerve cells of fasting leeches will be stated in Chapter X. Bialaszewicz ('19) found but slight decrease in the fat of leeches during starvation.

Pütter ('11) states that in the blood-leech one meal of blood may last six or seven months, and that an additional six or seven months or more of fasting may be endured without the slightest injury. Weber ('14) says the blood-leech has an enormous gastric capacity (five or six times the volume of the entire empty body) and may not feed for months.

Smallwood and Rogers ('10) noted that the leech *Semiscollex* kept without feeding for long periods gradually decreased in size. When the nerve cells from such starved animals are examined, either fresh or in stained sections, great changes are noted. "The whole cytoplasm of the cells has the appearance of a coarse foam structure. Here and there may be found the remnants of previously existing solid particles of stored up material." These particles were interpreted as food material, which is consumed during starvation.

Similarly in the fish parasite, *Pisciola*, Erhard ('11) observed that droplets of glycogen occur normally in the glia tissue around the large ganglion cells. After three days of starvation, however, the droplets of glycogen begin to decrease around the nerve cells, but now appear *in* the cells. Glycogen is said to behave similarly also in other parts of the body.

#### ECHINODERMATA

The investigations of inanition in the Echinodermata have concerned chiefly the effects of partial inanition (various salt deficiencies) upon the develop-

ment of the sea-urchin and the starfish. A few observations have also been made upon general (total) inanition in these forms.

**Echinoidea.**—The effects of calcium deficiency upon the development of the sea-urchin were studied first by Pouchet and Chabry ('89, '89a, '89b), who reared the larvae in sea-water from which a part or all of the calcium had been removed by precipitation with sodium or potassium oxalate. In media with about nine-tenths of the calcium remaining, the development appears normal up to about 40 hours. "Mais, à la 60 heure, elles sont encore à l'état de gastrula, tandis que les temoins ont des spicules ramifiés et un intestin complet. Après 90 heures ces larves, sans prendre des spicules, entrent dans une véritable phase *pluteus*, caractérisée pour elles par le différenciation de l'intestin en trois régions: oesophage, estomac et rectum. Mais la forme générale reste sphérique, sans prolongements, et la mort survient après quelques jours d'existence en cet état.

"En poursuivant une élimination plus complète de la chaux, les larves ne dépassent plus le stade *gastrula* et même le nombre de cellules qui l'atteignent devient de moins en moins grand. Lorsqu'on reste, au contraire, en deçà de la quantité que nous avons indiquée, le développement des spicules est simplement retardé, et ils subissent en outre, une déformation variable. Sur quelques larves, on observe la formation d'un appendice probosciforme, médian, et qui semble tenir la place des deux prolongements antérieurs frontaux, sans spicule interne." Thus calcium deficiency results in retarded and abnormal development, especially in the skeletal system.

The necessity and significance of the various salts in development was further revealed by the brilliant investigations of Herbst ('97). In artificial sea-water of varied composition he studied the effects of various deficiencies at various stages in the development of numerous organisms. He used chiefly sea-urchin and starfish, but made incidental observations upon several other invertebrates (also the fish *Labrax lupus*). The salt mixtures used contained various combinations and proportions of NaCl, KCl, MgSO<sub>4</sub>, MgCl<sub>2</sub>, CaSO<sub>4</sub>, CaCO<sub>3</sub>, Ca<sub>3</sub>P<sub>2</sub>O<sub>8</sub> and FeCl<sub>3</sub>. Chemically pure salts were found desirable, since in some cases (*e.g.*, iron), mere traces appear notably to affect the results.

In the sea-urchin (*Sphaerechinus granularis* and *Echinus microtuberculatus*), the results may be summarized as follows: In **phosphorus-free** solutions, the segmentation of the fertilized ova is abnormal and soon arrested (Fig. 17). Experiments beginning with later stages (blastula, gastrula or pluteus) likewise resulted in prompt arrest of development and rapid death of the organisms. In **sulphur-free** solutions, the fertilized ova undergo retarded development, which proceeds only up to the formation of abnormal gastrulae (Fig. 18). Experiments beginning with later stages (blastula, gastrula or pluteus) resulted in death without further development. **Chlorine** and **potassium** (Fig. 24) were similarly found essential for segmentation, and also for continued development beginning at the later stages. In **magnesium-free** solutions the fertilized ova show no apparent difference from controls up to the gastrula stage (second day), but thereafter become retarded in development, not exceeding an abnormal pluteus stage with imperfect skeleton (Fig. 20). Magnesium was found essential also for development in experiments beginning with later stages. **Calcium**

was likewise found necessary for development of the fertilized ova. Even with  $\text{CaSO}_4$  and  $\text{CaCl}_2$  present in the solution, the development proceeds no further than an abnormal pluteus, with rudimentary skeleton (Fig. 22). The presence of  $\text{CaCO}_3$  was found necessary, not only for the development of larvae with a normal skeleton, but also for the preservation of the already formed skeleton in

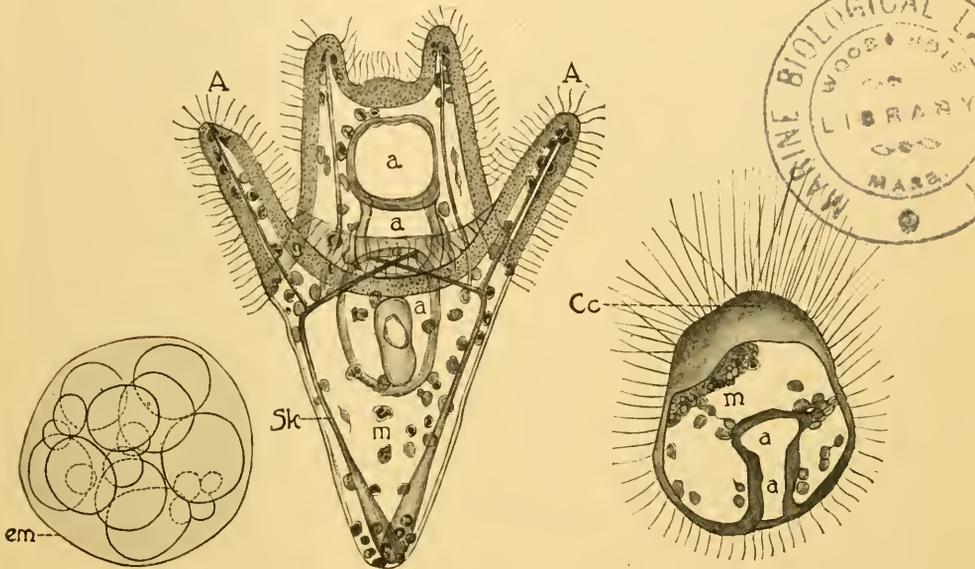


FIG. 17.

FIG. 16.

FIG. 18.

FIGS. 16 to 25 illustrate the effects of various salt deficiencies upon the development of the sea-urchin, causing inhibition or distortion of the normal growth process. After fertilization in normal sea-water, the ova were placed in artificial media containing various salt mixtures. The normal controls in the complete salt mixtures pass through the segmentation stages, blastula (Fig. 25) and gastrula stages, reaching the normal pluteus stage shown in Fig. 16. All these figures (16 to 25) are taken from the monograph by Herbst ('97).

FIGS. 17 to 24 represent the most advanced stages reached in the solutions variously deficient. (After Herbst '97.)

A, arms; a, a—segments of alimentary canal; Bc, blastocoele; Cc, (abnormal) ciliated crown; em, egg membrane; m, mesoderm cells; Sk, skeletal rods; Sp, "snout-like" process; Vac, vacuoles in blastula cells.

FIG. 16.—Normal pluteus stage of the sea-urchin *Echinus*, reared in a complete salt mixture containing NaCl, KCl,  $\text{MgSO}_4$ ,  $\text{CaSO}_4$ ,  $\text{CaCO}_3$ ,  $\text{FeCO}_3$ , and  $\text{CaHPO}_4$ . Fourth day.

FIG. 17.—This stage of (abnormal) segmentation represents the maximum development reached in the same salt mixture as the foregoing (Fig. 16), with omission of the phosphate. Most of the ova failed to segment at all, or were arrested in still earlier stages of abnormal segmentation. This illustrates the necessity for phosphorus in normal development of the sea-urchin, *Echinus*.

FIG. 18.—Abnormal gastrula of *Echinus*, representing the maximum stage of development reached in an S-free mixture of NaCl, KCl,  $\text{MgCl}_2$ ,  $\text{Ca}_3\text{P}_2\text{O}_8$ ,  $\text{CaCO}_3$  and  $\text{FeCO}_3$ . Third day. Shows that sulphur is necessary for normal development.

experiments beginning with the pluteus stage. Finally, the fertilized ova and later stages were observed to undergo retarded and abnormal development unless iron was present, at least in traces (Fig. 23).

The abnormal form and structure of the larvae appeared variable, yet to some extent characteristic according to the type of deficiency, as shown by Figs. 16 to 25. Herbst reached the general conclusion that "Das wichtigste

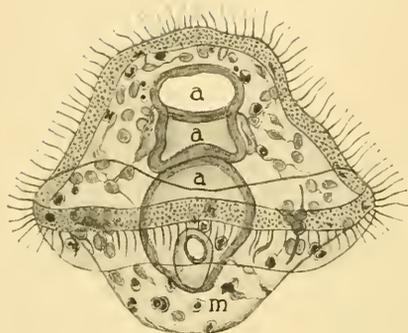


FIG. 19.

FIG. 19.—Larva (abnormal pluteus) of the sea-urchin *Echinus* reared in a solution the same as the preceding, but with addition of  $MgSO_4$ . Fourth day. Except for the absence of the skeleton, the internal structure corresponds somewhat to that of the normal pluteus stage (cf. Fig. 16); but the external form is very different, arms undeveloped, etc. The addition of  $CaSO_4$  to the medium permits normal development, indicating that the organism requires this salt as a source of sulphur, that in  $MgSO_4$  being inadequate.

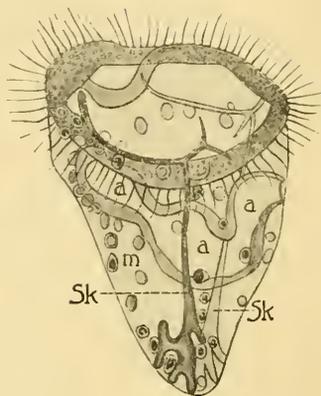


FIG. 20.

FIG. 20.—Abnormal pluteus representing the maximum stage of development reached by the sea-urchin *Echinus* reared in an Mg-free mixture. Third day. No arm-processes or oral invagination. Gut and skeletal development somewhat retarded. Indicates the necessity of magnesium for normal development.

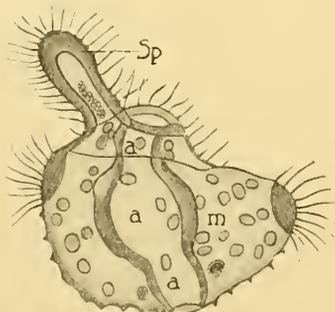


FIG. 21.

FIG. 21.—Abnormal pluteus of sea-urchin *Sphaerechinus* reared in a mixture containing  $CaHPO_4$ , but not  $CaCO_3$ . Third day, showing the maximum stage of development reached. The form is abnormal; the "snout-like" process and absence of skeleton being especially characteristic in the absence of calcium carbonate.

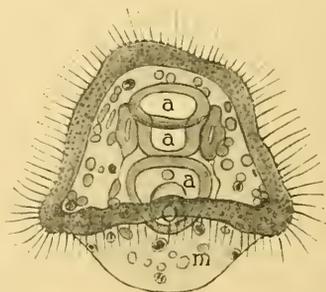


FIG. 22.

FIG. 22.—Abnormal pluteus of the sea-urchin *Echinus*, reared in mixture containing  $NaCl$ ,  $KCl$ ,  $MgSO_4$ ,  $CaSO_4$ ,  $Ca_3P_2O_8$  and  $FeCO_3$ . Deficiency in  $CaCO_3$  results in complete absence of skeletal development, and in abnormal external form differing from that shown for *Sphaerechinus* in the preceding figure. Third day, representing the most advanced stage of development reached.

meiner Versuchsergebnisse besteht in dem Nachweise, dass die zum Aufbau des Embryo nothwendigen Baustoffe im Ei nicht in solchen Quantitäten vorhanden sind, dass sie bis zu dem Stadium, wo die Vermehrung des Bildungsmaterials durch Nahrungsaufnahme möglich ist, also zum Pluteusstadium reichen, sondern dass sie dem Meerwasser zum Theil bereits bei der Furchung entzogen werden. *Die normale Entwicklung der Seeigellarven hängt also nicht nur von einer bestimmten physikalischen, sondern vor allen Dingen von einer bestimmten chemischen Beschaffenheit des umgebenden Mediums ab.*" Herbst's results upon the starfish and other animals (Coelenterata, Platyhelminthes, Tunicata and fish) are mentioned under the corresponding sections.

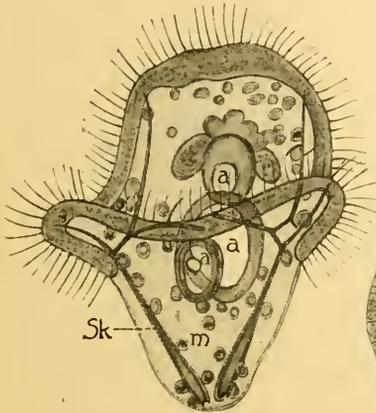


FIG. 23.

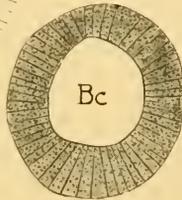


FIG. 24.

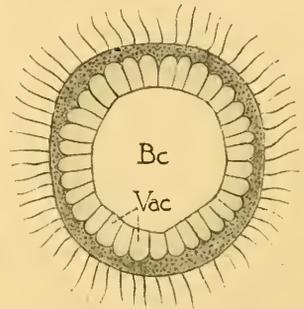


FIG. 25.

FIG. 23.—Abnormal pluteus of the sea-urchin *Echinus*, reared in mixture of NaCl, KCl, MgSO<sub>4</sub>, CaSO<sub>4</sub>, Ca<sub>3</sub>P<sub>2</sub>O<sub>8</sub> and CaCO<sub>3</sub>. Third day, representing the most advanced stage of development (rarely reached) in Fe-free media. Indicates that iron is essential for normal development.

FIG. 24.—Abnormal blastula of sea-urchin *Sphaerechinus*, reared in same mixture as the specimen shown in Fig. 25, excepting absence of potassium salt. Note small size, thick wall, absence of cilia and vacuoles. Demonstrates that K is necessary for normal development.

FIG. 25.—Normal blastula of sea-urchin *Sphaerechinus*, reared in complete salt mixture. Control to the preceding Fig. 24. Note size of blastula, cilia and cellular vacuolation.

In a later investigation, Herbst ('00) studied in greater detail a peculiar histological change found in the developing sea-urchin and other forms placed in Ca-free solutions. "Durch das Fehlen von Calcium im umgebenden Medium wird der Verband der Furchungszellen membranloser Eier der Seeigel derartig aufgelockert—und zwar bei *Echinus* radikaler als bei *Sphaerechinus*—dass die einzelnen Zellen zum Teil sogar durch grössere Zwischenräume von einander getrennt werden. Trotz dieser gänzlichen Isolation oder Auflockerung verläuft aber die Furchung bis zu Ende, ja es trifft sogar Differenzirung in Wimperzellen ein, die, auch wenn sie gänzlich isolirt sind, doch einige Zeit am Leben bleiben und sich munter bewegen können. Der Calciummangel wirkt also zunächst nur specifisch auf den Zusammenhalt der Zellen, nicht aber auf die Lebensenergie ein, deren endlichen Erlöschen vielleicht überhaupt nicht an dem Fehlen des Kalkes, sondern vielmehr an der Isolation, an dem Herausreissen aus dem Gesamtorganismus liegt." Experiments on later stages gave similar

results. When the egg membrane is left around the segmenting ovum in the Ca-free water, complete separation of the cells is prevented, and upon restoration to normal sea-water they may reunite and continue normal development. These results of Herbst have been applied in the theory of calcium deficiency in scurvy of vertebrates.

We have already noted the pioneer work of J. Loeb ('92) in demonstrating the necessity for potassium, sodium and magnesium salts for the normal growth, development and regeneration of the Coelenterate *Tubularia*. This work was continued by Loeb ('05, '11), extending his results in general to Echinodermata (*Arbacia*), Crustacea (*Gammarus*) and Vertebrates (*Fundulus*). With the fertilized *Arbacia* eggs, placed in various mixtures of NaCl, KCl, and MgCl<sub>2</sub>, Loeb found that any one salt permitted segmentation (often abnormal) only up to a maximum of 64 cells (in MgCl<sub>2</sub>). A mixture of two chlorides (MgCl<sub>2</sub> and CaCl<sub>2</sub>) may permit reaching the blastula stage; while three chlorides (NaCl, CaCl<sub>2</sub> and KCl) made it possible to reach the gastrula, or even the pluteus stage, without skeleton. The addition of Na<sub>2</sub>CO<sub>3</sub> gave plutei with normal skeleton.

While Loeb's results are thus to a certain extent in general agreement with those of Herbst, his interpretation of them is quite different. On account especially of his experiments with *Fundulus* eggs, Loeb believed that the injurious effect of various salt deficiencies is due, not to the direct need for the deficient salt in the developing organism, but rather to the toxic effect of the other salts remaining in solution. Thus Loeb ('05) concludes: "It seems to me that my experiments necessitate the introduction of a new conception, namely, that of *physiologically balanced salt solutions*. By this I mean salt solutions which contain such ions and in such proportions as completely to annihilate the poisonous effects which each constituent would have if it were alone in solution." The principle that certain salts may function in neutralizing the toxic action of others has been referred to previously in the chapter on plants.

As to the mechanism of this protective action, Loeb ('11) states: "These observations on the sea-urchin egg, therefore, suggest the possibility that the combination of the three salts in their definite proportion and concentration has the function of forming a surface film of a definite structure or texture, around the protoplasm of each cell, by which the protoplasm is kept together, protected against and separated from the surrounding media."

The effects of total inanition upon the larvae of the sea-urchin, *Strongylocentrotus lividus*, were carefully studied by Runnström ('12, '12a). The rate of involution varies directly with the temperature, but the larvae may survive starvation for 60 or 70 days at 18-19°C., decreasing to one-half the diameter of the original ovum, or less. Two types of involution occur: (1) the skeleton is less affected and the arms persist, although the alimentary canal shows marked changes; or (2) the skeleton is markedly resorbed and the arms greatly shortened, although the other structures may be less changed. In general the hindgut (rectum) undergoes the most marked reduction. The lining epithelial cells becomes first cylindrical, later shortened and finally detached and migratory. The mesenchyme cells are actively phagocytic and migratory, transporting

materials (including disintegrating pigment cells) from the regions undergoing atrophy to those where further growth occurs. Thus, by a process of "auto-differentiation," further development (*e.g.*, anlagen of the pedicellariae) may occur at the expense of the remainder of the body. The inanition involution is therefore not purely a reversal of the normal developmental process. Runnström refers the morphological changes directly to physico-chemical conditions, varying with the food supply and resulting differences in the acidity, permeability, etc. of the various cells and tissues.

**Asteroidea.**—The experiments of Herbst ('97) upon the effects of various salt deficiencies, which have already been described for the sea-urchin larvae, were also in some cases extended to the developing starfish (*Asterias glacialis*) with very similar results. In phosphorus-free salt mixtures the fertilized ova fail to segment normally and development never goes beyond the blastula stage. Bipinnaria stages in phosphorus-free solutions die within a day. Sulphur (sulphates) and potassium salts were likewise shown to be necessary for the normal early development of starfish. Tests were not made for the other substances found necessary in the development of the sea-urchin.

Mead ('00) obtained great differences in size between fed and unfed starfish. He noted that sexual maturity is correlated with the attainment of a certain size (50 mm.). "When food is accessible, the starfish eats voraciously and grows with great rapidity, but, on the other hand, it will live for months almost without food and apparently remain healthy, though it does not grow."

Schultz ('08b) kept recently metamorphosed larvae of the starfish *Asterias rubens* in filtered water to see whether they undergo a "reduction" to embryonal form as he found in *Hydra* and *Planaria*. Growth ceases, but no developmental reversion occurs. At the end of three weeks, most of the starfish show no change in size or structure, excepting the intestinal gland-cells or granule-cells, which become fewer and may disappear entirely. Even in more prolonged starvation, no typical "reduction" occurs, but degeneration gradually supervenes. The cells of the epithelial band soon become detached. Proliferated and degenerated cells fill all the cavities of the body, the gut-lumen first, and the stone-canal last. The lumina of the blood-vessels and water-vascular system become obliterated, and the body cavity filled with connective tissue. The muscle and nervous system persist unchanged, however, and the size of the nuclei in general is unaffected.

#### MOLLUSCA

Of the phylum Mollusca, the effects of inanition have been studied chiefly in the class Gastropoda, with a few observations upon the Pelecypoda.

**Gastropoda.**—The remarkable resistance to inanition by the snail *Helix* was noted by several earlier observers cited by Lucas (1826). *Helix* (sp.?) was said by Macbride (1774) to endure starvation for a period of 15 years! For *Helix nemoralis*, Müller noted a period of one year. For *Helix pomatia*, Sorg (1805) observed endurance for six months, and Wiesmann for one year. Semper ('81) stated: "I myself kept various species of land-snails for years

wrapped in paper and quite dry in wooden boxes, and thus wholly without food, and many of them are at this day alive and active."

In various species of (edible) *Helix* during starvation, Sabrazes ('02) found: "La perte de poids peut se chiffrer par la moitié du poids primitif, et cela dans un laps de temps de quelques jours au bout dequels les escargots s'accolent les uns aux autres et sont protégés contre la dessiccation par une mince membrane, d'une aspect parcheminé, parfois creusée d'un petit opercule, tendue à orifice de la coquille. Les animaux peuvent rester ainsi, à l'état de vie latente, plusieurs mois . . . M. Devaux a observé aussi des faits analogues."

More recently Krahelska ('13) found that *Helix pomatia* endures starvation at 17°C. for six months to a year, but that *Helix arbustorum* is less resistant.

Slowtzoff ('03a) found in *Helix pomatia* subjected to total inanition a gradual loss of body weight up to 25.74 per cent, the loss affecting the shell as well as the soft parts. The change in chemical composition was determined.

From their experimental studies on the cytology of invertebrate nerve cells, especially in the molluscs *Planorbis*, *Limax agrestis*, and *Limax maximus*, Smallwood and Rogers ('08, '09, '10,) conclude that the lipochrome pigment granules contained in these cells vary according to nutritive conditions. They slowly decrease in size and number during hibernation and prolonged starvation, with corresponding increase in cytoplasmic vacuolation. The pigment granules in the nerve cells of *Limax maximus* disappear entirely in advanced starvation, apparently with no shrinkage of the cell body or nucleus. The granules represent stored nutriment, probably comparable to the Nissl bodies. Legendre ('09) described in detail the various forms of degeneration observed in *Helix pomatia* after prolonged inanition and other nutritional disturbances. The cell changes are variable, including chromatolysis and cytoplasmic vacuolation.

Although hibernation represents a special condition not comparable to ordinary starvation, it may be noted that Cattaneo ('92) observed decreased ameboid activity in the blood cells of *Helix* during hibernation; and Erhard ('11) found a decrease in the glycogen droplets in the nerve cells and surrounding glia tissue. I have not been able to obtain the thesis by Bellion ('09), but Moglia ('10) and Legendre ('13) noted an apparent increase in the pigment granules of the nerve cells during hibernation.

The most extensive study of inanition in molluscs was made by Krahelska ('10, '12, '13). In her first ('10) paper, the losses in body weight were found subject to variation according to individuals and species (*Helix pomatia*, *Helix arbustorum*, *Helix fruticum* and *Leucochroa candidissima*), the total loss varying from 10.76—47 per cent or more. In general the loss during hibernation is much less than that during a corresponding period of inanition while awake.

After two months of starvation, the kidneys of *Helix arbustorum* show marked histological changes. The cytoplasm of the epithelial cells becomes greatly reduced in amount and often syncytial in character, being homogeneous, finely fibrillated or vacuolated (beginning degeneration). It also shows enlarged concretions in vacuoles. The nuclei are sometimes enlarged and vesicular, sometimes almost pyknotic. After four months, these changes are more pro-

nounced; all nuclei are now small and variably pycnotic. The changes during hibernation are somewhat similar, but slighter, and there is no cytoplasmic atrophy, probably because of the preparatory period preceding hibernation.

Krahelska later ('12, '13) studied thoroughly the histological changes in the albuminous gland (accessory gland of the hermaphroditic sexual duct) of *Helix pomatia* and *Helix arbustorum* during inanition and hibernation. In *Helix pomatia*, during five or six months of total inanition, with loss of 40

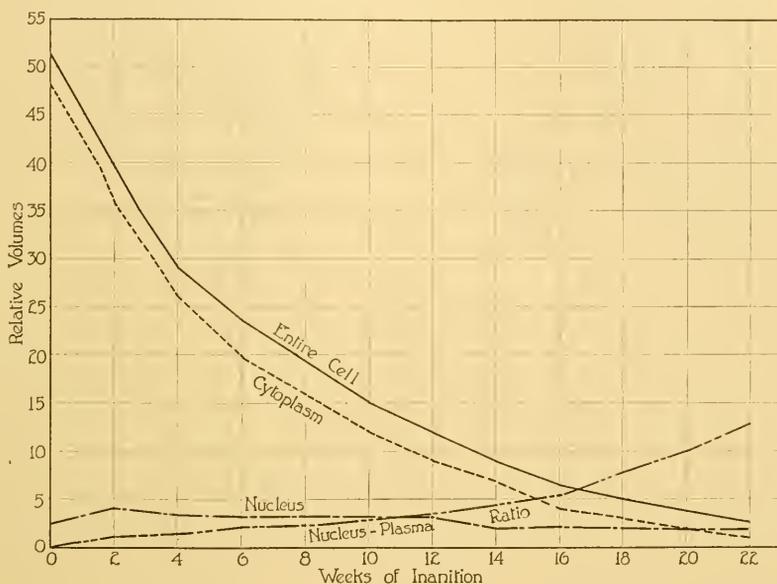


FIG. 26.—Chart showing the changes in the volumes of entire gland-cell, cytoplasm and nucleus, in the albuminous (accessory sexual) gland of the snail, *Helix pomatia* during inanition up to a period of twenty-two weeks. (From Krahelska '13.) The volumes were estimated by projecting the magnified cells in sections upon paper, and measuring the corresponding average areas of cell, cytoplasm and nucleus. There is a marked and progressive decrease in the entire cell and the cytoplasm. The nucleus decreases but slightly, however, which causes a marked rise in the nucleus-plasma ratio.

per cent (or more) in body weight, the non-glandular sexual ducts are not greatly atrophied, but the albuminous gland undergoes reduction to about one-half in length. The color of the gland also changes from milk-white to yellow, later orange-brown. The individual gland-tubules show marked atrophy (Fig. 27). The corresponding progressive decrease in the size of the cells, together with changes in the relative amount of nucleus and cytoplasm, are shown in Fig. 26. It is evident that the cytoplasm decreases much more rapidly than the nuclei, resulting in a marked increase in the nucleus-plasma ratio. The "parenchyma" (stroma) nuclei, which at first are only half as numerous as the glandular epithelial nuclei (in a given field) proliferate by amitosis and become more abundant, finally becoming almost equal to the glandular nuclei in number.

The cytoplasmic changes during inanition (Figs. 27, 28, 29, 30) may be roughly classified in two stages. (1) During the phase of "reduction," the cells become undifferentiated, and return to a somewhat embryonal condition (Fig.

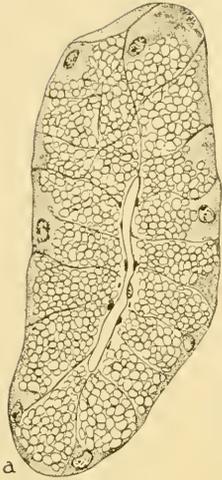


FIG. 27.

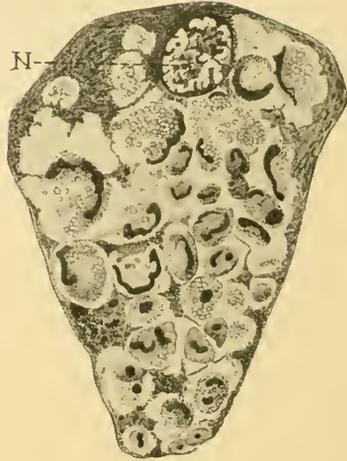


FIG. 28.

FIG. 27.—Cross sections of two gland-tubules from the albuminous (accessory sexual) gland of the snail, *Helix pomatia*; to show the effect of inanition. (From Krahelska '13.) *a*, section of a normal gland tubule; bases of the cells external, with nuclei and granular cytoplasm; the vacuoles in the cells correspond to the secretion granules; lumen lined by a flattened syncytial layer. *b*, corresponding section of a gland-tubule after about five months of starvation. Tubule and constituent cells greatly reduced in size; cells fused into a syncytial mass, enclosing the deeply-staining, pycnotic nuclei.

FIG. 28.—Normal gland cell from the albuminous (accessory sexual) gland of the snail, *Helix arbustorum*. (From Krahelska '13.) This corresponds to a single cell of those shown in Fig. 27*a*, but more highly magnified ( $\times 800$ ). The nucleus, *N*, is at the base of the cell; the cell body is largely composed of vacuoles enclosing secretory granules and their associated "chromatoplasts" (chromidial apparatus).



FIG. 29.

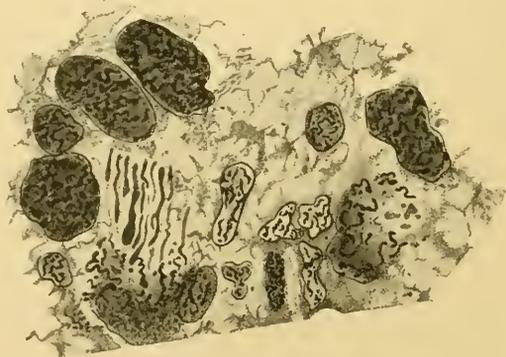


FIG. 30.

FIG. 29.—Three gland cells from the albuminous (accessory sexual) gland of the snail, *Helix pomatia*, after eight weeks of starvation. (From Krahelska '13.)  $\times 800$ . The nuclei are hyperchromatic but slightly changed in size; while the cytoplasm is greatly reduced in volume. Two of the cells contain a large vacuole, enclosing granular remnants of the secretion-granules and associated structures.

FIG. 30.—A portion of a gland-tubule from the albuminous gland of the snail, *Helix pomatia*, after twenty weeks of starvation.  $\times 800$ . (From Krahelska '13.) Degenerative stage, the nuclei of gland cells and stroma being intermingled in a scanty vacuolated degenerated mass of cytoplasm. Many cells show necrosis, with disintegrating nuclei.

29). The secretory granules undergo a progressive absorption, and the "chromatoplasts" (chromidial apparatus, etc.) undergo regressive changes. This phase occupies about two months. Then follows (2) the phase of degeneration, with syncytial cell-fusion, karyorrhexis and pycnosis. These are destructive changes leading to necrosis (Fig. 30).

If the ordinary room temperature (17°C.) is increased to 32°C., the inanition changes usually requiring four months are attained in three weeks. Changes very similar to those during inanition appear also as a result of functional exhaustion at the end of the normal egg-laying period. No structural changes occur in the gland during hibernation, unless artificially prolonged. In a snail richly fed for two days after five months of starvation, evidences of recuperation were found already beginning in the gland cells.

**Pelecypoda.**—Sorg (1805) noted death from starvation in 18 days in *Mya pictorum*. Mead ('00) made a few incidental observations indicating that the relations of growth and nutrition in the clam and oyster are similar to those already mentioned for the starfish. Maas ('07, '12) noted that in Ca-free water the calcareous substance in the shells of young mussels (species not stated) may be resorbed without injury to the soft parts. Schultz ('08b) found that during inanition, in filtered water, the young mussels *Mytilus* (like the starfish) cease to grow, but undergo no "reduction" to embryonal type and die in about three weeks. Sections show no important changes. "Die Verdauungsorgane erleiden natürlich während des Hungers die ersten Veränderungen, und die Zellen der Leber, z.B., verschmelzen und bilden ein Syncytium."

### TROCHELMINTHES

The effects of inanition in the rotifers (wheel animalcules) have been studied chiefly in their relation to reproduction and sex. Leydig noted that when rotifers are kept a few days in water without food, the ovary shrinks, and the granular yolk-mass almost entirely disappears. All such individuals produce winter eggs. Regarding the effects of nutrition upon sex, he concludes: "Wenn wir sehen, dass bei Aphiden, Daphniden, Rotatorien, Männchen unter dem Einfluss allgemeiner Ursachen, als da sind Nahrung, Wärme und Kälte, zum Vorschein kommen, so haben wir einstweilen einen Anhaltspunkt zu der Vermuthung dass die Differencirung des Geschlechts auch in anderen Gruppen ähnlichen allgemeinen Einwirkungen unterworfen sein könne."

Nussbaum ('97) concluded: "Bei *Hydatina senta* bestimmt während einer gewissen Entwicklungsphase die Ernährung das Geschlecht des ganzen Geleges eines jungfräulichen Weibchen. Wird das auskriechende Weibchen bis zur Reifung seines ersten Eies gut ernährt, so legt es nur weibliche Eier; wird es bis zur Geschlechtsreife mangelhaft ernährt, so legt es nur männliche Eier. Vor und nach dieser Periode hat die Ernährung auf das Geschlecht keinen Einfluss." Nussbaum's results were confirmed by Lenssen ('98), but opposed by Punnett ('06), who concluded that the sex is due to internal factors, unaffected directly by food or temperature.

Whitney ('08) likewise obtained negative results with *Hydatina senta*. Temperature has no influence upon sex-determination (versus Maupas), and "starving the young females for the first few hours after they hatch does not cause them to produce a higher percentage of male eggs."

Shull ('10, '11) after careful and extensive experiments upon *Hydatina senta* concluded that while sex-production is dependent upon both internal and external factors, the *quantity* of food probably has no influence in this respect. Starvation may be accompanied by an increased proportion of parthenogenetic male-producers, but this is probably only an indirect effect, due to a decrease in certain substances incidentally introduced by the food. Thus the question as to the effect of nutrition upon sex-production in rotifers still remains somewhat uncertain.

#### ARTHROPODA

In the phylum Arthropoda, the effects of inanition have been studied most extensively in the class Insecta. There have also been numerous observations upon the Crustacea, and a few on the Myriapoda and Arachnida.

**Crustacea.**—The investigations in this class have included both the subclasses, Malacostraca and Entomostraca, and those in the latter group will be considered first. The Entomostraca, like the rotifers, have attracted attention on account of the apparent effect of inanition upon sexual reproduction. Leydig included the water flea *Daphnia* among the forms in which sex is determined by external factors, including nutrition. Kerhervé ('92) claimed that *Daphnia magna* is parthenogenetic during abundant nutrition, but is quickly transformed into sexual reproduction by unfavorable conditions, especially by inanition. Cuénot ('94) noted a similar condition in *Moina rectirostris*. Issakowitsch ('05) in *Simocephalus vetulus* found that sexual reproduction is induced during the asexual stages by either low temperature or inanition. Woltereck ('08, '09, '11) admits the hereditary cycle in daphnids, but claims that in *Daphnia longispina* a peculiar variety of different body form is produced by unfavorable environment, chiefly by malnutrition. The effects of environmental factors apparently may be hereditary in *Daphnia longispina* and in *Hyalodaphnia cucullata*. The external factors affect sex only in the "labile period" and then only indirectly, through influence upon the internal mechanism of sex-production. Finally McClendon ('10) concludes that "The life cycle of a Daphnid is therefore an hereditary tendency but can be influenced by nutrition and probably by temperature and the accumulation of excretions."

On the other hand, Green ('19) has recently made careful and extensive experiments upon *Simocephalus vetulus*, concluding that: "The sexual state is probably determined in the ovary of the preceding generation. There are almost certainly predisposing factors in the environment but it is not certainly known what they are. Food or lack of food does not offer a sufficient explanation." It would therefore appear that among the Entomostraca, as already noted for the rotifers, the effect of inanition upon sex-production is still an open and uncertain question.

Kerb ('10) found that *Daphnia* during starvation may undergo repeated ecdysis, moulting in spite of rapid decrease in body weight (from 105-111 mg. to 24-28 mg. in 11 days). Lipschütz ('13) cites similar observations by Knörrich ('01) and Wolff ('10).

Among the Malacostraca, Haller (cited by Lucas, 1826) stated that the crab, *Cancer maurinus*, can endure a starvation period of eighteen months. Mead ('00) noted incidentally that the relations of nutrition and growth in the lobster (*Homarus*) are similar to those already stated for the starfish. Prziham ('07) described the regeneration of appendages in certain Crustacea (*Trypion spongicola*, etc.) and concluded: "But not only may the means of regeneration and compensation be clearly shown to occur in this case but also reduction is involved to an appreciable degree, especially if the crayfish is starved during the experiment. Then each moult shows the shedding of a smaller skin and the animal is at the end of the transposition in all dimensions smaller than at the time of the operation."

Irvine and Woodhead ('88, '89) experimented with common edible shore crabs (*Cancer*) which, after ecdysis, were placed in artificial sea-water. They were found able to obtain the calcium carbonate necessary for the calcareous exoskeleton when  $\text{CaCl}_2$  is the only calcium salt present in the sea-water, but cannot utilize  $\text{CaSO}_4$  for this purpose. J. Loeb ('11) found that the marine *Gammarus* dies quickly in distilled water, even when made isotonic by addition of sugar solution. The addition of  $\text{NaCl}$  alone, or of  $\text{KCl}$  and  $\text{CaCl}_2$ , is insufficient; but if all three salts are added in proper strength, life is made possible. Loeb's theory of the action of the salts in such cases has been stated in connection with the Echinoderms.

Brunow ('11) in a biochemical study of the crayfish *Astacus fluviatilis* found the loss in body weight proportional to the length of inanition, decreasing from 19.16 g. to 17.47 g. (loss of 8.8 per cent) in 70 days, and to 16.26 g. (loss of 15.1 per cent) in 140 days. Morgulis ('23) found but 3 per cent decrease in the body weight of the lobster (*Homarus*) after 56 days of starvation, and cites observations (by Moore and Herdman) showing no loss in weight after eight months of fasting, the loss in dry substance being masked by absorption of water.

**Arachnida.**—Lucas (1826) observed that the spider *Epeira phalangoides* lived one and one-half months without food, while Haller noted a period of several months for *Epeira Walk*. According to Lucas, De Geer found an apparent increase in the weight of *Epeira diodema* kept one month without food in 78 cubic inches of air. Treviranus gave 18 months as the starvation period for *Scorpio europaeus*. Morgulis ('23) cites reports by Blackwell of 17 months of starvation for spiders, and by Jacquet of 368 days for scorpions.

**Myriapoda.**—Plateau ('78) observed circular constrictions of the intestine in the Myriapod *Julius* starved 15 days. Childs ('21) starved *Parajulus* for 13-42 days and obtained results somewhat resembling those of Needham ('97) on dragon-fly nymphs. "Prolonged absence of food matter from the midgut of *Parajulus* causes more or less irregular thickenings of the epithelium which give the margin of the lumen a wavy contour and are attended by a reduction in the thickness of the brush border. These thickenings are caused by the inhibition

of the tendency toward senescence and discharge on the part of the mature cells, coupled with continued reproduction and growth on the part of the regenerative cells."

Cattaneo ('92) observed that in the Myriapod *Glomeris*, as in the snail *Helix*, the ameboid activity of the blood cells appears decreased during hibernation.

#### INSECTA

Baumberger ('19) concluded that growth of insects in general may be limited by lack of protein. More or less extensive observations upon the effects of inanition of various types upon insects have been made upon all of the principal orders, excepting the Aptera.

**Orthoptera.**—According to Lucas (1826), Vaillant noted a starvation period of five months in the grasshopper, "eine grosse Heuschrecke" (Sp.?). Sanford ('18) noted that the cockroach *Periplaneta orientalis* may endure starvation for three weeks; or even two months or more if the crop is distended with food. The epithelium of the crop may absorb and store large globules of fat which are slowly absorbed during inanition. Bodine ('21) found that the grasshopper *Melanoplus femur rubrum* endures total starvation without water 73 hours, or with water, 144 hours; the loss in body weight being 30–35 per cent. *Melanoplus differentialis*, a large species, endures 96 hours without water, or 172 hours with water; loss in body weight, 20–25 per cent. Quiescent nymphs of *Chortophaga* live without food for about two weeks at 0°–9°C., one week at 23°, but only three or four days at 38°; the maximum loss in body weight at death being 20–25 per cent.

**Neuroptera.**—Lucas (1826) observed death from starvation in *Hemerobius* (Perla) after two days; in *Perla bicaudata* after two and one-half days; in *Agrion* (Fabr.) Virgo after four days; and in *Nemoura* (Latr.) *nebulosa* after seven days. Needham ('97) studied the midgut epithelium of dragon-fly nymphs, and found that after two months of fasting the columnar cells increase three-fold in height. The striated border has mostly disappeared, and the cells are filled with secretory granules. The small cells in the depressed cell-nests increase in number, and appear to be centers of regeneration for the surface epithelium. Slowtsoff ('04) found that the *Libellulidae* (dragon-flies) die after only 60–84 hours of total inanition, with excessive loss of water, which perhaps causes the rapid death. The loss in body weight averages 22.55 per cent.

According to Grassi, among the Termites ("white ants") the development of workers and soldiers is regulated by the character of the nutrition.

**Hemiptera.**—Dufour (1833) found that the bedbug (*Cimex lectularius*) may live for a year in a closed vial without taking food. In a Brazilian species, *Conorhinus megistus*, Neiva ('10) observed a female specimen which had been alive 57 days in a tightly closed box. According to Weber ('14): "Von der Bettwanze wird angegeben, dass sie in den Bettvorhängen eines 6 Jahre lang unbewohnten Zimmers angetroffen wurde, blattdünn und fast durchsichtig." Riley and Johannsen ('15) noted that the ability of the bedbug

to endure starvation is one factor explaining the long periods in which deserted houses and camps may remain infected.

Among the plant-lice (*Aphidiidae*), as in the case of the rotifers and daphnids, the effects of inanition have been studied chiefly in their relation to sexual reproduction. Kyber (1813) noted that male forms result from underfeeding, a result apparently confirmed by Leydig and others. Göldi ('85) found that withdrawal of food results in the appearance of the winged forms in *Pemphigus xylostei*, *Pemphigus bumeliae* and *Lachnus*. Thus even in June the winged forms of *Schizoneura lanigera* are obtainable, leading directly to the sexual generation. Keller ('87) and Behr ('92) observed that also in the grape-louse, *Phylloxera vastatrix*, deficiency of food causes cessation of parthenogenesis and the appearance of the sexual, winged forms, containing males as well as females. According to Keller ('87), this confirms the theory of Landois and Düsing as to the relation of nutrition to sex, the males appearing only under unfavorable conditions.

**Diptera.**—Cuénot ('99) found that in the maggots of flies the sex-ratio is not materially affected by the quality or quantity of food. Tangl ('09) found that in fasting larvae of *Ophyra cadaverium*, the metabolism is chiefly at the expense of the fat. Starvation of the larvae retards the process of metamorphosis. In connection with a study of the chromidia, Popoff ('10) noted changes in the fat cells, "oencytes" and pericardial cells of the housefly during feeding and inanition. Guyénot ('13, '13a, '13b, '13c) made a series of studies upon the relations of nutrition and reproduction in the fruitfly, *Drosophila ampelophila*. If the larvae are reared on sterilized potato, instead of yeast, they undergo metamorphosis but with atrophic gonads, sexual maturity being markedly retarded. The eggs laid by such abnormal forms are few in number and give rise to weak and short-lived larvae. In the second article ('13a), it was shown that the fecundity depends upon the environment, not only of the larvae, but also of the pupae and the adult fly. *Drosophila* is thus intermediate between these insects (certain butterflies) whose sexual maturity is determined entirely by larval nutrition, and those (*Calliphora*) where the sexual maturity is not so affected and depends almost entirely upon adult nutrition. Later ('13b) it was shown that when adult females are placed on poor nutriment (potato or carrots) the eggs become abnormal and greatly reduced in number. "Après avoir pondus quelques oeufs, donnant des larves, les femelles pondent quelques oeufs dans lesquels se forme un embryon, généralement anormal, qui meurt à un stade plus ou moins avancé." Later the malnourished females lay unfertilized ova, even when conjugation with the male occurs, the spermatozoa apparently being resorbed in the seminal receptacle of the female. Finally, Guyénot ('13c) demonstrated that the process of egg deposition is, in part, determined by the nutritional conditions.

Further studies on the nutritional relations of the fruitfly (banana-fly) *Drosophila* were made by J. Loeb ('15, '15a) who grew five successive generations on a solution of glucose, cane sugar, ammonium tartrate, citric acid, dipotassium phosphate and magnesium sulphate. Bacteria and yeast were not excluded, however. Loeb and Northrop ('16), by special precautions, reared

twelve completely sterilized generations on a nutrient solution containing baker's yeast and citric acid. In many experiments on other media (e.g. filter paper plus cane sugar and salts; likewise with addition of casein, edestin, egg albumin, milk or a mixture of aminoacids), the larvae attained normal size, but did not undergo metamorphosis. Sterile flies, grown on sterile bananas or potatoes, show no sexual development. Yeast is apparently the only adequate food for these flies. Loeb and Northrop ('17) and Northrop ('17) found that, unless yeast is added, growth of *Drosophila* ceases on aseptic cultures and that by inadequate feeding during the larval period the total normal duration of life of nineteen days may be prolonged up to twenty-nine days. The length of life of the imago is not affected by the earlier period of malnutrition.

Baumberger ('19) concluded that "*Drosophila* living in fermenting fruit are dependent for their food supply on the synthetic and absorptive powers of yeast cells. In a similar manner, my study of the relation of *Musca domestica* to manure, of *Desmometopa* to decaying meat, and of *Sciara* and *Tyroglyphus* to decaying wood shows clearly that these Arthropods also feed on microorganisms." Both adults and larvae of *Drosophila* require sugar as food, but cannot live on sugars or nucleoproteins alone. Since *Drosophila* can be reared normally on yeast nucleoprotein, sugar and salts, any "special substance" required must be present in this mixture. The larvae can be maintained for a long time on a minimum of protein (banana diet) at constant or slowly increasing size, and may later develop to normal size on adequate (yeast) diet. The total span of life may therefore be increased eleven days to forty days of more. There is a tendency for the larva to pupate after a certain length of time, whether it reaches the maximum size before this period or is still undersized from malnutrition.

Pearl and Parker ('24) made an extensive experimental study of the duration of life in *Drosophila melanogaster* during complete (total) inanition. The mean duration is slightly less than two days. The duration in the females is more variable than in the males, both absolutely and relatively, but in both sexes the variability is relatively much less than during full feeding. The females are longer lived than the males, during inanition as well as when full fed. Although the normal wild-type flies during full feeding live about three times as long as the vestigial type, during total inanition the mean duration of life is nearly the same in both types. The genetic significance of these results is discussed.

Vinokuroff ('22) found the mean duration of life in the common housefly (*Musca domestica*) to be 1.3 days when starved without water, or 1.8 days on water alone. Similar observations were made by Glaser ('23).

**Lepidoptera.**—Lucas (1826) noted death from starvation in the moth *Bombyx* in three days; in another case (*Bombyx cerura* Schrank) in 15 days, in June. In the saturniid moths, which normally take no food in the imaginal stage and live only about eight days at ordinary temperature, Rau and Rau ('12) found the duration of life extended to about 18 days at low temperatures.

Semper ('81) stated that T. Gentry of Philadelphia, found underfed larvae of *Acronyeta* (sp.?) produce smaller pupae and moths. Von Linden ('07) observed that one specimen of adult *Hylophila prasinana* lost 43 per cent of its body weight

in 11 days of starvation; another lost 70 per cent in 17 days; while a larger *Papilio podalirius* lived only ten days with loss of 29 per cent. The loss of the corresponding pupae is much less, being only 7.8 per cent for the *Hylophila* in 30 days. The loss is relatively greatest in the latter part of the fasting period for the pupae, but in the earlier part for the imago. Kellner ('87) noted a slight prolongation of the larval stage in underfed silkworms (*Bombyx mori*). Kellogg and Bell ('03) found that underfeeding the larvae in this species causes dwarfing of the moths, the effect being decreasingly evident in the second and third generations. They further ('04) noted that starvation of the larva one to four days does not affect the time of metamorphosis, or the size or fertility of the moth. Starvation of four to seven days, however, reduces the last intermoult stage, resulting in a normal (though smaller) cocoon and moth. Death occurs if the larva is starved eight days or more. The cocoon loses about four per cent of its weight on the first day. The pupa loses slightly but steadily during the pupal period (2-10 days), with total loss of about 14 per cent. In the Tent caterpillar (*Clisiacampa*) and the Mourning-cloak butterfly (*Ewanessa antiopa*) the loss is steady but greater, amounting to 35 and 65 per cent, respectively. Kopec ('24) during intermittent starvation of the larvae of the moth, *Lymnantria dispar* L., found a considerable prolongation of the larval life with a slight abbreviation of the pupal period. The body weight is decreased and the adipose tissue exhausted. Kopec ('24a) further noted that when the female moths derived from starved caterpillars are mated with normal males, the eggs laid are reduced in number but apparently develop normally. The spermatozoa of the male moths from starved caterpillars appear normal, and are capable of fertilizing normal eggs, but the resultant larvae show a higher mortality and the pupae appear dwarfed. Thus inanition is more injurious to the male than to the female.

As to the effects of inanition upon the sex of butterflies, Treat ('73) found a larger proportion of males resulting from underfeeding the larvae of *Papilio asterias*, *Vanessa antiopa*, and *Dryocampa rubicunda*. Poulton ('93) found no evidence to indicate that the sex in *Smerinthus populi* can be determined by external conditions. "It may be admitted that the larger female larvae require more food, chiefly to prepare for the amount of material to be stored up in the ova. It would not therefore be at all surprising if the female larvae were starved before the males when a minimum food was supplied." Cuénot ('99) cited the negative results of Riley, Bessels, Briggs, Andrews and Fletcher in starvation experiments on butterfly larvae. Kellogg and Bell ('04) likewise obtained no evidence that underfeeding the silkworm larvae produces an excess of males, although they ('03) found fertility greatly reduced. Kopec ('24a) obtained similar results.

In the underfed silkworm larvae, Kellogg and Bell ('03) also found great individual variation in the resistance to inanition. The time required for metamorphosis is abnormally prolonged, usually with five moults instead of four, and the silk-production is greatly reduced. Pictet ('05, '05a) also found in malnourished butterflies a prolongation of the larval period, with shortening of the pupa period. There is also an imperfect pigmentation of the imago, which

increases with each generation and may persist for a time even after abundant refeeding.

**Coleoptera.**—Great variations have been observed in the time required for death from starvation in various beetles. Sorg (1805) noted six days for *Chrysomela populi*, 13 days for *Dermestes lardarius* and *Cerambyx fuliginator*, and 36 days for *Lampyrus noctiluca*. Fingerhuth (cited by Lucas, 1826) found two days in *Coccionella 14-guttata*, three days in *Calandra granaria*, five days in *Curculio scrophularia*, six days in *Melolontha horticola*, nine days in *Carabus auratus* and *Cicindela campestris*, 14 days in *Geotrupes* Latr. (*Scarabaeus stercorarius*), 27 days in *Lucanus cervus*, and one month in *Cetonia aurata*.

Wodsealek ('17, '21) observed a remarkable endurance in the larvae of *Trogoderma tarsale* kept without food at constant room temperature. Newly-hatched specimens, about one millimeter in length, lived four months; older and larger larvae lived progressively longer, the maximum for full-grown (8 mm. in length) being over six years. The larvae gradually decreased in size during inanition. They usually dwindled to the hatching size of one millimeter before death, representing for the larger larvae a decrease to  $\frac{1}{600}$  of the original mass. In the latter paper ('21) it is stated: "In another experiment groups of specimens varying in size from 2–8 mm. in length are undergoing periods of feasting and fasting. The larvae in various stages of starvation when given plenty of food again begin to grow in size. For example, some of the large specimens are on their way to their fourth "childhood" after having attained the maximum larval size four times; while specimens originally 4 mm. in length are on their way to their ninth "childhood" after reaching 4 mm. eight times."

According to Chapman ('20), "*Tribolium confusum* has its egg stage shortened from ten to five days by a rise from 24° to 34°, and it will develop one generation after the other throughout the year. On the other hand, the life cycle may be prolonged by a reduction of the amount of moisture and also by a limitation of the quantity or quality of the food. Thus the length of life and the number of broods may be altered by changing any one or all of these three factors. A larva now under observation has had its life prolonged from thirty to ninety days due to food conditions, and during this time it has moulted twelve times rather than the normal six times."

Biedermann ('98) found that certain intranuclear particles ("Kernkristalloide" of Frenzel) in the midgut epithelial cells of the meal-worm, *Tenebrio molitor*, become smaller and finally disappear during starvation. Similar cytoplasmic granules, crystalline or irregular in form, decrease but never disappear, even after prolonged starvation. Kriznecky ('14) and Szwajsówna ('16) observed that in this species starved larvae undergo metamorphosis earlier.

Slowitzoff ('03) noted in May-beetles on absolute inanition a loss of about 24 per cent in body weight. The daily loss is greater at first (2.39 per cent), then sinks to a minimum (0.66), with a premortal rise. *Geotrupes stercoralis* loses 21.73 per cent in body weight during starvation of five to eleven days. The studies of Fatta and Mundula ('08) and Manca and Fatta ('03-'04, '05) were inaccessible.

**Hymenoptera.**—Lucas (1826) cites Trembley ("Biologie") as authority for the statement that "Die Insecten-geschichte gibt uns Beispiele von Bienen, Ameisen, verschiedenen Raupenarten von Würmern, Schmetterlingen und Fliegen, welche ganze Monate ohne die geringste Nahrung hinbringen." This probably refers to the period of dormancy or hibernation, however, as perhaps likewise the period of one year noted by Reaumur for the wasp, *Vespa vulgaris*. Lucas himself found the following periods required for death from starvation: ant, *Formica fusca*, two days (in May); bee, *Apis terrestris*, three days; *Apis mellifica*, four to six days or more (in June); *Vespa vulgaris*, eight days. Slowt-zoff ('04a) observed that the bumble-bee, *Bombus terrestris*, dies after only 24-48 hours of absolute inanition, with loss of about 24 per cent in body weight. The loss is chiefly in water content, which is considered the cause of death.

The effect of the nutrition upon sex-development in the Hymenoptera has attracted much attention. Von Siebold observed in the wasp, *Nematus ventricosus*, a progressive increase in the percentage of females during the spring and summer, probably due to the effects of increased warmth and food. In the honey-bee (*Apis mellifica*), however, it is well known that sex is determined by fertilization, the unfertilized eggs producing the males (drones). If larvae from the fertilized eggs are well-fed with the "royal diet," they become queens, with functional reproductive tract; but if fed with the less rich, ordinary diet, they become workers, with rudimentary reproductive tract. According to Von Planta the "royal diet" is relatively twice as rich in fats as the ordinary diet, though slightly poorer in glucose and protein. The drones are males resulting from unfertilized eggs and are not due to difference in the diet.

Eimer ('88) concluded that "Geschlechter giebt es in der Hummelfamilie nur zwei: Männchen und Weibchen, denn die kleinen und grossen Arbeiter sind nichts als in Folge von schlechteren Ernährung, vor Allem der mangelnden Honigfütterung während des Larvenlebens, geschlechtlich unvollkommen entwickelte Weibchen." Attempts to determine sex by nutrition of the honey-bee larvae have been unsuccessful (Dalla Torre, '10).

Popovici-Bazosanu ('10) observed that among the bees *Osmia rufa* and *Osmia cornuta* a greater amount of food is deposited in the cells of the larvae producing females than in those producing males. Experimental removal of a portion of this food resulted in a marked reduction in the size of the adult bees, both male and female.

Among the ants (Formicidae), according to Emery ('94), the females, like those of termites and bees, exhibit a remarkable "Nahrungspolymorphismus." In this case, the *quality* of the food apparently determines whether the larva shall become queen or worker. There are, moreover, two different kinds of workers, small and large, probably determined by the *quantity* of food supplied. In some species, there are intermediate stages between the large and small workers. O. Hertwig ('20) adopts Spencer's theory that these intermediate forms may depend upon the developmental stage at which the larvae are subjected to inanition. Apparently no experimental evidence upon this question is available.

## UROCHORDA (TUNICATA)

A few observations have been made upon inanition among the Tunicates, a sub-phylum of the Chordata, closely related to the Vertebrata. Herbst ('97), in connection with his study of the effects of various salt deficiencies upon the development of Echinoderms and other organisms, noted that in *Phallusia mammillata* and *Ciona intestinalis*, "Die Furchung geht also bei Ascidiën auch in phosphorfreiem Medium vor sich, für die spätere Organbildung und deren Ablauf ist aber die Phosphorzufuhr von aussen unentbehrlich." The Ascidian ova thus appear to have an unusually large initial supply of phosphorus. The tendency to loosening of the intercellular substance, resulting in the detachment of the cells as a result of calcium deficiency was also noted (among other forms) in the larvae of *Ciona intestinalis* by Herbst ('00). Schultz ('07) found that the "reduction" phenomena during regeneration in *Clavellina lepadiformis* resemble those produced by inanition, since the regeneration process withdraws nutriment from the remainder of the organism.

## PART II

# THE EFFECTS OF INANITION UPON VERTEBRATES

The second part of the present work concerns the effects of inanition upon vertebrates, including man. The general effects upon the body as a whole will be considered first, followed by chapters upon the various systems and organs of the vertebrate body. In general, each organ or part will be considered in relation to the effects of (*A*) total inanition, or on water alone; or (*B*) the various forms of partial inanition (deficiencies in protein, salts, vitamins, etc.). As previously noted, subsistence on water alone, although by definition a form of partial inanition, is for convenience considered with total inanition, on account of their similarity in effects.

### CHAPTER IV

#### EFFECTS OF INANITION ON THE BODY AS A WHOLE

The effects of inanition upon the vertebrate body are of great interest and importance in relation to the corresponding conditions met in human famine and disease. The general effects will first be summarized briefly, followed by a more detailed consideration of the data.

#### SUMMARY OF THE EFFECTS OF TOTAL INANITION ON THE BODY AS A WHOLE

The **duration of inanition** among vertebrates (as in invertebrates) varies exceedingly, ranging from a few days in small birds and mammals to possibly years in some reptiles. In general, the period of endurance is greater if water is allowed; in larger and older than in smaller and younger animals; in carnivora than in herbivora; and in cold-blooded than in warm-blooded animals. An increased amount of stored food reserves, especially of fat, increases the endurance, while exercise and cold are unfavorable. In general, all factors are effective in proportion to their influence upon metabolism. Also the duration of human disease is often limited by the capacity to withstand the inanition involved.

The relative **loss in body weight** during inanition is subject to less variation, the maximum averaging about 40 per cent (range 30–50 per cent), as shown by Chossat ('43) and many later observers. The loss in general is less in younger and greater in fat animals, and is also somewhat variable according to the type of inanition, species and environment. The curve of loss in body weight is logarithmic in type, resembling an inverted growth curve. The head loses

relatively less than the remainder of the body, and hence becomes relatively larger. These rules in general apply likewise to conditions of human malnutrition.

The **embryonic** vertebrate is usually protected from inanition through storage of nutriment in the egg of oviparous forms and through sacrifice of the maternal organism in mammals. Starvation of the pregnant mother must be very severe in order to reduce the birth weight of the offspring. Attempts to reduce the size of the human fetus by restriction of the diet during pregnancy therefore appear generally impracticable.

Even under relatively normal conditions, there is a large amount of malnutrition among **children**, and this is greatly increased by the conditions of war and famine. The best simple physical **index of nutrition** (with the possible exception of Bornhardt's index) is probably the weight:height<sup>3</sup> ratio, but this is normally variable, even in individuals of the same age and race. Such indices may serve a useful purpose in directing attention to suspicious cases, but require confirmation by clinical evidence.

During "physiological inanition," certain **growth changes** may proceed in the body of young vertebrates, as illustrated by the salmon during migration, by amphibia during metamorphosis and by the human infant during the post-natal loss in weight. In various mammals (including man), despite under-feeding or malnutrition sufficient to prevent increase in weight, there is a persistent tendency to growth in certain parts (especially skeletal) at the expense of others, resulting in **dystrophic growth** with characteristic abnormal proportions, the body being elongated and the head enlarged. These dystrophic growth changes are contrary to Liebig's "law of the minimum," if strictly interpreted.

**Recovery from inanition** is generally possible, unless extreme stages have been reached. Recuperation under proper nutritional conditions is especially rapid in the young, but permanent stunting or dwarfing with failure to attain normal adult size may occur when the inanition has been severe or prolonged, and especially when occurring at a very early age. The conditions limiting the possibility of recovery from inanition and malnutrition are of practical importance in human medicine.

#### EFFECTS OF TOTAL INANITION, OR ON WATER ALONE

The topics considered under this heading include the duration of inanition, the effects on body weight in adult and young, nutritional indices, dystrophic growth, changes in adult proportion (head, trunk and limbs), and recovery upon refeeding. The effects of partial inanition will be discussed in the next chapter.

**Duration of Inanition.**—That different animals exhibit marked variations in their resistance to inanition has long been known and the earliest experiments were concerned chiefly with this feature. Many of the earlier observations (by Redi, Spallanzani, Haller, Blumenbach, and others) were compiled by Lucas (1826), whose data for invertebrates have been noted in the previous

chapter. The periods of endurance for vertebrates (usually for inanition with water) are stated by him as follows:

Fishes: *Esox lucius*, 2 months; *Cyprinus carpio*, 50 days.

Amphibians: *Rana* (sp.?), 1 year. *Bufo* (sp.?) 4 months to "several years;" *Salamandra* (sp.?), 6 months to 1 year; *Proteus* (sp.?) over 2 years.

Reptiles: *Testudo terrestris*, 18 months; *Lacerta africana*, 8 months; *Lacerta crocodil.*, 8 months; *Lacerta muralis*, 1½ months; *Lacerta lacustr.*, 2-3 months; *Chamaeleon* (sp.?), 1 year; *Coluber vipera*, 6-10 months; *Chamaeleon cerastes*, 5 years; *Vipera vulgaris*, 10-12 months; *Vipera caudisona*, 5-6 months.

Birds: *Vultures*, 11-21 days; *Aquila regia*, 21-28 days; *Falco mulvus*, 18 days; *Cuculus canorous* (young), 3 days; *Fringilla canaria*, 3 days; *Fringilla cacebs*, 3 days; *Fringilla domestica* (10 days old), 16 hours; same (14 days old), 27 hours; same (adult) 3 days; *Columba oenas* 2-13 days; *Phasianus capo* (total inanition), 5-9 days; same (on water only), 20-24 days.

Mammals: *Antilope* (sp.?) 20 days; *Viverra Zibetha*, 10 days; *Canis familiaris* (nursing puppy), 3 days; same (adult), 25-39 days, *Canis lupus*, 5 days; *Felis catus*, 25-39 days; *Sciurus vulgaris*, 2½-3 days; *Scavia porcellus*, 4-6 days; *Lepus cuniculus*, 8½-9 days; *Manis* (sp.?), 2 days.

For the *human species*, Lucas cites a long series of fasting cases of variable credibility, including the following: newborn child, 8 days; a boy, 5 days; girls, 11 days to 7 years (!); adult men, 5-71 days; adult women, 34 days to 10 years (!). Some of the longer periods are merely impostures or incredible legends of religious fanatics; some, however, refer to cases of insanity or other neural disturbances (cataleptic and similar states somewhat comparable to hibernation) in which a lowered rate of metabolism may render possible a period of inanition far beyond that possible in normal individuals. Reviews of the literature on long fasts are given by Hammond ('79) and Rochas ('02).

Since the publication by Lucas (1826), a large number of observations has accumulated in the literature concerning the endurance of various types of inanition by various species, some of which are mentioned later (Table 1). The weight of evidence indicates that for normal human adults the extreme limit of endurance, even under favorable circumstances and with water *ad libitum*, will rarely exceed 2 months. Several human fasts of 30 days or more will be mentioned later. The variations observed in fatal cases range from 24 days (Voelkel '86) to 72 days (Lussana '68). For total inanition the time is much shorter, ranging from 1-2 weeks (Birch-Hirschfeld '92), rarely more. In congenital atresia of the esophagus, death from inanition occurs in 3 or 4 days (Hirschsprung '61); and in complete duodenal atresia in 4-12 days (Theremin '77). Further data concerning periods of endurance of inanition in various species are cited especially by Bardier ('13), Beeli ('08), Chossat ('43), Colin ('73), Falck ('81), Fowler ('71), Rosenstern ('11), and Schaeffer ('98).

**Factors Involved.**—Some of the various factors influencing the duration of inanition may be mentioned briefly. As to the type of inanition, total inanition is usually fatal in a much shorter time than partial inanition, with water. In birds, however, there is usually but little difference. Other forms of partial

inanution, with deficiencies in proteins, salts, etc. may be endured for various (usually much longer) periods of time, to be mentioned later. As to age, the young are much less resistant than adults, as will be discussed later. Among animals, the carnivora endure inanition longer than the herbivora, the cold-blooded longer than the warm-blooded, and, in general large animals longer than small animals. Individuals with large amounts of stored food reserves, especially of fat, can endure starvation for longer periods. Exercise, exposure to extremes of temperature, infections, etc. are unfavorable factors.

In general, all factors are effective in proportion to their influence upon metabolism. An increased rate of metabolism will more rapidly exhaust the stored food reserves, or reduce them below the necessary minimum, with resultant death from starvation. On the other hand, a lowered rate of metabolism during inanition will prolong the period of endurance. This, together with the special provision of food reserves, makes possible the extensive periods of inanition during hibernation and some allied conditions of "physiological inanition" (*cf.* Alexandre '88, '89).

**Loss of Body Weight in Adults.**—For adult vertebrates a large amount of data is available upon various species for the loss in body weight during both total and partial inanition. Chossat ('43) established 40 per cent as the usual average of maximum loss in adult vertebrates, but recognized some exceptions and variations, as are apparent in Table 1. The range is usually between 30 and 50 per cent. On the whole, however, there is in the various classes of vertebrates comparatively little difference in the percentage of body weight which may be lost in extreme inanition. The most important factor is the amount of stored food reserves (especially fat). Many of the observed variations (for example, sex differences) are probably due to this factor; although Ott ('24) finds a lesser resistance in the female frog, in spite of the large ovarian mass available for resorption (Table 6). Larger species or individuals will usually endure a greater loss, while unfavorable environment (temperature, etc.) may produce death with a smaller loss of body weight. Kahan ('85) observed that in pigeons the daily average loss in weight increased with repeated intermittent fasts, but this was not confirmed by Seeland ('88) in rabbits or by Stewart ('16) in albino rats.

As to the course of the loss in body weight of animals during inanition, Chossat ('43) concluded that in birds the loss is greatest in the first third of the inanition period, least in the second third and intermediate in the last third. Bourgeois ('70) confirmed this for mammals. Moleschott ('59), however, found that the final acceleration of loss is variable or absent. Lazareff ('95) for 60 guinea pigs on total inanition found a progressive decrease in the daily loss rate, the average percentage loss for the eight successive days being roughly 9, 7, 6, 5, 4, 3, 3, 1.5. According to Rosenstern ('11) similar results were obtained by Finkler (pigeons), Kuckein (chicks), Richet (ducks), Rubner (rabbits), Pettenkofer, Luciani, and Laborde (dogs). For loss of body weight in various animals during hibernation, see Polimanti ('05, '13), Valentin ('57); Rulot ('01).

The data of Falck ('75) for dogs on total inanition may be taken as typical, and the curves for two adults are shown in Fig. 31. Morgulis ('23) shows similar curves for fasting dogs, based on Avrovov's data.

In the human adult, no accurate data are available as to loss of weight during total inanition. On water alone, a loss of about 40 per cent may occur before death, according to Bright ('77), Duflocq (*cf.* Fernet '01) and Meyer ('17). In about 400 autopsies on victims of the Madras famine of 1877-8, Porter ('89) estimated that about 86 per cent of the men and 83 per cent of the women had lost one-third or more in body weight, emaciation being the most outstanding symptom.

The loss in body weight in many of Porter's cases was partially masked by dropsy or "hunger edema," a condition which has been noted frequently by

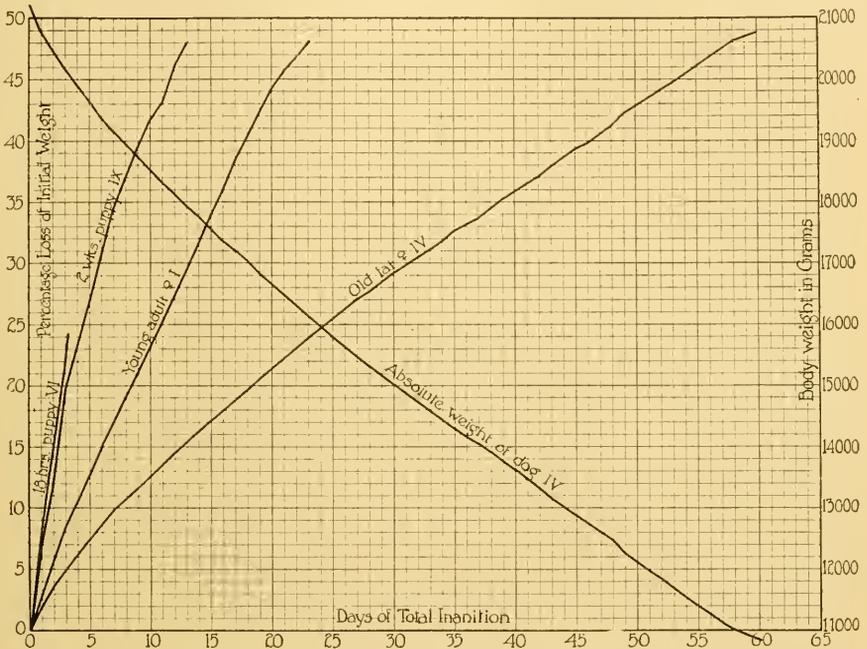


FIG. 31.—Chart showing curves of body weight in dogs on (complete) total inanition. The curves showing the percentage of loss of the initial weight demonstrate that the loss becomes progressively slower with age. The descending curve shows the loss in absolute body weight by the adult dog IV. (Falck '75.)

other observers in cases of chronic malnutrition and especially during famine or allied conditions. Edema under such conditions has been noted by Abel ('23), Aron ('20), Bigland ('20), Beyermann ('19), Bürger ('19, '20), Croftan ('17), Digby ('76), Enright ('20), Flügge ('22), Gaspard (1821), Hecker ('44), Kraus ('19), Landa ('17), Lange ('17), Leys ('14), Lubarsch ('21), Maase and Zondek ('17, '20), Mann, Helm and Brown ('20), Matthias ('19), Maver ('20), McLeod ('81), Menzies ('20), Oberndorfer ('18, '19), Paltauf ('17), Park ('18), Prince ('21), Prinzing ('16), Rössle ('19), Schiff ('17), Schittenhelm and Schlecht ('18), Strauss ('15), Tallquist ('22), Vacker ('71), Vandervelde and Cantineau ('19), Wells ('18) and Nicolaëff ('23). While many of the authors ascribe "famine edema" and allied conditions to a general total (incomplete) inanition, others

believe it to be caused primarily by one or more forms of partial (especially protein) inanition, as will be mentioned in the next chapter.

Some data upon the loss in weight of the human body in various fasting periods (on water only) were cited by S. Weber ('02) (see table on p. 73).

The course of the body weight on water alone has been carefully studied in voluntary fasts of 30 days or more by Luciani ('89, '90), Paton and Stockman ('89), Penny ('09) and Benedict ('15). The 40 day fasts of Succi and Dr. Tanner and the 50 day fast of Merlatti were less rigidly controlled. The Tanner case is discussed by Taylor ('20). The Italian "hunger artist,"

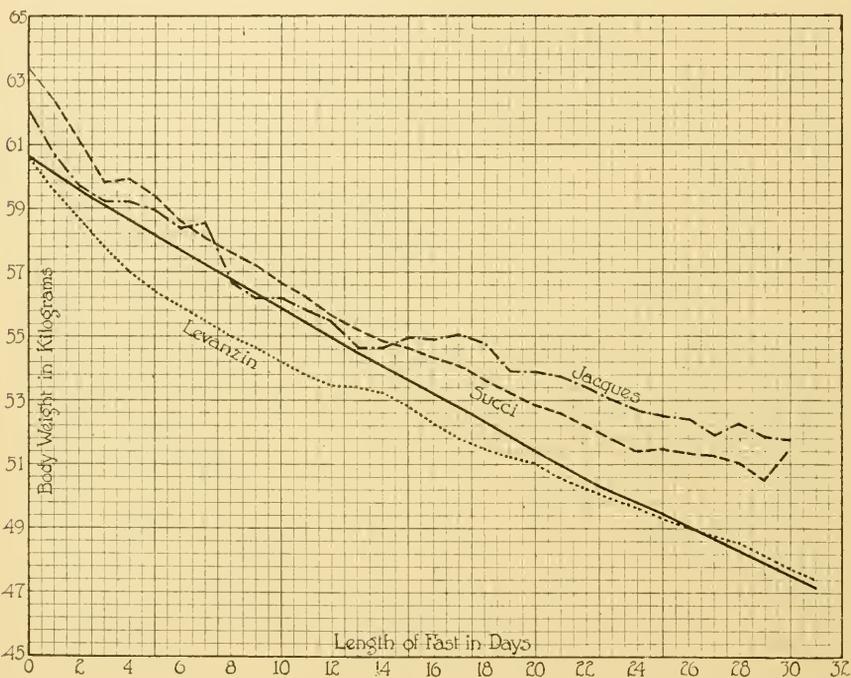


FIG. 32.—Chart showing the individual curves of body weight in three men (Jacques, Succi and Levanzin) fasting 1 month, on water only. The curves are nearly parallel, although there are evident irregularities and individual variations. The fourth curve (continuous line) represents the theoretical curve (according to Mayer's formula) for Levanzin, assuming that each daily loss represents the same percentage of the body weight at the beginning of the corresponding day. It is clear that the actual loss is relatively greater in the earlier stages, and relatively less in the latter part of the period.

Succi, underwent four fasts of 30 days each at different times, the percentage losses in body weight for the successive fasts being 22.7, 21.7, 19.2, and 17.2 (Schöndorff '13).

Individual variations are evident in the three curves of body weight shown in Fig. 32. That of Levanzin (Benedict '15), with loss of 21.6 per cent in 31 days, is the most regular, that of Jacques (Paton and Stockman '89), with loss of 16.6 per cent in 30 days, the most irregular, and that of Succi (Luciani '89, '90), with loss of 19.2 per cent in 30 days, intermediate in character. Falck ('81) stated that the decreasing body weights form a straight line; but it is clear

that the rate of loss in body weight in general is greatest in the earlier days, gradually decreasing later. Luciani attempted to devise a formula to represent the course of the decrease in body weight, but without success.

Subject (and observer)	Length of fast, days	Initial weight, kilos	End weight, kilos	Weight decrease, per cent	Daily weight decrease, per cent
Schwede (Johannson).....	5	67.80	62.79	7.37	1.48
Breithaupt (Senator).....	6	60.07	56.45	6.03	1.01
Cetti (Senator).....	10	57.00	50.65	11.16	1.12
Succi (Luciani).....	30	63.22	51.18	19.04	0.63

As shown by the continuous line in Fig. 32, the formula by Mayer ('14) for starving medusae does not fit the present case, as the relative loss in the human body is too great in the earlier stages. The course of the body weight during inanition in man and mammals more nearly resembles a reversed growth curve of the logarithmic type, as found by Morgulis ('23) in curves based on Avrovov's data for the fasting dog.

Kohlschütter ('87) presented some curves showing loss of body weight in adults with typhoid fever. Although he recognized that these curves are logarithmic in form, he rejected the idea that the loss might be due to starvation, since the only data available to him indicated a uniform loss (straight line) during inanition. He attributed the loss in weight during typhoid and tuberculosis to the increased oxidation of body substance due to the fever.

**Incomplete Inanition.**—The types of inanition heretofore considered have been complete, either total or on water alone. With incomplete diets the food given is inadequate in amount, the effect varying with the extent and character of the deficit. Thus Chossat ('43) found that birds on one-third normal rations lived twice as long as those without food, but the total body loss in weight was about the same. Petroff ('83) noted that rabbits on one-fourth of the normal ration (water *ad lib.*) lived only 36 days, or slightly longer than on water alone. On one-third ration the time was extended to 47 days. Ochotin ('86), however, found that a rabbit on one-fourth normal ration lived only 15 days with loss of 48.75 per cent.

**Loss (or Retardation) in Body Weight during Inanition in the Young.**—It has already been noted that age is an essential factor, the resistance to inanition in general increasing progressively from birth to maturity. Resistance in the young is lessened by the apparently smaller storage of reserve food materials (especially fat). The food requirement is also relatively greater in the young because metabolism is more intense, and the needs for growth as well as for maintenance must be supplied. Thus it is quite possible for a growing organism to starve to death on a diet sufficient to maintain the body without loss of weight. According to the degree of inanition, we may find an actual loss in body weight, maintenance, or merely a retardation in the normal growth rate.

Some of the data indicating the relative effects of inanition upon body weight and length of life in young vertebrates may be mentioned briefly, for comparison with the effects in adults. The effects upon the prenatal as well as the postnatal stages must also be considered.

Although the lesser resistance of the young was noted even by Hippocrates and Galen, the first accurate, quantitative observations were made by Chossat ('43). He found that on total inanition young turtle doves (initial weight 110 g.) survived only 3 days with loss of 25 per cent in body weight; adolescent (143 g.) survived 6 days with loss of 36 per cent; while adults (189 g.) survived 13 days with loss of 46 per cent.

The more extensive experiments on chicks by Petroff ('86) are summarized in the accompanying table. The exceptional endurance of the very young chicks may be due to the presence of unabsorbed yolk material, and also to additional protection from loss of heat under the wings of the mother.

EFFECT OF TOTAL INANITION UPON CHICKS AT VARIOUS AGES (PETROFF '86)

Age of chicks (from hatching) days	No. of obser- vations at each age	Average time of survival hours	Average loss of body weight, per cent	Average loss in weight per hour, per cent
0	14	122	38.3	0.31
3	15	104	42.9	0.38
5	30	92	41.8	0.45
10	12	89	38.1	0.43
15	12	97	41.7	0.43
25	15	94	42.6	0.43
30	12	79	41.4	0.52
40	12	121	41.8	0.34
50	12	144	46.5	0.32
75	12	117	40.5	0.34
90	12	270	49.2	0.17

Among mammals, Falck ('75) observed that 3 puppies placed on total inanition at 18 hours of age survived 2.8-3.4 days, with loss of 19.3-26.3 per cent in body weight; 2 puppies at 14-16 days of age survived 13-15 days with loss of 46-48 per cent; young adult dog (1 year) survived 23 days with loss of 48 per cent; an old adult (fat) survived 60 days with loss of 49 per cent (see Figs. 31 and 33).

Von Bechterew ('95) found that a newborn puppy on total inanition lived 6 days with loss of 37 per cent in body weight; one at 3 days lived 8 days with loss of 34 per cent; two at 11 days lived 15-17 days with loss of 38-41 per cent. Similarly a kitten aged 2 days lived 4 days with loss of 18 per cent; one at 4 days lived 6 days with loss of 22 per cent; while one at 6 days lived 6 days with loss of 26 per cent.

On water alone, Dehon ('05) found that 7 kittens aged 3-17 weeks lived 4-8 days with loss of 10-45 per cent in body weight. Similarly, Howe,

Mattill and Hawk ('09) noted that a puppy aged 1 month lived 6 days with loss of 22 per cent, while adult dogs survived 48-117 days with loss of 53-63 per cent.

In reptiles (serpents), Pellegrin ('01) observed that 10 young *Tropidonotus natrix* on total inanition survived an average of 36 days with loss of 38 per cent, while 10 on water alone lived 116 days with loss of 43 per cent. (Adult *Pelophilus* survived 3-4 years.)

In amphibia, Swingle ('18) starved yearling tadpoles of *Rana catesbiana* for 5 months with marked shrinkage of the body (weight undetermined).

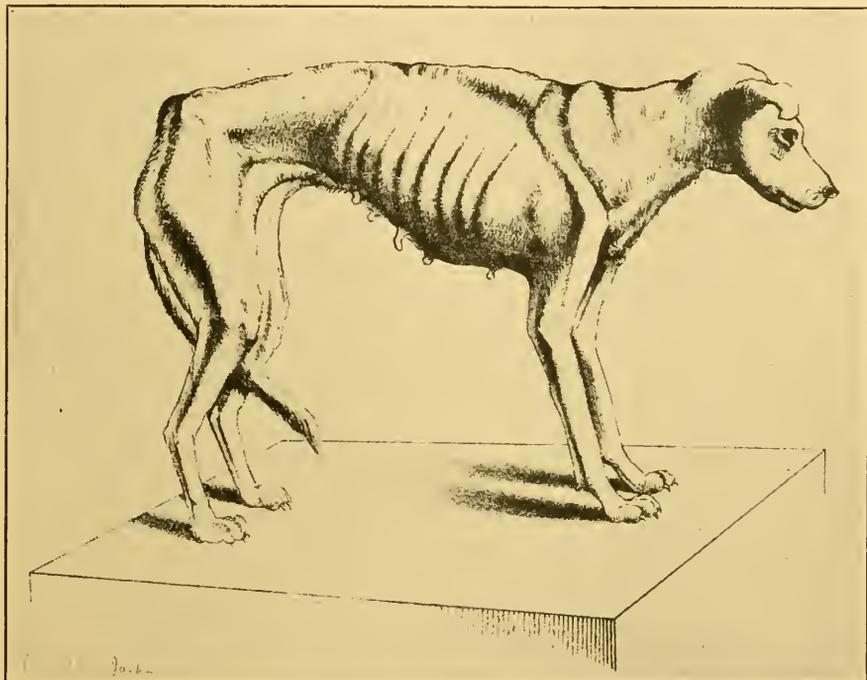


FIG. 33.—From a photograph of a female dog after 60 days of complete total inanition with loss of 49 per cent in body weight. (Falck '75.)

On incomplete inanition (diet merely restricted in amount), Aron ('11) discovered that growing puppies can be held at maintenance (constant body weight) for several months; but ultimately the amount of food has to be increased so as to permit some increase in body weight, otherwise death from inanition results. Jackson ('15a) similarly observed that albino rats held at maintenance by underfeeding live only about 2 months unless a slight increase in body weight is permitted, and Stewart ('18, '19) found that newborn albino rats can be held at maintenance by underfeeding for only 2-3 weeks.

Thus the period of survival in growing animals on maintenance diet varies directly with the age. A diet below the maintenance requirement will produce death more rapidly, with actual loss of body weight, while a diet above the

maintenance requirement, but still subnormal in amount, will cause a retardation in growth proportional to the degree of deficiency. Thus Evans and Bishop ('22) found that on optimum standard diet the albino rat at one year reached a body weight of about 330 g.; slightly underfed, 220 g.; on two-thirds normal ration, 140 g.; and on half ration, 60-85 g. (see Fig. 34). As will be shown later, however, the dystrophic growth under such circumstances is not only decreased in rate but also often abnormal in character.

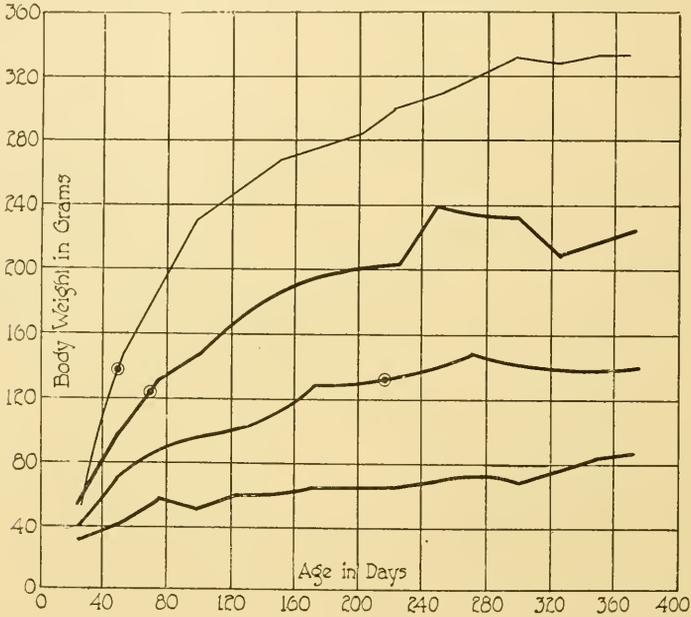


FIG. 34.—Chart showing curves of average growth in female albino rats on various planes of nutrition. The upper curve (light line) represents the average normal growth of littermate controls on an abundance of "Standard Diet I." The 3 lower curves in heavier line represent averages for the groups in which this ration was reduced slightly (in the upper curve), about one-third (in the middle curve), and about one-half (in the lower curve), respectively. Circles mark the average times of occurrence of the first estrus, which did not occur at all in the most underfed group. (Evans and Bishop '22.)

**Prenatal and Larval Inanition.**—Since the resistance to inanition in general varies directly with age, it may be inferred that during prenatal or embryonic stages, the organism is particularly susceptible to nutritional deficiencies. This is probably true, but it is somewhat difficult to prove. Especially in mammals the embryo and fetus are carefully protected against inanition by the food supply through the placenta from the mother, even when the latter is severely underfed. In oviparous forms the eggs are usually provided with an abundance of nutrient yolk material, which in part may be carried over into the embryonic body as a reserve supply and may for some time aid in the resistance to inanition.

Among fishes, Fabre-Domergue and Biatrix observed that the young may perish from inanition before complete absorption of the yolk material. In amphibia, Brehm ('12) cites a remarkable case in which Nussbaum observed that an adult *Proteus anguinus* after 13 months of starvation gave birth to a

defective young proteus 12.6 cm. long. This had possibly developed at the expense of other eggs in the oviduct. Swingle ('18) observed that larvae of *Rana pipiens* after emergence from the egg capsule may survive inanition for over 100 days (doubtless due to the large amount of yolk material present). Podhradsky ('23) noted shorter periods (up to 32 days) in young tadpoles of *Rana fusca*. Yung ('78, '83) found that in the later developmental stages malnutrition retards the growth in size and prevents metamorphosis of frog tadpoles until they become sufficiently large. In tadpoles of *Rana fusca*, however, Barfurth ('86, '86a, '87) discovered that at the time of metamorphosis into frogs starvation actually accelerates this process, and thus hastens the development. Wolterstorff ('96) concluded that the result varies according to the stage of the tadpoles used. Although Barfurth's results were denied by Bataillon ('91), Bohn ('04, '04a) noted that while in the earlier larval stages of *Rana temporaria* the removal of the albuminous capsule (which serves as nutriment) retards growth, it causes metamorphosis into tadpoles at a subnormal size. Kopeć ('22, '22a) found that starvation of tadpoles before they are 50 days old retards their development, but after 65 days of age inanition accelerates their metamorphosis.

Even normally, according to Barfurth, the frog tadpole eats but little during metamorphosis, so fasting merely accelerates the normal process. This was confirmed by Duesberg ('06), who described the histological process of absorption in the tail during metamorphosis (cf. also Morse '18 and Morgulis '23). Pflüger states that larvae of *Alytes obstetricans* cease to eat when 8.1 cm. long, and live 5 weeks during which time the extremities are formed at the expense of the tail. According to Chauvin ('76) and Kaufman ('18) a similar "physiological inanition" occurs during the metamorphosis of the Axolotl; and, according to Powers ('03), the metamorphosis of *Amblystoma tigrinum* is accelerated by starvation. The "physiological inanition" during amphibian metamorphosis recalls the similar conditions found in insects; and also the well-known fasting period of the migrating salmon, during which the sexual products are matured at the expense of the musculature (Valenciennes '48; Siebold '63; Miescher '97; Stone '97; Paton '98; Greene '10, '12; Heitz '18). A similar phenomenon apparently occurs in the male fur-seal (Parker '17) and the gander (Stieve '22), which fast during the reproductive season.

In mammals, the results on this point have been conflicting. Ver Eecke ('01) and Jägerroos ('02) found that the offspring of underfed pregnant animals (rabbits and dogs) develop normally, at the expense of the maternal organism. Similar conclusions were reached for the calf fetus by Tapke ('10) and by Eckles ('16), the latter stating that "All the data indicate that the weight of a calf at birth is not ordinarily influenced by the ration received by the mother during gestation." Zuntz ('19) found that the rat fetus is but slightly modified in weight, even when the fasting mother loses greatly in weight.

On the other hand, Roloff ('66) stated that underfeeding pregnant animals usually produces fetal maldevelopment. Rudolski ('93) starved pregnant rabbits and a dog, obtaining apparent reduction in the size of the offspring. Similarly positive results were obtained by Paton ('03) for guinea pigs, and by

Reeb ('05) for rabbits and dogs. King ('15, '21) observed subnormal average weights of young albino rats born (sometimes stillborn) from mothers in ill-health, and ascribed the result to prenatal malnutrition.

The extensive experiments of Barry ('20, '21) indicate that underfeeding of the pregnant albino rat must be severe in order to obtain positive results. When starvation is instituted shortly after copulation, pregnancy is interrupted by resorption of the ovum. If inanition is instituted in the second half of pregnancy, death and degeneration of the fetus occur in a few cases. No abortions were observed (contrary to Diatschenko ('97, '99) and Reeb ('05) in rabbits) the pregnancies proceeding to full term, as was likewise observed by Paton ('03) and Rudolski ('05). Forty-one of 120 offspring were apparently stillborn,

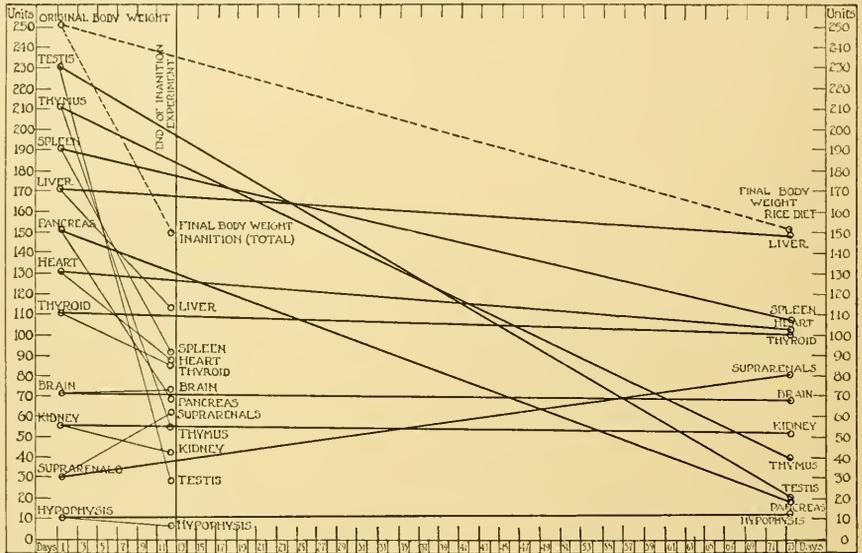


FIG. 35.—Diagram showing the relative degree of atrophy (change in weight) of the body and of various organs in pigeons during (1) total inanition and (2) partial inanition (milled rice diet, deficient in various respects). The loss in body weight is about 40 per cent in each case. There is a marked increase in weight of the suprarenals; the brain and hypophysis show little or no change; while the other organs show variable losses in weight. (From McCarrison '21; "Studies in deficiency disease," Oxford Med. Publ.; body weight corrected.)

however, and the average body weight of the newborn rats from these severely starved mothers was only about 3 g. or 40 per cent below the normal birth weight of 5 g. (see Table 4).

**Human Prenatal Inanition.**—In the human species, the possibility of reducing the fetus by underfeeding the pregnant mother has received much attention on account of its clinical importance, especially in cases of maternal contracted pelvis. The conflicting views found in the literature during the past century have been summarized by Hoffmann ('92), Florschütz ('95), Reijenge ('96), Schaeffer ('02) and Reeb ('05). A low maternal diet during pregnancy in order to reduce the size of the fetus was proposed by Brünninghausen (1804) and was advocated by Ackermann (1804), Reisinger (1820), Bandelocque (1820),

Depaul ('49) and others. The plan was opposed, however, by Jörg (1806), v. Siebold (1806), Osiander (1820) and others (*cf.* Cyr '69), as ineffective or as dangerous to the mother.

Prochownick ('89, '01) modified the plan by restricting, not the *quantity*, but the *quality*, of the diet, making it rich in protein, but poor in carbohydrates and water. This modified diet has been approved by Fraenkel ('96) and other clinicians, although Bondi ('13) stated that it is unsupported by either clinical experience or animal experiments. Prochownick ('17) still maintained his position, although admitting that the restricted war diet produced no evident decrease in average birth weight.

The evidence afforded by the birth weights in Europe during the war period is of much interest. In Germany the general shortage of food resulted in an average loss in adult body weight of about 15 per cent, as estimated by Rubner ('19). Kettner ('16) of Charlottenburg claimed the appearance of an atrophic type of newborn, but later ('16a) admitted that it could hardly be due to maternal underfeeding. A statistical comparison with the prewar records by Tschirch ('16) in Jena, Mössmer ('16) in Posen, Momm ('16) in Freiburg, Ruge ('16), Bendix ('16), Rabnow ('16), Brüning ('18) and Lindé ('19) in Berlin, Hofmann ('19) in Rostock, Soergel ('18) in Halle, Loenne ('18) in Bonn, Schmidt ('18) in Tübingen, Jahreiss ('19) in Augsburg, and Linke ('21) in Heidelberg (?) reveal no significant change in the German birth weight during the war period. Beninde ('19), however claimed that by 1918 the conditions were worse, resulting in a decreased birth weight in some regions. David ('22) found an average apparent decrease of 3-3.75 per cent in weight of the newborn, and of 2.5-3.2 per cent in length, but did not establish a relation to the skrinkage in diet during the war period.

In Austria (Vienna), Peller ('17), Richter ('17) and Schauta ('17) found no appreciable reduction in average birth weight. Similarly, Murray ('24) found no significant decrease of the average birth weight in London during the war period. In Belgium, Demoor and Slosse ('20) claim that the prewar birth weight of about 3,000 g. was reduced to an average of 2,500 g. during the war famine. It seems probable that in most of the countries involved in the war, the food shortage, although markedly affecting the general population, was not severe enough to reduce the weight of the newborn, excepting districts of actual famine. Ivanovsky ('23) states that in Russia, although the number of births decreased enormously, there was a marked increase in the premature or stillborn, also in the occurrence of monsters and various anomalies. Troizky found no decrease of birth weight in 22,000 Russian cases (up to 1917).

**Effect on Sex Ratio.**—In the first three chapters, the evidence was reviewed as to the effect of nutrition upon sex determination among plants and invertebrates. It appears that in many species the effect of malnutrition is to produce a preponderance of males. While in some cases this may be due merely to a selective mortality, in others it appears probable that nutrition may, under certain conditions, affect the sex from the beginning.

Among vertebrates the evidence as to the influence of nutrition upon sex determination is more conflicting and less conclusive. In the human species, there is a widespread tradition that relatively more males are born following

periods of war or famine (Ploss; Ruge '16), but convincing statistical evidence is lacking. Richter ('17), Loenne ('18) and Linke ('19) found no evident change in sex ratio during the world war.

Among domestic animals, Girou de Buzareingues (1828) found that the percentage of male lambs from 150 abundantly nourished ewes was about 40; while in 150 poorly fed ewes the percentage of male lambs was increased to 60.

Girou's conclusion was supported by the experiments of Duesing ('85) and by Wilckens ('86), the latter presenting statistical data from about 30,000 domestic mammals (including 16,000 colts, 4,900 calves, 6,750 lambs and 2,300 pigs). Wilckens concluded that good nutrition *in utero* tends to produce relatively more females; malnutrition, more males. Slonaker and Card ('23), however, found an increased ratio of females in albino rats on a restricted vegetable diet.

Among amphibians, the earlier experiments of Born ('81, '94) upon *Rana fusca* indicated that relatively more females are obtained from larvae placed on a nourishing diet; and Yung ('83, '85) in *Rana esculenta* apparently produced more females on richly protein diets. Cuénot ('99), however, obtained negative results with *Rana temporaria*. King ('07), in careful and extensive experiments upon larvae of the toad (*Bufo lentiginosus*), likewise failed to find any significant differences in sex ratio on various diets (meat, wheat, mixed, and egg-yolk); but her underfeeding experiments failed on account of the high mortality. The problem of sex determination in amphibians is greatly complicated by the difficulty in distinguishing the sexes during the early larval stages, and the question is still unsettled.

In reviewing the evidence, Geddes and Thomson ('01) concluded that in vertebrates, as well as invertebrates, sex may be determined by various external factors, especially nutrition. Mitchell ('11), on the other hand, concluded that "In nearly every case, however, other observers have obtained conflicting results, or placed another interpretation on similar results, whilst in none of the cases has the factor of selective mortality been sufficiently excluded." In the recent biological literature, the views concerning sex determination have been dominated largely by the "accessory chromosome" theory, according to which the sex is supposed to be determined by the relative amount of nuclear chromatin present in the gametes at the time of fertilization. It may be pointed out, however, that even under these conditions the sex ratio might still be affected by previous malnutrition of the gonads in the parent organism during the process of oögenesis and spermatogenesis. Further investigation is therefore necessary before this important question can be settled.

**Postnatal Loss in Birth Weight.**—The normal postnatal decrease in human body weight was discovered by Chaussier about a century ago, according to Benestad ('14). A similar decrease in newborn puppies, kittens and rabbits was denied by Kehrer ('70) but was found in the guinea pig by Minot ('91) and by Bessen and Carlson ('23). According to Ostwald ('08), such a loss is very general in animals. Although chiefly due to other factors (loss of meconium, urine, etc.), it is generally admitted that a part of this postnatal decrease in body weight is due to inanition, on account either of insufficient

food intake or of inability of the digestive system to adapt itself suddenly to the new conditions.

The postnatal decrease in the human infant usually reaches a maximum of about 200 g. on the third day (*cf.* data cited by Vierordt '06), and the birth weight is normally recovered by the tenth day (Winckel '62). Further details are given by Kehrer ('70), Monti ('89), Schaeffer ('96), Gundobin ('12), Robertson ('14, '15, '23), Benestad ('14), Bailey and Murlin ('15), and Ramsey and Alley ('18). Schick ('15) was able to prevent the initial loss in 12 cases by abundant feeding of breast milk. On the other hand, in cases of deficient breast milk, artificial feeding or digestive inability (especially in prematures), the loss may be greater and continue longer, with corresponding retardation in recovery. Thus Brüning ('18), Hofmann ('19) and Kütting ('21) found that although the German "war-babies" were normal in birth weight, they failed to thrive normally in the first ten days, probably on account of deficient quality in the maternal milk.

**Inanition during Infancy and Childhood.**—We come now to the consideration of the effects of inanition upon the body as a whole during infancy and childhood. A case of actual starvation in twins one month old was described by Jones ('89). Infantile malnutrition is very common and varied in character and in degree of severity. When pronounced, it leads to a marked condition of infantile atrophy, which, according to Albarel ('05), was first described by Soriano, a Spanish physician of the 16th century. It was described under the name "athrepsie" by Parrot ('77). Other terms which have been applied to the condition are "inanition," "cachexia," "marasmus," "hypotrophie," "pedatrophy," "decomposition," "denutrition," etc. These terms have been used by various authors with different meanings, which are discussed in the works of Thiercelin ('04), Rosenstern ('11), Vigor ('11), Lesage ('11), Czerny ('12), Nobécourt ('16), Raimondi ('17), Marfan ('20), Talbot ('21), Variot ('21), Utheim ('22), and others.

For present purposes, it suffices to note that infantile atrophy is usually considered, not a definite clinical entity, but a condition of malnutrition which may result from many different causes. Anything which interferes with the normal nutrition of the tissue cells is a cause of inanition. As mentioned in the introduction, this may result from a food-intake deficient in quantity or quality; from varied lesions of the alimentary tract preventing proper ingestion, digestion or absorption of the food; or from imperfections in the blood or vascular transporting system. Even when all of these extrinsic factors are absent, however, and adequate nutriment is brought to the cells, they may still be unable to absorb and assimilate it, due to intrinsic defects in their protoplasm, as emphasized by Czerny ('08). Such intrinsic defects may be congenital or even hereditary in origin (Variot and Guyarder '04, Lesage '11) or they may be caused by the action of toxins produced in the system (*cf.* Stransky '22). Intestinal infections may cause inanition both as an extrinsic factor, through interference with digestion and absorption, and as an intrinsic factor, through toxic action directly upon the cells of the body.

Utheim ('22) has recently reviewed in detail the question as to the etiology of infantile atrophy, as studied in Marriott's clinic, and reaches the following conclusions:

"Based on the material in this clinic, it is believed, then, that in the etiology of athrepsia, feeding is the main factor, a quantitative and especially a qualitative starvation being responsible for the development of most cases, that the constitutional factor is of less importance and that the parenteral infections will often contribute in developing the picture."

In agreement with the observations upon the young of lower animals, the human infant perishes quickly from total inanition, with a relatively slight loss in body weight. Chauvin ('40) reported an incredible case of a premature (7 months) infant which remained quiescent and at constant body weight without food or drink for 7 weeks after birth, with ultimate recovery. Cantalamassa ('92) observed a case of premature (7 months) twins, one of which died without nursing in 11 days with loss of 24 per cent in weight; the other nursed slightly and died in 23 days with loss of 22 per cent. Bouchaud ('64) noted 34 Paris cases, mostly prematures with incomplete inanition, all of which lost over 25 per cent, and 18 over 30 per cent in weight. The extreme case was one of a premature (6 months) of 1,400 g. which lost 570 g. (40.7 per cent) in 17 days.

Thiercelin ('04) states that among athreptics, "il n'est pas rare de voir des enfants de trois semaines qui ne présentent que la moitié de leur poids de naissance," but apparently no other author has noted such an extreme loss in weight. According to Richter, a child may die of starvation in 5 days with a loss of less than 25 per cent in body weight.

Of 38 Breslau infants dying with loss of over 25 per cent in body weight, Quest ('05) found the maximum loss at death to be 38.0 per cent, and 34.8 per cent in those which recovered. His results were confirmed by Rosenstern ('11), who observed only 3 nurslings surviving a loss of over 32 per cent (maximum 35 per cent). Four fatal cases reached 35 to 38 per cent. Czerny ('11) states that nurslings during chronic inanition may survive a loss of one-third in weight, but the danger point is reached before this during acute inanition.

In 12 cases of deaths from (chiefly chronic) inanition in infants 5-255 days of age, final body weights 1,695-3,972 g., and body lengths from 46-64 cm., the losses in body weight were estimated by Jackson ('21) in different ways as follows: loss in body weight, the final weight being compared with the maximum observed during life, average loss 19.2 per cent (range 13.7-25.5); loss in body weight, the final being compared with the normal for final body length, average loss 28.5 per cent (range 7.4-52.3); retardation in body weight, the final weight compared with the normal for corresponding age, average deficit 56.8 per cent (range 41.6-71.6) (see also Table 3).

In cases of incomplete inanition (underfeeding) or of partial (qualitative) inanition, the weight of infants may be stationary or merely retarded to a variable degree, depending upon the length and severity of the malnutrition. Camerer noted that artificially fed infants lag considerably behind the normally breast-fed.

As to the effects of inanition during childhood, a large amount of data has accumulated from observations upon school-children. One of the first established facts is that the children of the poorer classes average in height and weight below those of the well-to-do of the same age (Pagliani '79; Landsberger '87; Geissler and Uhlitzsch '88; Geissler '92; Boas '97; Pfaundler '16; and others). This is ascribed to underfeeding and malnutrition, along with other unfavorable hygienic conditions. Even among the wealthier classes, many children are malnourished, due to improper feeding (including various types of partial inanition) rather than to underfeeding.

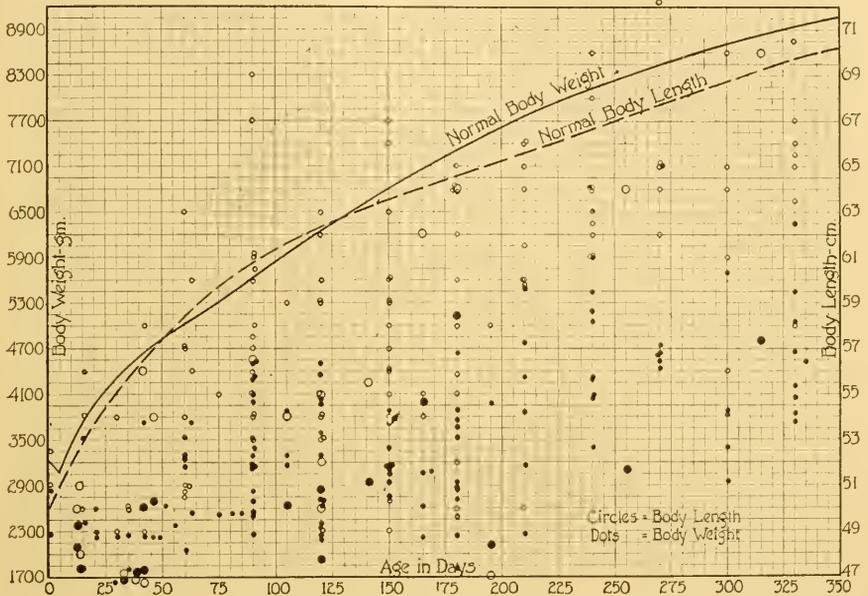


FIG. 36.—Field graph showing the body lengths (circles) and weights (dots) for atrophic infants of the first year, plotted according to age. The larger circles and dots represent original Minnesota data; the others are from various sources. The curves for normal body weight and length are from data compiled by Prof. R. E. Scammon. Note that in the malnourished cases the weight is subnormal to a much greater degree than the height.

Medwedjew ('82) observed the growth in length of 50 individuals during the great Russian famine, but his original publication was inaccessible to me. Nicolaëff ('23) found the body weight 20–40 (sometimes 50) per cent subnormal for age among children 1–16 years old at Kharkow during the recent Russian famine. The conditions in Russia are described also by Morgulis ('23). Stefko ('23a) found that the girls, having more body fat, showed greater loss in weight, but lower mortality.

Even in countries like the United States, where extreme poverty is relatively infrequent, numerous investigations have revealed a surprisingly large number of apparently malnourished school-children, at least in the large cities. Thus Sill ('09) found 40 per cent of 1,000 primary school-children, in the Jewish quarters of East Side New York, malnourished and subnormal in weight. He cites evidence of a similar prevalence of malnutrition in London and Edin-

burgh. A somewhat smaller, but still alarming, amount of malnutrition among New York school-children was found by Chapin, Baker, Mitchell, and others. In a recent investigation by the Bureau of Child Hygiene (Baker '18a, '18b), 171,691 school-children in the Borough of Manhattan were classified according to the Dumferline scale as follows: No. 1 (normal) 17.3 per cent; No. 2 (passable) 61.1 per cent; No. 3 (distinctly undernourished) 18.5 per cent; No. 4 (pronounced malnutrition or marasmus) 3.1 per cent. As to age, of the children up to 6 years, 22.5 per cent were undernourished. The percentage increased to a maximum of 25.2 per cent at 9 years; then decreased to 12.1 per cent at 16 years. Similar conditions probably exist in one million school-children in New York City. Nationality was not found to be an important factor, although the percentage of undernourished varied from 19.8 in children of Russian and Polish origin to 28.7 per cent among those of Italian parentage. Among 894 New York school-children, Mitchell ('19) found 69 "special" and "open air" cases; of the remaining 800 children 16.8 per cent were 7 per cent or more subnormal in weight according to height, in comparison with norms based upon data of Holt, Burk and Boas. As an example of conditions in a smaller city of the Middle West, Brown ('20) found that 41 per cent of the children in the Lowell School of Kansas City were more than 10 per cent underweight (compared with the standard table of Dr. Wood).

From a large series (172,000) measurements of American children in 1918-19, Woodbury ('21) concluded that 4.4 per cent were notably deficient in stature, and 15.7 per cent were deficient in body weight. The largest proportion of deficient cases occurred in infants below one year of age, the deficient group at this age averaging almost 25 per cent below normal in weight. These data, from material secured in the "Children's Year" measurements, indicate a lesser extent of malnutrition than those above mentioned.

It seems probable that the percentage of undernourished children was increased by the scarcity and high price of food during the recent war period, (Chapin, *et al.* '18) even in countries not directly involved; although this was not found evident in Amsterdam school-children by Lubsen ('17). In Belgium Demoor and Slosse ('20) state that children of 6-14 years at the end of the war were retarded at least one year in height and weight. Calmette ('19) found even greater apparent retardation in Lille, amounting to 4 or 5 years in the older children. Newman estimates that fully 10 per cent of the English school-children are seriously malnourished.

In Vienna, evidence of marked undernourishment of the children is given by Gribbon and Paton ('21) and Gribbon and Ferguson ('21). Among children from 1-14 years of age, the worst effects were found in those from 2-3 years of age, which averaged 13.6 per cent below normal in height for that age, and 26.5 per cent subnormal in weight.

In Germany, numerous observers have described severe malnutrition and retarded growth in children as a result of the war conditions (Fuhge '18; Addams and Hamilton '19). Beninde ('19) found conditions progressively worse since 1917. Schlesinger ('20) presents extensive data and concludes that malnutritional effects of the war appeared later in children than in adults, consisting in (1) retardation (average of 2 cm.) in growth in length; (2) loss in weight; (3)

constitutional disturbances. In Munich, even before the war, Oppenheimer and Landauer ('11) found much malnutrition; and at the close of the war, Pfaundler ('19) concluded that the Munich children of 6 years had been retarded by 3 cm. in height and 1 kg. or more in weight. In Berlin, Czerny ('21) states that no bad results among children were visible in the earlier years of the war, but retarded growth became apparent later. Goldstein ('22) among the institutional children of Berlin found 89 per cent subnormal according to age and 50 per cent were 10-20 per cent subnormal in weight for height. They were also retarded 1-3 years in height. Fuhge ('18) made a study of the metabolism in such retarded children, finding the growth retarded by insufficient food, with relatively small proportion of protein and fats.

**Indices of Nutrition.**—In connection with the study of malnutrition, especially in childhood, the desirability of some exact method of determining the degree of undernourishment has been increasingly evident in recent years. A favorite method has been to compare the height and weight with those given in standard tables as normal for the corresponding age, but this is unsatisfactory on account of the great variability even among healthy children of the same age. Since emaciation of the body is the most outstanding symptom of inanition, a comparison of the ratio between length and weight (independent of age) should be useful. In order to obtain a normal index which is approximately constant for age, however, it is obvious that the simple height: weight ratio (as used by Dreyfuss '06 and earlier authors) is inadequate, since the weight (or volume) of the body in general increases as the cube of the height, assuming the body proportions to remain constant. But even the ratio height<sup>3</sup>: weight does not remain constant, since Quetelet (*Anthropometrie*, 1835) demonstrated that between birth and maturity the human body normally becomes relatively elongated, so that a constant ratio is expressed more nearly by height<sup>5</sup>: weight<sup>2</sup>. Not even this ratio remains constant, however, and no completely satisfactory formula or index has yet been discovered.

Various indices or modifications have been proposed, which are discussed in the papers of Fleischner ('06), Rohrer ('08, '21), Pirquet ('16), Matusiewicz ('14), Pfaundler ('16), Manny ('16, '18), Holt ('18), Davenport ('20), Dreyer and Hanson ('20), Retan ('20), Emerson and Manny ('20), Gerber ('21), Wagner ('21), Huth ('21), Carter ('21), Bardeen ('20, '21, '23), Guttman ('22), Clark ('22), Van der Loo ('22) and Davenport ('23).

It is impossible to discuss the various proposed indices in detail, but a few more important points may be mentioned. The original "*Index ponderalis*"

of Livi ('86) was in the form:  $100 \frac{\sqrt[3]{\text{weight (grams)}}}{\text{length (cm.)}}$ . This was modified by

Rohrer ('08) as the "Körperfüllenindex" =  $100 \frac{\text{weight}}{\text{length}^3}$ . Pirquet ('16) prefers

the sitting height instead of the total body length in his index "Pelidisi" =

$\frac{\sqrt[3]{10 \cdot \text{weight (grams)}}}{\text{sitting height (cm.)}}$ . Pirquet's index has been used by Helmreich and

Kassowitz ('23) and others.

Guttman ('22), using Bornhardt's ('86) index, and Van der Loo ('22) claim that by using the chest measurement as one factor in the formula, a better correlation with the clinical findings is obtained. The thoracic circumference is utilized also in the index of Pignet (cited by Ivanovsky '23), and by Dreyer and Hanson ('20); while Davenport ('23) uses the ratio weight:chest-girth<sup>2</sup> as the "index of build."

Bardeen ('20) uses a weight-height formula with the English units of inches and pounds. For the sake of uniformity, however, the metric system is preferable, and in the present work I have used Rohrer's weight-height index =  $100 \frac{\text{body weight (grams)}}{\text{height (cm.)}^3}$ . Assuming the density as one, this expresses what

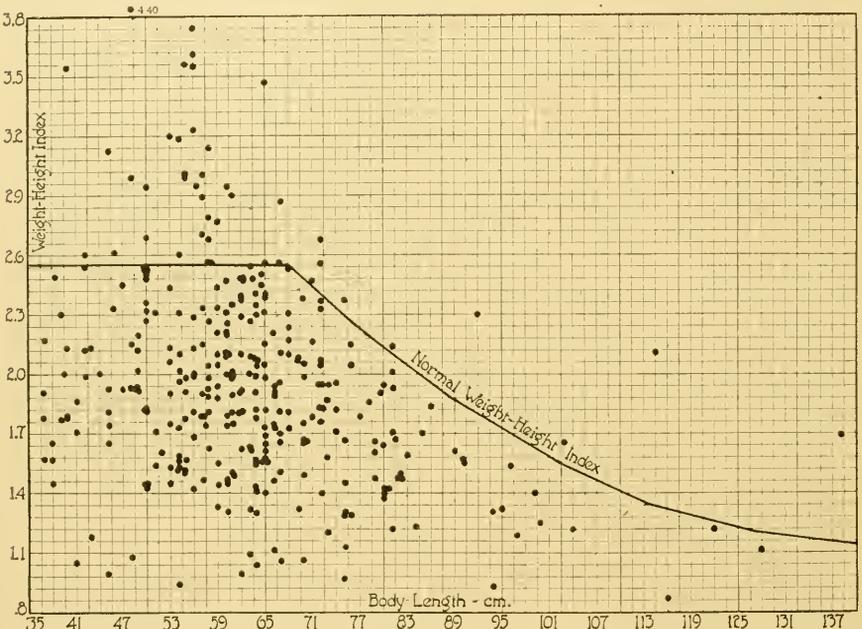


FIG. 37.—Field graph showing the weight-height index  $\left(\frac{\text{weight (g.)}}{\text{height (cm.)}^3} \times 100\right)$  in 334 consecutive necropsies of children at the Johns Hopkins Hospital. Data obtained through courtesy of Professor John Howland. Note that in only 43, or 12.9 per cent, of these cases is the weight-height index above Bardeen's norm, and the extremely emaciated cases are more than 50 per cent below.

percentage of the volume of the cube of the body length would be occupied by the body. According to the data compiled by Bardeen ('20), this weight-height index normally remains at about 2.54 in the fetus and infant up to about six months of age, then decreases gradually to about 1.20 at maturity.

Since the weight is relatively depressed during emaciation (see Fig. 36), this index is correspondingly lowered during inanition. The relative degree of emaciation may therefore be accurately expressed by the weight-height index, as shown by Fig. 37, indicating graphically the index for 334 consecutive cases of children autopsied in the Johns Hopkins Hospital. It will be noted that in

only 43 cases, or 12.9 per cent, was the index above the normal average. The remaining 87 per cent are below the normal average to a variable extent.

This brings us to the difficult problem of determining, if possible, the point below which the weight-height index should be considered abnormal, denoting pathological emaciation. It must be remembered that in general at any age, and in each sex of a given race, the individual heights and weights are normally variable, the frequencies at various intervals above and below the average being distributed roughly according to the "probability curve." Robertson ('23) estimates that in children of a given age the normal variability in weight varies (at different ages) from 11-20 per cent, and that in stature from 4-6 per cent. This necessarily affects the normal weight-height index, which Matusiewicz ('14), Pfaundler ('16), and Gerber ('21) have shown to be subject to marked individual variation. A low index therefore does not necessarily indicate malnutrition in the individual case, as Pfaundler ('21) and others have repeatedly emphasized. On the other hand, malnutrition may exist in some cases without marked depression of the weight-height index. Nobécourt ('16) describes two types of infantile denutrition, one ("cachexie") with emaciation and one ("hypotrophie") without. With reference to the racial factor, Dublin and Gebhart ('23) have shown that the Wood-Woodbury weight-height tables fail as an index of malnutrition in Italian children of New York. Davenport ('23) concludes that body-build is determined largely by heredity, probably acting through the endocrine glands.

Of the various indices proposed, aside from Bornhardt's index (or others involving the thorax), the weight-height index is perhaps the most convenient and reliable single physical index of the nutritional condition of the body, but no single index can be conclusive for every individual case. A low weight-height index is presumptive evidence of malnutrition, but it needs confirmation by clinical evidence. The various physical signs and symptoms of malnutrition in children have recently been summarized by Roberts ('23) and Goldberger ('23). As a result of clinical experience, Holt ('18) proposed an arbitrary zone of 10 (or 12) per cent or more below the normal weight-height relation as an indication of malnutrition, while Emerson and Manny ('20) and Emerson ('22) draw the line at 7 per cent (below the Boas-Burk norm). Baldwin ('24) finds in healthy school-children an average variability of 6-9 per cent in weight, according to height, age and sex. Any such boundary line is necessarily arbitrary and misleading, however, unless the limitations above mentioned are kept clearly in mind. Thus in a series of 506 healthy children, Clark, Sydenstricker and Collins ('23) found 13 per cent of the individuals more than 10 per cent underweight according to Dreyer's standard (stem length and chest circumference tables); 20 per cent were more than 10 per cent underweight according to the Wood standard (height-weight-age tables); and 17 per cent were subnormal according to Pirquet's standard, having a "pelidisi" of 94 or less. None of the indices so far proposed appears to be very closely correlated with clinical findings (Huth '21; Van der Loo '22; Clark, Sydenstricker and Collins '23; Helmreich and Kassowitz '23 and others). The subject needs further investigation (*cf.* Taylor '22).

In infantile atrophy and allied conditions of inanition, the weight-height index may drop very low. Thus in 12 fatal cases studied by Jackson ('22) the index averaged 1.65 (range 1.20-2.05), or about 35 per cent below Bardeen's norm (2.54) (see Table 3). A similar degree of emaciation is indicated in a series of 82 observations by Porter ('89) on older children who perished in the Indian famine (Fig. 38). Only two (on account of dropsy) of these were above normal in weight according to height. The data shown in Figs. 37 and 38 indicate that a weight-height index 50 per cent subnormal is rarely reached, even in cases of fatal inanition. In many cases of chronic inanition the index is



FIG. 38.—Field graph showing the weight-height index  $\left( \frac{\text{weight (g.)}}{\text{height (cm.)}^3} \times 100 \right)$  in youthful victims of the Madras famine of 1877-78. (Data from Porter '89.) Of the 82 cases, only 2 (probably dropsical) appear above Bardeen's normal weight-height index. The average varies from about 33 per cent below in the younger to 40 per cent below in the older.

lowered not only by the resultant loss in body weight, but also by an actual coincident increasing body length, due to a persistent skeletal growth, which will next be considered.

**Dystrophic Growth.**—That inanition may result in deformity of the body in growing organisms has long been known, but the effect in general was usually attributed merely to variation in the relative reduction of the various organs or parts, as in adults. It is true that (as previously mentioned) cases of "physiological inanition" had been recognized in amphibia at the time of metamorphosis and in the migration of the salmon, during which certain growth changes proceed at the expense of the remainder of the body, with no intake of food from the exterior. These were considered exceptional cases, however, without parallel in the phenomena of inanition in other vertebrates. The possibility of a con-

tinued growth in some parts at the expense of other during inanition has but recently been recognized as a general phenomenon. Although apparently (in vertebrates) first observed in the human species, we may first consider the phenomena as found in lower animals.

Waters ('08, '09), at the Missouri Agricultural Experiment Station, held 15 young (yearling) steers at maintenance by underfeeding for several months and noted some curious changes. The skeleton continued to grow, resulting in progressive increase in height and length, apparently at the expense of the adipose and muscular tissues. Although remaining constant in weight, the body underwent various changes in proportions, the head becoming larger and the thorax elongated dorsoventrally. About the same time, Lassabriere noted in 3 malnourished puppies a dissociation of growth in length and weight, similar to that found by Variot in human infants (to be mentioned later). Aron ('10, '11) likewise noted that puppies underfed so as to maintain nearly constant body weight continued to increase in length and height on account of persistent skeletal growth. Other changes noted will be mentioned later. A similar persistent growth of the skeleton at the expense of the remainder of the body was also noted by Falke ('10) in underfed calves, by Aron ('13, '13a) in underfed rats, and by Mendel and Judson ('16) (judging by ash-content) in underfed mice; although Tschirwinsky ('10) had obtained negative results in undernourished lambs.

The first complete and systematic analysis of the relative weight changes in the various parts of the growing body as a result of underfeeding was made by Jackson ('15a) in the albino rat, beginning at three weeks of age or later. Although there was an increase in body length, and especially in tail length, as a result of persistent skeletal growth, the changes in general body proportions otherwise were not marked. There was apparently a slight increase in the head weight, counterbalanced by a similar decrease in the trunk and extremities (Fig. 39). Judson ('16), Thompson and Mendel ('18) likewise noted changes in the proportions of underfed white mice, the head becoming relatively enlarged and the tail elongated. The various abnormalities of growth on insufficient or inadequate diet were reviewed by Mendel ('17).

The results of Jackson ('15a) upon albino rats underfed beginning at 3 weeks (age of weaning) or later were confirmed by Stewart ('16). In experiments beginning on the newborn rats, however, Stewart ('18, '19) found somewhat different results. In this case, in addition to the increase in body and tail length, there was a marked increase (45 per cent) in the head weight, while the body weight decreased slightly (4 per cent). The differences in other organs were even more strongly marked, as will appear later.

In albino rat fetuses retarded in growth by underfeeding the mother during the latter half of pregnancy, Barry ('20, '21) found a slight increase in the weight of the head and limbs, with a corresponding decrease in the trunk. The body length and tail length were also nearly normal, the skeletal growth being much less pronounced than that found by Jackson and Stewart during postnatal inanition. The results therefore appear to differ materially according to the age at which the inanition occurs.

The investigations of Waters upon the growth of steers at various planes of nutrition were continued and extended by Van Ewing and Wells ('14), by Trowbridge, Moulton and Haigh ('18, '19) and by Moulton, Trowbridge and Haigh ('21, '22). The results confirmed those of Waters as to changes in the form and proportions of the body, with additional observations upon the various organs (to be mentioned later).

A persistent growth in length of very young fasting tadpoles of *Rana fusca* was recently found by Podhradsky ('23).

Head 20.6 per cent.	Head 22.7 per cent.	Head 10.1 per cent.
		Fore-limbs 6.9 per cent.
Fore-limbs 9.6 per cent.	Fore-limbs 8.5 per cent.	Hind-limbs 15.6 per cent.
Hind-limbs 15.7 per cent.	Hind-limbs 15.4 per cent.	
Trunk 54.1 per cent.	Trunk 53.4 per cent.	Trunk 67.4 per cent.

Controls at 3 weeks    Constant 3-10 weeks    Controls at 10 weeks

FIG. 39.—Graph showing the changes in the relative weights of the head, trunk and limbs in young albino rats held at constant body weight by underfeeding from 3 weeks to 10 weeks of age, in comparison with normal initial and final controls. (Jackson '15a.)

In children, Auboyer ('81) ascribed the abnormal growth in length of the extremities sometimes observed during and after certain fevers to the stimulation of the epiphyseal cartilages by the febrile toxins. Camerer ('93) noted an apparent increase in length during illness, but in the absence of exact measurements concluded that this was an illusion, the length appearing exaggerated by the emaciated condition. In 1905, however, Camerer, Jr. observed a case of chronic gastrointestinal trouble in a child beginning at 9 months and extending up to 5 years of age. There was marked retardation in weight, but normal

increase in length, which Camerer attributed to dissociation of growth in weight and length during undernourishment. He concluded:

“Der Umstand, dass das Längenwachstum trotz chronischer Unterernährung keineswegs zu klein ist, beweist die Unabhängigkeit des Längen- vom Gewichtswachstum bei Unterernährung and liefert einen schlagenden Beweis für die Selbständigkeit der assimilierenden Kraft wachsender Organe.”

Fleischner ('06) observed that in malnourished children of the same weight but at different ages the height shows a regular increase with age. He failed to demonstrate the significance of this apparent increase, however.

Variot ('07) from cranial measurements on living hypotrophic infants, as well as from brain weights at autopsy, concluded that the growth of the brain proceeds independently during undernourishment. In a remarkable series of publications during the succeeding year, Variot ('07a, '07b, '07c, '07e, '08, '08a) demonstrated beyond question the frequent dissociation of statural and ponderal growth during chronic infantile inanition. The growth in height is retarded relatively less than the growth in weight, and in severe cases the height may increase while weight is stationary or even slightly decreasing. He found the dissociation more distinct in prematures, twins, and weaklings, especially in atrophy of gastrointestinal origin.

Variot ('08b) also demonstrated that a “physiological” dissociation of statural and ponderal growth occurs during the normal postnatal loss in body weight. In a series observed, the average birth weight at the end of 10 days had increased but slightly (from 3,000 to 3,100 g.) while the body length simultaneously increased from 49.5–51.8 cm. Lascoux ('08) confirmed in general the results of Variot, but found in some exceptional cases an *inversion* of the dissociation, increase in weight occurring during stationary body length.

Freund ('09) claimed that short, acute infections depress weight, with no marked influence upon growth in height, while malnutrition produced by chronic infections almost always causes complete cessation of growth in both height and weight. Numerous cases illustrating the dissociation of growth in weight and height during infantile malnutrition are cited by Vigor ('11), Birk ('11), Lust ('13), Opitz ('13), Stolte ('13), and Aron ('14). Birk ('11) found that in very young undernourished infants (receiving too little breast milk) growth in both length and weight were nearly stationary; while in older infants the growth in length was more persistent. Lust ('13), on the contrary, found the growth in length inhibited less in atrophic nurslings than in cases arising later. The whole question of the abnormal (dissociated or uncorrelated) growth during infantile malnutrition is reviewed and discussed fully in the treatises of Baudrand ('11), Lesage ('11), Schloss ('11) and Tobler and Bessau ('14) (*cf.* also Jackson '23).

More recently, Waser ('20) concludes that the variable relations of statural and ponderal growth during malnutrition in nurslings may be classified as follows: (1) body weight and length stationary (during inanition in pyloric stenosis, underfeeding, dyspepsia, and “decomposition” with transient inhibition of the growth impulse); (2) decrease in weight, length stationary (in dyspepsia, “decomposition” and pyloric stenosis); (3) increase in weight, length stationary

(in rapid recovery from malnutrition); (4) increase in length, weight stationary (in "decomposition" and metabolic disturbances); (5) increase in length, weight decreased (in dyspepsia and "decomposition" during the first 3 months of infancy).

Jackson ('22) in 12 fatal cases of atrophic infants (Table 2) found that the actual loss of body weight, the final being compared with the maximum recorded during life, averaged 19.2 per cent; when the final body weight is compared with that normal for the final body length, the apparent loss is greater, averaging 28.5 per cent. The average difference of 9.3 per cent in the latter case is evidently due to the average increase in length due to skeletal growth during the period of malnutrition.

**Summarizing** briefly the dystrophic growth changes in the young of man and other vertebrates, it is clear that growth does not necessarily cease during insufficiency or even total absence of food intake. Under such conditions of inanition, certain tissues appear able to appropriate nutriment and grow at the expense of other parts of the body. Cases of "physiological inanition" in which such developmental or growth changes occur are found in the migrating salmon, the metamorphosis of amphibia, and the human infant during the postnatal loss of birth weight. The most frequent change in the form of the body during dystrophic growth is an abnormal elongation, due to persistent skeletal growth, which accentuates the emaciation caused by the atrophy of the softer tissues. In some cases there is also an enlargement of the head, and disproportionate growth of the extremities. The extent and character of this disproportionate (or uncorrelated) growth varies according to age. As will appear later, it also varies remarkably according to the type of inanition (various forms of partial inanition) and in the different parts and organs of the body. All of these dystrophic growth changes apparently contradict Liebig's "Law of the minimum or limiting factor," as strictly interpreted by some authors (*cf.* von Bunge '01).

**Changes in Adult Proportions (Head, Trunk and Extremities).**—It has already been shown that inanition may produce certain changes in the form of the body in the young, with dystrophic skeletal growth resulting in elongation of the body and accentuating the emaciation. A tendency to abnormal growth of the head and changes in the proportions of the extremities were also noted. It remains to consider what changes in the form of the body and the proportional size of the parts may result from inanition in adult vertebrates.

Among the lower vertebrates, Harms ('09) observed a definite shortening of the vertebral column in *Triton taeniatus* and *Triton cristatus* in 2 or 3 months of inanition. The tail, however, remained unchanged and thus became relatively longer. In the salamander *Diemyctylus*, however, Morgulis ('11) found a greater shrinkage of the tail than of the body during starvation. According to Kammerer ('12), in *Proteus anguinus* fasting in a dark, cool place, the tail becomes relatively shorter, the extremities longer, and the head larger; whereas in a warm, light place the body proportions remain normal.

In adult albino rats, the proportions were studied by Jackson ('15), 15 rats being subjected to acute inanition (water only) with average loss of 33 per cent in body weight in 9 days; while 6 were subjected to incomplete inanition (insuffi-

cient normal diet) with loss of 36 per cent in 5 weeks. In comparison with normal controls, the tail appeared relatively elongated, probably due to an actual decrease in the trunk length during the inanition period. The relative changes in the weights of the head, limbs and trunk are represented graphically in Fig. 40. It is evident that the head and fore-limbs become *relatively* heavier, since during inanition they lose in absolute weight less than the body as a whole. The hind-limbs likewise increase in relative size during acute inanition, but remain nearly unchanged in relative (percentage) weight during chronic inani-

Head 9.10 per cent.	Head 11.2 per cent.	Head 11.4 per cent.
Fore-limbs 5.0 per cent.	Fore-limbs 7.2 per cent.	Fore-limbs 6.9 per cent.
Hind-limbs 15.0 per cent.	Hind-limbs 17.5 per cent.	Hind-limbs 15.3 per cent.
Trunk 71.0 per cent.	Trunk 64.1 per cent.	Trunk 66.4 per cent.
Normal initial	Acute inanition	Chronic inanition

FIG. 40.—Graph showing the changes in the relative weights of the head, trunk and limbs in adult albino rats subjected to acute inanition (water only) with loss of 33 per cent in body weight and to chronic inanition (underfeeding) with loss of 36 per cent in body weight. (Jackson '15.)

tion. In both cases the trunk decreases in relative weight, compensating for the relative increase in head and limbs. Certain changes in the proportions of adult steers on submaintenance rations were noted by Benedict and Ritzman ('23).

Changes in body weight and circumferences of thorax and abdomen in Germany during the war famine are discussed by Fischer ('23). In 2,114 adults 20–55 years of age, examined before, during and after the Russian famine, Ivanovsky ('23) found marked atrophic effects resulting in emaciation

and senile appearance. The loss in body weight often exceeded 30 per cent. The trunk became bent and shortened, with a decrease in stature of 3.8–6.6 cm. in the males and 3.6–4.8 cm. in the females. There was apparently both absolute and relative decrease in the size of the head, also a tendency to increased dolichocephaly and minor changes in nasal measurements. The thoracic circumference was markedly decreased; but the extremities appeared elongated, in relation to stature.

**Recovery from Inanition.**—It is well known that recovery from inanition is generally possible, if adequate nutriment is provided before the extreme stage is reached. After a certain point, varying according to species, individual, type of inanition and environmental conditions, recovery becomes impossible and death is inevitable. The process of recovery upon proper refeeding after inanition will be considered briefly, first among vertebrates in general and second in man.

As examples of the extreme extent of inanition from which recuperation is possible, Kahan ('85, '86, '04) obtained recovery after loss of 30–45 per cent in the body weight of adult pigeons; and after loss of 50 per cent in a hen and 30.9 per cent in rabbits. In the dog, Laborde ('86) noted recovery after loss of 48 per cent in body weight; and Howe, Mattill and Hawk ('09) after a loss of 63 per cent in a fast (water only) of 117 days. Liberge reports the recovery of a cow after total inanition for 40 days (weights not stated). Kammerer ('12) found that in advanced stages of fasting, *Proteus* refuses food and is therefore incapable of recovery, though remaining alive for a long period.

The recovery after repeated periods of alternating inanition and refeeding has also been studied. Kahan ('85, '86) noted that adult pigeons upon refeeding after repeated inanition acquired a body weight greater than the initial weight; and the same tendency was observed in rabbits ('86a). Similar results were obtained by v. Seeland ('87) in pigeons and chicks; and by Noé ('00) in guinea pigs and rabbits, but not in rats. Thus intermittent fasting in adult animals may result in increased body weight. Morgulis ('13) found that in salamanders a single protracted fast is less injurious than intermittent fasting.

Rowntree ('22) states that one of Poletaeff's dogs survived 22 days (total inanition) with 47 per cent loss in body weight. In a subsequent starvation it succumbed only after a loss of 60 per cent. The necropsy showed some fat still present. A rabbit survived 8 days of total inanition, with loss of 32 per cent in body weight. After 7 days, it was again starved and died on the 10th day, with loss of 40 per cent.

The effects of inanition upon the subsequent growth in young animals have also been frequently studied. In the first place numerous investigators (Minot '91 and Lepine '75a in guinea pig; Hatai '07, Ferry '13, Stewart '16, Jackson and Stewart '18, '19, '20, in the albino rat; Robertson '15 in mice; Springer '09 and Morgulis '11, in the salamander) have found unusually rapid growth upon refeeding after inanition, so that (unless the inanition is prolonged) the organism tends to recover the body weight normal for its age. According to Tobler and Bessau ('14), the abnormally rapid growth following retardation is probably due to the fact that cell-division has proceeded meanwhile, making conditions

unusually favorable for growth on refeeding. Robertson ('23) and others have thought that inanition may facilitate subsequent growth by the removal of accumulated inhibitory products.

**Ultimate Effects.**—As to the question of the ultimate effects of the inanition and the possibility of a permanent stunting in the later growth of the body, the results of animal experiments appear somewhat conflicting. Thus Hatai ('07) and Stewart ('16) and Jackson and Stewart ('18, '20) obtained complete

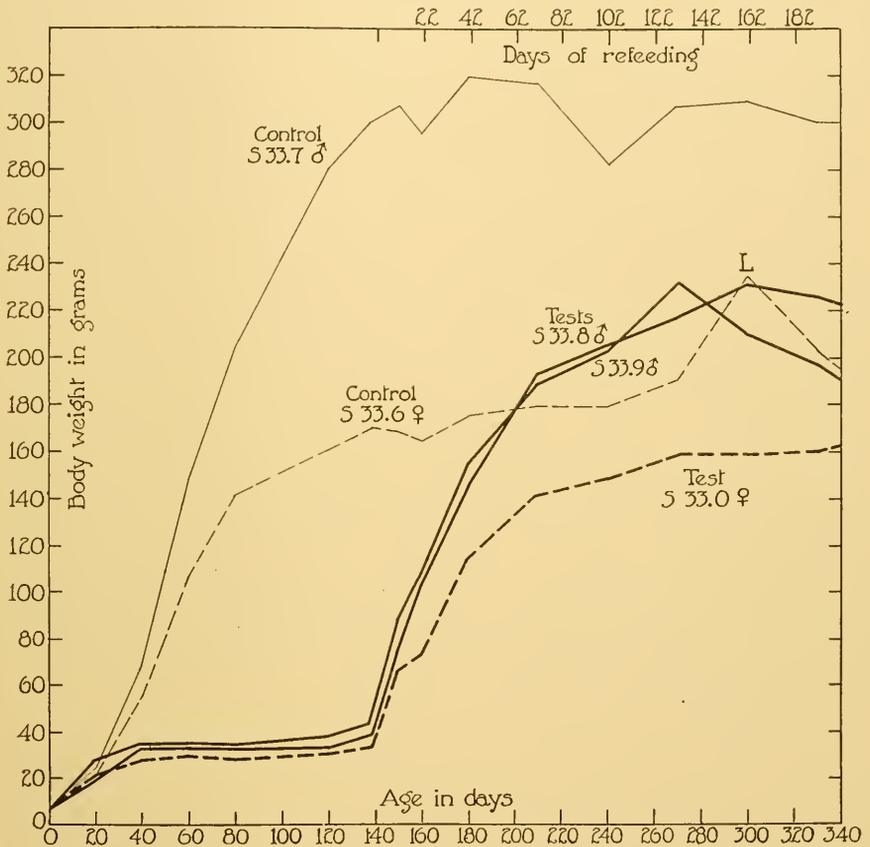


FIG. 41.—Chart showing curves of growth in albino rats amply refeed after underfeeding from 3 to 20 weeks of age. (Jackson and Stewart '20.) L indicates the birth of a litter in the control female.

recovery upon refeeding young albino rats which had been underfed for various periods beginning at three or four weeks of age. Aron ('14) noted no permanent stunting of rats underfed less than 150 days. Similar results were obtained by Osborne and Mendel ('14a, '15a), who found no suppression of growth capacity in young rats whose growth had been retarded for long periods by various inadequate diets (to be mentioned later). On the other hand, Aron ('10, '11, '14) and Brüning ('14) found that severe underfeeding of young dogs and rats apparently prevents them from reaching normal adult size upon later full feeding. Jackson

and Stewart ('19, '20) obtained the same result if the inanition of the rats is begun at a very early age or is protracted over a long period. They therefore conclude that "The ultimate effect varies according to the length of the underfeeding period, the age at which the inanition occurred, the sex (body weight more affected in males), the severity and the character of the inanition" (see Figs. 41 and 42). In steers held at maintenance by underfeeding for nearly a year, Moulton, Trowbridge and Haigh ('21) failed to obtain full recovery of the normal body weight, length, width and circumference, even after 3 years of full refeeding.

As to recovery of normal proportions, the results of Stewart ('16) and of Jackson and Stewart ('19) indicate that upon refeeding young albino rats after

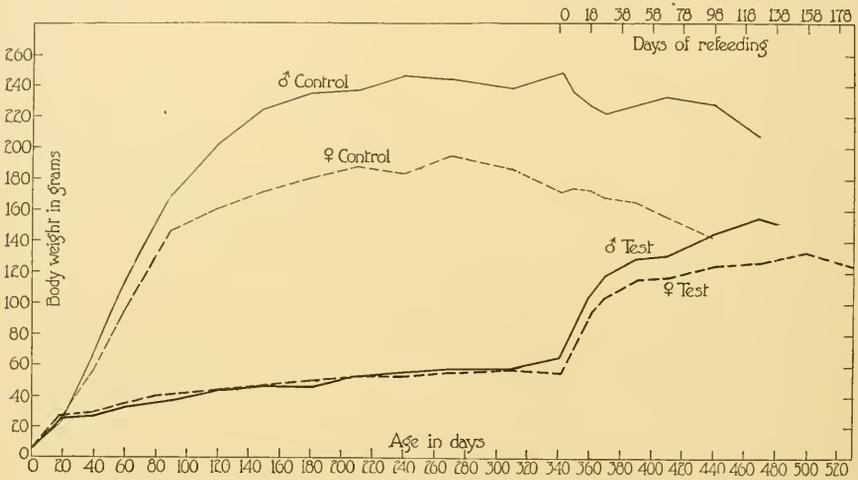


FIG. 42.—Chart showing curves of growth in albino rats amply refeed after underfeeding from 3 weeks to 1 year of age. (Jackson and Stewart '20.) The test rats fail to recover fully, remaining permanently stunted.

underfeeding for various periods, the head, limbs, trunk and tail rapidly regain their normal conditions (Table 7). Even in rats permanently dwarfed by long underfeeding, Jackson and Stewart ('20) found that the parts of the body regain the weights nearly normal for corresponding body weight, although body length and tail length become slightly subnormal relative to body weight (Table 8).

In the *human species*, the available evidence indicates that the process of recovery from inanition is very similar to that in other mammals (*cf.* Carrington '08). As previously mentioned, numerous voluntary adult fasts of 30 days or more are recorded, with subsequent recovery from loss of 20–25 per cent in body weight. Recovery from still greater losses is not unusual after periods of malnutrition due to chronic illness. Duflocq (Fernet '01) noted complete recovery in a hysterical girl, aged 15, who had lost 38 per cent in weight through total inanition. In the Russian famine, Ivanovsky ('23) observed recovery from extreme emaciation. On the other hand, there are definite limits beyond which recovery is impossible, as in the case reported by Meyer ('17), where recovery

failed in a man after loss of about 40 per cent in body weight from a fast of 60 days on water alone.

Some data concerning the recovery from inanition in infants and children have already been mentioned. Rapid recuperation after temporary retardation of growth has been noted by Coudereau ('69), Pagliani ('79), Camerer ('93), Filliozat ('09), Holt ('18), Czerny ('21), Goldstein ('22), and others. Quest ('05) found that in infants a loss of more than 34 per cent in weight is usually fatal, while Rosenstern ('11) has observed only 3 cases of nurslings surviving a loss of over 32 per cent (the maximum being 35 per cent). Baudrand ('11) distinguishes *primary* atrophy (constitutional, due to defect in the germ cell) from *secondary* atrophy (due to inanition from extrinsic causes), only the latter type being capable of recuperation. Thus in 73 underweight (not premature) newborn, Opitz found that 28.7 per cent made quick recovery of normal weight; 27.4 per cent continued growth parallel to the normal curve; while 43.9 showed continued retardation, the growth curve becoming progressively subnormal. It is generally believed that children poorly nourished over long periods will not attain normal adult size (Burk '98, and others) although this is difficult to prove. Tobler ('13) observed a child weighing 4,500 g. at birth which upon weaning at 7 months suffered a chronic malnutrition from dyspepsia, which retarded growth until well into the second year. Although the digestive trouble was later fully overcome, the child was permanently stunted in growth, with a length of only 89 cm. and a weight of 10,500 g. at 8 years of age.

Recent data published by the German public health office on the height and weight of 69,000 Leipzig children of the *Volkschulen* (Jour. A.M.A., Nov. 4, 1922, 79:1623) indicate an increase in their average height in the period 1919-1921, especially for the ages 7 to 10. The increase in weight was proportionately less, and was greater in 1919-20 than in 1920-21. The present weights are still below those just previous to 1914 (prewar period). These children may yet become normal, but it is quite possible that permanent dwarfing may occur as a result of severe or protracted inanition during infancy or childhood, in accordance with the results obtained by experimental inanition upon animals.

## CHAPTER V

### EFFECTS OF INANITION ON THE BODY AS A WHOLE (*Continued*)

#### EFFECTS OF PARTIAL INANITION

Under this heading will be considered the changes produced by deficiencies in the various essential food factors—protein, fats, carbohydrates, inorganic salts, vitamins and water. Some of these have already been referred to incidentally under total inanition. In many cases, indeed, it is quite probable that the effects of total inanition, especially when incomplete (general underfeeding), are in reality due not to caloric insufficiency, but to the inadequacy of some one of the special dietetic factors, in accordance with Liebig's "law of the minimum." During protracted underfeeding, the limiting factor will be that essential which is the first to become exhausted in the body so that the deficiency becomes manifest. The time required for exhaustion of the various essential substances will depend upon (1) the amount of each substance which is stored in the body as available reserve; (2) the rapidity with which each substance is consumed in the body (which in turn depends upon various factors influencing metabolism); and (3) the intake of each substance in the food, in case of incomplete inanition. The exact character of the deficiency in total inanition, either complete or incomplete, is therefore exceedingly variable according to the species, age, individual, environment, etc.

Exhaustion of all the essential food substances in the body at the same time is practically impossible; and the depletion of but a single substance is rare under ordinary circumstances. What usually happens during under-nutrition is that more than one substance becomes exhausted, or falls below the minimum required, so the symptoms are likely to be those of a mixed deficiency. The variation in the factors which become exhausted may explain why the "deficiency diseases" are so variable in their character, with more or less resemblance to total inanition on the one hand, and to the various individual forms of partial inanition on the other. Of interest in this connection is the claim of F. Müller ('97) that several emaciating conditions (infectious fevers, malignant growths, severe diabetes, etc.) exhaust the protein content of the body more than does ordinary inanition. Opitz (*Zentralbl. f. Gyn.*, 1924, 48:2) holds that the so-called toxicoses of pregnancy are essentially deficiency manifestations of inanition in the maternal organism. The general pathology of partial inanition is discussed by Weill and Mouriquand ('19).

The **cause of death** from inanition, either total or partial, has often been discussed but is still uncertain (Howe '12). Various theories have been proposed. It was early recognized that death is not due simply to exhaustion of stored food materials, since fat may persist in appreciable amount. Collard de Martigny (1828) ascribed death from starvation to impoverishment of the blood, resulting

from loss of solids. Chossat ('43) concluded that death is caused by the fall of temperature. Although accepted by Bourgeois ('70), this cannot be the primary cause, since it is obviously inapplicable to cold-blooded animals; and even in the warm-blooded, death cannot be prevented by artificial maintenance of heat. Lukianov believed that death is due, not to exhaustion of reserves, but to inability of the organs to utilize them; but he failed to explain this inability. Beeli ('08) held that death is due to asphyxia, the accumulation of toxic materials causing paralysis of the respiratory center in the medulla. Lipschütz ('18) concluded that death from inanition is produced by auto-intoxication, due to toxins resulting from disordered metabolism of the malnourished tissues.

Whether it be a direct effect of the inanition, or indirectly caused by toxins in circulation, a lowered resistance to infection is a well-known result of various types of inanition, both total and partial. Thus the immediate cause of death following inanition is frequently an infectious complication, such as terminal bronchopneumonia in the human species. The effects of inanition upon the ductless glands may also form an important complication as will be mentioned later under the various organs. It is therefore evident that the immediate cause of death from inanition may vary according to circumstances.

On the other hand, since most diseases, especially the chronic disorders, interfere more or less with the process of nutrition, inanition is usually present as a complication. As expressed by Chossat: "L'inanition, on peut donc le dire, est la cause de mort qui marche de front et en silence avec toute maladie, dans laquelle l'aliment n'est pas à l'état normal. Elle arrive à son terme naturel, quelquefois plus tôt, quelquefois plus tard que la maladie qu'elle accompagne sourdement et peut devenir ainsi maladie principale là où elle n'avait été qu'épiphénomène."

The general effects of partial inanition upon the body as a whole will now be summarized briefly, following which the various individual types of partial inanition will be considered.

#### SUMMARY OF EFFECTS OF PARTIAL INANITION ON THE BODY AS A WHOLE

Various essential proteins (amino-acids), salts (of P, Ca, Na, Fe, I), vitamins (A, B, C and probably others) and water cannot be synthesized in the vertebrate organism and must therefore be present in the food-intake. If they are absent from the food-intake, or inadequate in amount, decline in body weight with various other characteristic symptoms of malnutrition supervene, as soon as the available supply of reserves of these substances stored within the body is exhausted. The period required for such depletion varies according to the substance in question, the species, age and previous nutritive condition of the individual, as also according to various environmental factors influencing the process of metabolism whereby the essential substances are consumed.

Each of the essential food factors has its special function in nutrition, and the deficiency in each case results in the characteristic symptoms of the corresponding "deficiency diseases." Thus malnutritional edema and pellagra are

probably due chiefly to protein insufficiency. Phosphorus and calcium are especially important in the formation of bone, and their deficiency (with lack of a special vitamin) may result in rickets or similar disorders with skeletal lesions. Deficiencies in vitamins A and B give rise to characteristic syndromes (the former to xerophthalmia; the latter to beriberi and polyneuritis), and deficiency in vitamin C causes scurvy. Water is also essential, but fats and carbohydrates may be replaced by an excess of protein in the diet. In most cases of partial inanition, more than one essential factor is simultaneously depleted, the resulting malnutrition therefore being due to a mixed deficiency.

In a strict sense, a total inanition is non-existent. Even in the complete absence of food-intake, the living cells of the body are not entirely deprived of nutriment, being still nourished by the blood-stream and lymph, which are more or less imperfectly replenished by absorption of such stored or reserve materials as may be available in the organism. When this nutriment becomes inadequate with respect to any essential factor, the cells of the tissues most concerned with that factor will undergo disordered metabolism, although in young animals an abnormal, dystrophic growth may continue for some time. Ultimately, and especially when the cell-nutriment becomes inadequate to supply the energy required for the vital functions, cell atrophy and degeneration occur (as will be shown later), the body weight falls and death follows.

On account of this fundamental similarity between total and partial types of inanition, it is not surprising to find that they resemble each other in many of the more general effects. Thus in both cases there is usually a marked and progressive loss of body weight with resultant emaciation in the adult, the limits being about the same in both types of inanition. In the young there is in both cases a retardation or inhibition of growth, frequently accompanied by dystrophic growth phenomena which vary according to circumstances. Finally there is, after partial as well as total inanition, the possibility of recuperation upon adequate refeeding, depending upon the character and extent of the injury produced by the inanition. In both cases, there is an upper (somewhat variable) limit beyond which death is inevitable. There is also a lower limit, below which perfect recovery is possible. Between these upper and lower limits of inanition, there is probably in all cases a degree of injury possible which permits of only partial recovery, resulting in a variable degree of dwarfing and deformity of the body. The available evidence indicates that in some cases the long-continued suppression of growth during partial (inadequate protein) inanition injures the capacity of subsequent growth much less than does total (incomplete) inanition. The more specific effects of the various types of inanition will be considered in the subsequent chapters upon the individual organs.

#### EFFECTS OF VARIOUS TYPES OF PARTIAL INANITION ON THE BODY AS A WHOLE

**Protein Deficiency.**—It has long been known that protein forms an essential factor in human and animal nutrition. The earlier experiments (*cf.* Munk '91; Rosenheim '91) upon protein deficiency, however, were unsatisfactory in two important respects. In the first place, they neglected other factors, such

as inorganic salts and the recently discovered vitamins, so that they often represent mixed deficiencies of uncertain character from which no definite conclusions can be drawn. In the second place, only within the past decade has it been generally recognized that the *quality* of the dietary protein is even more important than the quantity (Hart, McCollum, Steenbock and Humphrey '11). Chiefly through the investigations of Osborne and Mendel ('11, '11a, '12a, '12b, '14, '15, '15a, '16b, etc.) and their co-workers it is now recognized that among about 18 amino-acids which, in varying proportions, constitute the ordinary proteins of foods, several, though essential for nutrition, cannot be synthesized in the animal body and must therefore be present in adequate amount in the food-intake. Among these essential amino-acids, tryptophan, lysin, tyrosin, and cystin are especially important for normal growth, which is prevented or retarded in the absence or insufficiency of any one of them. Liebig's "law of the minimum" is therefore considered applicable to the essential amino-acids in the diet (Osborne and Mendel '15a, '16b). Thus on account of their varying amino-acid content, diets with some isolated proteins (gliadin, edestin, glutenin, casein) may permit maintenance of young rats without growth for long periods, while others (zein, gelatin) do not even suffice for maintenance, but occasion more or less rapid decline in body weight.

Contrary to the previously mentioned results of (incomplete) total inanition in man and animals, Osborne and Mendel ('11, '11a), in young rats held at maintenance for long periods (up to a year or more) by incomplete protein diets, found no changes in the body proportions, excepting the possibility of continued growth in the nervous system. Mendel and Judson ('16), however, described persistent skeletal growth in mice retarded by diets inadequate in protein or salts, as well as by simple underfeeding. Mendel later ('17) described abnormalities of growth on various insufficient or inadequate diets.

**Recovery upon Refeeding.**—Osborne and Mendel also ('11, '11a, '12a, '12b, '14a, '15a; Mendel '14, '15) found in the retarded rats a remarkable capacity for recuperation upon adequate refeeding, and concluded that it seems impossible by this type of inanition, no matter how long continued, to suppress the capacity for growth, or to produce permanently dwarfed individuals. It also appears possible in this way to increase the total span of life in rats, and refeed females have borne apparently vigorous young after the normal age of menopause (Osborne and Mendel '17). Wheeler ('13) likewise obtained normal recovery in young mice retarded in growth for long periods on gliadin or casein diets.

This failure to produce permanent dwarfing by long continued suppression of growth in rats and mice on incomplete protein diets is in striking contrast with the (previously mentioned) results of Jackson and Stewart and others in animals dwarfed by underfeeding. It should be noted, however, that the incomplete protein experiments were not begun upon very young animals, and it is possible that a similar retardation of growth at earlier stages (between birth and the weaning period) would result in permanent dwarfing, as found in rats by the underfeeding experiments, and in certain types of partial inanition (to be mentioned later).

Among experiments representing protein deficiency, complicated by absence of other essential factors, may be mentioned those of Hatai ('04, '07), who obtained loss of about 30 per cent in body weight in young rats on starch-suet diets, with rapid recovery on normal refeeding. Schulz ('12) found no increase in length or weight in puppies fed farinaceous gruels. On refeeding adequate diet after 3½ months, full recovery was obtained if the experiment began with puppies at 2 to 4 weeks of age, but not with those at 4 days of age. Brüning ('14) also found that young rats soon cease to grow on an unbalanced carbohydrate diet, recalling the "Mehlnährschaden" of human infants. Albrecht ('13) stated that protein-poor diet affects pregnant mares, though not the development of the fetus; but Evvard, Cox and Guernsey ('14) observed that feeding maize diet (mixed deficiency) to pregnant sows causes reduction in the size and vigor of the newborn pigs. Funk and Macallum ('14) held the body weight of a young chicken nearly constant (at 150-160 g.) for about 7 months on a diet of rice and cod liver oil (mixed deficiency).

In the growth of the frog tadpoles, Emmett and Allen ('19) concluded that the quality of the protein in the diet is more important than the quantity. Evans and Bishop ('22) demonstrated the effect of variable quantities of protein upon the growth curve of albino rats. Slonaker and Card ('23, '23a, '23b, '23c, '23d) have shown that in general the growth and reproduction of albino rats are much less upon a protein-poor mixed vegetable diet than upon the same with the addition of animal protein (omnivorous diet).

**Malnutritional Edema.**—That general or localized edema (with or without ascites) may be produced in rats by deficiency in protein (or fats), with abundance of water in the diet, is the conclusion reached by Denton and Kohman ('18) and Kohman ('19, '20). This may also be responsible for the dropsy occurring in malnourished sheep, cattle and horses. (Friedberger and Fröhner '08; Hoare '15; Fröhner and Zwick '15; Hutyra and Marek '16). Many authors believe that this deficiency is likewise the primary (or at least an important) factor in the edema commonly observed in conditions of human famine (Cornish; Maase and Zondek '17, '17a; Schiff '17; Lange '17; Park '18; Wells '18; Schittenhelm and Schlecht '19; Maver '20; Prince '21; McCollum '22). This condition may resemble the dropsical type of beriberi (Budzynski and Chelchowski '16); and McCollum ('22) holds that "wet beriberi" is due to a double deficiency of protein and vitamin B. Edema may also be associated with pellagra (Enright '20). Harden and Zilva produced edema in a monkey on a diet without vitamin A, and Fracassi ('22) considers vitamin deficiency an important factor in "hunger edema." Many writers, however, as already mentioned, have considered that "famine edema" is due to general quantitative (incomplete total) inanition, rather than to qualitative, specific or partial inanition. Excess of carbohydrates and water is also frequently considered an accessory factor (McCarrison '21; McCollum '22). Curschmann ('22) believes the effect is due primarily to endocrine disturbance.

In describing the "famine edema" in German cities, Kraus ('19) states that "Die bleichen, bis 40 pct. ihres ursprünglichen Gewichtes abgemagerten, hydropisch geschwollenen, durch Muskelschwäche unbeweglich gewordenen

Menschen boten einen nicht weniger schrecklichen Anblick als die *Facies pestica*. Matthias ('19) describes two types of edema, one with ascites but without adipose atrophy, ascribed to partial inanition; the other involving general edema and brown atrophy of adipose tissue, ascribed to general inanition. The immediate cause of the edema in most cases is probably an injury of the capillary walls (to be considered in a later chapter), without renal or cardiac lesions. Croftan ('17) has emphasized the importance of edema as a danger signal in the starvation treatment of diabetes.

**Pellagra.**—This malady was observed in Spain by Casal about 1730 and in Italy by Frappoli (1771), who introduced the word *pellagra* ("skin lesion"). Various theories as to its etiology have been proposed, which have recently been reviewed extensively by Raubitschek ('15), Harris ('19), Snyder ('23) and Vaughan ('23). The characteristic condition of malnutrition associated with the disease was observed early, and the theory that pellagra is caused by general *inanition* was advocated by Soler (1791), Cerri (1804-'05), Robolotti ('65) and others.

That *maize diet* may be a factor in pellagra was suspected even by Casal, and was noted by many of the earlier writers. More specifically, the deficiency of this diet in *protein* as a causal factor was advanced by Marzari (1810), Morelli ('55), Lussana and Frua ('56) and Calmarza ('70) although other environmental factors were recognized. This theory of protein deficiency, in more or less modified form, has recently been supported by Boyd ('20), Roberts ('20), and by Goldberger and his associates in several papers, but is opposed by Hindhede ('23). The theory that pellagra is caused by *toxins* produced by changes in the maize was also supported by various early writers, and more recently by Lombroso and others, even down to the present (Marie '08, '10; Nichols '12, '13; Centani '14; Niles '16, '17). The theory of *infection* as a cause of pellagra has also had many adherents (*cf.* MacNeal '21), and recently the possibility of *avitaminosis* has been suggested by Rondoni ('15, '19) and by Funk ('22). McCollum and Simmonds ('17) state that typical pellagra-producing diets are deficient in the fat soluble A vitamin, inorganic salts, and protein.

Animal experiments to determine the cause of pellagra have been somewhat inconclusive. Maize or other presumably pellagra-producing diets were fed by Nicholls ('12, '13) to rats; by Rondoni ('15, '19) and Rondoni and Montagnani ('15) to guinea pigs; by Chittenden and Underhill ('17) to dogs; by Sundwall ('17) to rats, monkeys and pigs; by Sullivan ('20, '20a) to pigeons, and by Chick and Hume ('20) to monkeys. Varied symptoms of malnutrition were thereby produced, but apparently in no case did these resemble very closely those of typical human pellagra.

On account of the immense literature on pellagra (Raubitschek '15 gives a bibliography of 1,472 titles including "nur bemerkenswerte und wissenschaftliche Publikationen"), it will be possible to mention only a few of the papers, more especially those dealing with various phases of its pathology. As to the effects on the human body as a whole, there is noted a condition of general malnutrition, with variable loss in body weight, up to extreme emaciation

(Tuczek '93; Nichols '15, '19; Sundwall '17; Goldberger and Wheeler '20; and others). In some cases, there is a tendency to edema ("wet form" of pellagra), ascribed by Fraenkel ('69-'70) to renal and cardiac lesions in "pellagra typhosus."

Marie ('08, '10) states that loss in body weight is not a constant symptom, but occurred in 84 per cent of the females and 74 per cent of the males. Calderini ('47) found 514 out of 1,005 cases notably under weight. The decrease in weight is said to correspond to progressive repugnance for food, although some cases (especially of the typhoid type) may appear well nourished. In late stages there is usually extreme emaciation.

**Deficiency in Fats and Carbohydrates.**—It has generally been held that carbohydrates are desirable in the diet, in order to avoid the ill effects of the large amounts of protein or fat otherwise necessary to supply sufficient calories. It is well known, however, that dogs and other carnivorous animals may thrive upon a meat diet nearly free from both carbohydrate and fat. Prochownik ('89, '01, '17), advocated a diet rich in protein and poor in carbohydrates and water, in order to reduce fetal size. Osborne and Mendel ('12, '20a) obtained normal growth in rats on nearly fat-free rations. They ('21b, '21c, '21d) have recently shown that it is quite possible to obtain growth of rats to adult size on a diet practically free from digestible carbohydrates; and the body weight may be at least trebled without *either* fat or carbohydrate. Evans and Bishop ('22) have also obtained excellent growth in rats on diets nearly free from fats or carbohydrates.

Most of the earlier experiments on fat deficiency were complicated by the fact that the (then unrecognized) "fat-soluble A" vitamin was also eliminated, which is now known to be essential for growth. This probably explains the results of McCollum and Davis ('13), Hatai ('15) and Stepp ('17), who found growth retarded in rats on lipid-free diets. Drummond ('20) observed good health but subnormal growth (possibly due to other factors) on fat-free rations; but Drummond and Coward ('21) obtained normal growth from weaning to maturity in rats on a diet nearly free from neutral fat.

It is well known that both fats and carbohydrates may be synthesized in the animal body, and McCollum, Halpin and Drescher ('12) have shown that this is true also for lecithin (phosphatized fat). Normal nutrition is therefore possible in the absence of these substances from the diet, although the length of life during total inanition is materially affected by the amount of body fat present (Voit '01a).

**Deficiency of Inorganic Salts.**—The necessity for an adequate supply of salts in the food-intake has long been recognized, and was emphasized by v. Liebig. Their relative abundance in foods and their storage in the body are discussed by Forbes ('19). Forster ('73) reviewed the earlier literature on this question and experimented with low salt diets (also probably somewhat deficient in vitamins). On such diets, pigeons perish in 13-29 days, and dogs survive 26-36 days, with progressive weakness and paralysis. Gaube ('97) found that mineral hunger in pregnant rabbits causes abortion, with stillborn or poorly developed young. A diet poor in minerals (Na, Ca, Mg, K and Fe) likewise resulted in less vigorous chicks. Hart and McCollum ('14) concluded that the

restricted growth of herbivora, rat and swine on wheat or maize diets is not due to protein deficiency alone, since the addition of certain salt mixtures resulted in improved (though still subnormal) growth. McCollum and Davis ('15a) found that the addition of salts to wheat diets gives great improvement, but still less than half normal growth in rats, on account of other deficiencies. Czerny and Finkelstein emphasize demineralization as a factor in athrepsia. Grabley ('19) believes that mineral deficiency in the diet is a cause of imperfect growth and nutrition in man. Only slightly subnormal growth in rats on low salt diets was found by Evans and Bishop ('22), but H. G. Miller ('23) noted marked retardation in the growth of young rats with dietary deficiency of potassium.

Babcock ('05) noted that cattle ordinarily obtain from their rations sufficient sodium chloride for maintenance, but that during protracted lactation they become progressively malnourished and will perish unless additional salt is supplied.

Among experiments resulting in malnutrition or growth failure on diets considered deficient in **calcium** (in some cases also deficient in other essentials) are those by Chossat ('42) on pigeons with calcium-poor wheat diet; by Weiske ('74) on rabbits with "calcium-free barley;" by Hart and Steenbock ('19) on pigs with maize and oats; by Elliot, Crichton and Orr ('22) on pigs with oatmeal, etc.; by Russell and Morrison ('19) on cattle with oats; and by Haigh, Moulton and Trowbridge ('20) on a calf with silage and maize diet.

The maize diet fed by Evvard ('12) to pregnant sows, resulting in weak and underweight offspring, was deficient in calcium as well as in protein. Dibbelt ('10, '11) maintained that there is normally a physiological "calcium hunger" in newborn mammals (including human infants), the shortage of calcium in the maternal milk (denied by Wieland '13) being supplemented by absorption of calcium stored up in the bones of the offspring during the fetal period. McCrudden ('13) concluded that human dwarfing may be due to metabolic disturbance associated with calcium deficiency during the growth period. The constitutional effects of calcium deficiency in children have been reviewed recently by Stheeman ('21). This question will be discussed further in connection with rachitis, and in the chapter on the skeletal system. Some effects observed by Korenchevsky ('23) in the offspring of rats on diets deficient in calcium or vitamin A will be mentioned later under the vitamins.

Voit ('80) noted that in spite of the skeletal lesions the general growth of the body is not inhibited in dogs on calcium-poor diet. Stöltzner ('09a) claimed that this, as well as the continued growth of the body during experimental anemia with iron-poor diets, is contrary to the "law of the minimum" (as advocated by von Bunge). Similar results with diets deficient in phosphorus will be mentioned later. The calcium and phosphorus necessary for growth under these conditions are provided by absorption from the supply already stored in the skeleton. Osborne and Mendel ('18a), however, maintain that the "law of the minimum" holds for all essential salts in the diet, failure of growth in the whole body resulting where the limiting factors are deficiencies in the salts of chlorine, sodium, magnesium, potassium, calcium and phosphorus.

McCullum and Simmonds (McCullum '22) found that rats, kept at an early age upon diets in which the inorganic content is unsatisfactory, develop abnormal forms and become permanently stunted. They become stocky, owing to failure to grow in length. This permanent suppression of growth is contrasted with the successful recuperation after retardation by vitamin deficiency, likewise after inadequate protein diet (Osborne and Mendel) and resembles the results of general underfeeding (Jackson and Stewart).

The effects of **phosphorus deficiency** upon growth have likewise been demonstrated. Hart, McCullum and Fuller ('09, '09a) found that pigs at 40-50 pounds made normal gain in body weight up to 75-100 pounds on low phosphorus grain diets. Then followed loss of weight, weakness and collapse (presumably due to exhaustion of the available phosphates stored in the skeleton). Good results followed upon the addition of calcium phosphate to the diet.

Lipschütz ('10, '11) obtained continued though subnormal growth in puppies on a phosphorus-poor diet of rice and egg albumin, supplemented by salt mixtures. The skeletal lesions resembled those of scurvy (vitamin deficiency). Heubner ('11) similarly observed that puppies continued to grow for 7 weeks on rice diet, which is poor in phosphorus (also otherwise deficient), with subsequent decline. On a tapioca diet, growth ceased in 3 or 4 weeks, and marked emaciation followed. On refeeding with rich mixed diet, normal appearance and health were rapidly restored, but in body size and weight the dog remained permanently dwarfed, corresponding to a puppy of 3 months. Masslow ('13) also found that puppies on phosphorus-poor diet continue nearly normal growth for about one month, but later lose weight, become emaciated and die. Sherman ('11) concluded from a study of typical American dietaries that human malnutrition is frequently due to phosphorus deficiency. Further data on calcium and phosphorus deficiency will be mentioned later in connection with the discussion of rickets.

Emmett, Allen and Sturtevant ('20) and Swingle ('22) cite evidence that **iodin** is effective in causing the metamorphosis of amphibia, which recalls the well-known experiments of Gudernatsch, showing acceleration of metamorphosis by thyroid feeding. The question of iodine deficiency will be considered later in the chapter on the thyroid gland. Smith ('17) concluded that iodine deficiency in the diet during gestation in sows results in the birth of weak, hairless pigs of full size but with edematous skin and other abnormalities, ascribed to disturbance of function in the fetal thyroid gland. There may be a similar occurrence in sheep and other domestic animals.

Fetzer ('13) found that, on diets deficient in **iron** pregnant rabbits can supply from their own bodies the iron necessary for fetal growth only up to a certain limit, beyond which fetal death occurs. Hess ('22) cites evidence indicating that in some cases a lack of iron in the diet of infants may lead not only to anemia but also to marked retardation in growth, with prompt recovery upon addition of spinach.

**Rachitis.**—While the lesions in rickets appear most prominent in the skeleton (to be considered in a later chapter), it is nevertheless a general metabolic disorder with certain broader aspects which may be briefly mentioned here. The

etiology of rickets has been much disputed. It has generally been held to be due to dietary insufficiency of some kind, although infection, toxins, or bad hygienic conditions in general have been frequently considered primary factors, even down to the present (Looser '20; Paton and Watson '21). Esser ('07) claimed the production of rickets by overfeeding in young rats; and it has even been observed to appear spontaneously in this species by Erdheim ('14) and Pappenheimer ('14). Some consider that rickets is produced indirectly through effects on the endocrine system (Stoeltzner, '21).

Among those who consider rickets to be caused by dietary deficiency, there have been varied opinions as to what factor is deficient. For human rickets, a deficiency in fats was sometimes held responsible (Vincent '04, Cheadle and Poynton '07; opposed by Hutchinson '20 and others); although mineral deficiency has frequently been suspected, especially in rachitoid disorders in animals, such as that in cattle described by Lötsch and Lange ('12). Lehnerdt ('10) and Röhmman ('16) hold that rickets or "pseudorickets" may be caused by (1) deficiency of calcium salts in the diet; (2) deficient calcium absorption in the intestine; (3) excessive calcium excretion; or (4) defective calcium assimilation by the osteoblasts. The disputes as to whether the disorders produced by calcium and phosphorus deficiencies in animal diets are really identical with human rickets will be discussed in the chapter on the skeletal system.

Recently the controversy has shifted to the question concerning the causation of rickets by deficiency in vitamin A, which was advocated by Mellanby ('19), Nathan ('20), Higier ('22) and others; but was opposed by Hess and Unger ('19), Hess, McCann and Pappenheimer ('21), Mackay ('21), Paton and Watson ('21, '21a) and others. It may be stated here, however, that the most recent work on experimental rickets by E. Mellanby ('21), Sherman and Pappenheimer ('21) and by McCollum and his associates indicates strongly that the cause of rickets is not a single deficiency, but it is complicated in character and dependent upon various factors. For puppies, Mellanby ('21) considers the following as important: (1) a deficiency of calcium and phosphorus in the diet; (2) a deficiency of fat containing the antirachitic vitamin; (3) excess of bread, other cereals and carbohydrates; (4) absence of meat; (5) excess of the protein portion of caseinogen, free from calcium; (6) confinement. McCollum and his coworkers have recently shown that in young rats the experimental production of rickets (or closely allied conditions) depends largely upon the calcium-phosphate ratio in the diet, either low calcium or low phosphorus being effective, in the absence of a "fourth vitamin" (distinct from, though closely associated with vitamin A) which promotes calcium deposition in ossifying tissues (McCollum, Becker and Simmonds '22, '22a; McCollum '23). Byfield and Daniels ('23) found it impossible to produce typical rickets in rats on diets low in calcium, phosphorus or butter fat, except when the experiment was extended to the second generation. Chick *et al.* ('23) conclude from clinical observations and animal experiments that the three main factors in the etiology of rickets are (1) an organic dietary factor concerned with the calcification of bone; (2) light; and (3) the amount and relative proportions of calcium and phosphorus in the diet. An extensive

historical survey of the questions concerning the etiology of rickets has recently been made by Park ('23) and by Vaughan ('23).

**Human Rickets.**—For the present, we are concerned merely with the more general effects of rickets upon the growth of the body as a whole, leaving a consideration of the effects upon the skeleton and other organs for later chapters.

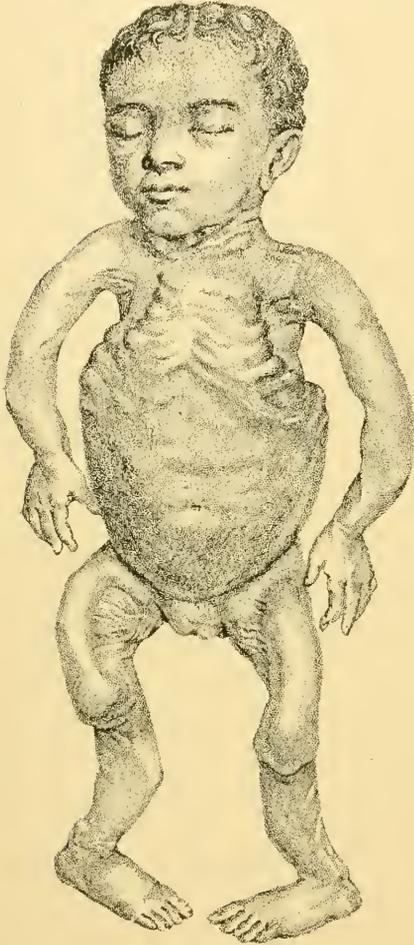


FIG. 43.—Ventral view of a child, 8 years old; died from rickets. Note the enlarged head, deformed limbs, distended abdomen and deformed thorax (marked groove in the costochondral region, with enlarged costochondral joints, forming a "rickety rosary"). (Beylard '52.)

The occurrence of fetal rickets has often been claimed, but according to Wieland ('10) it is very doubtful. Huenekens ('17) found premature infants especially susceptible to rickets, and J. H. Hess ('23) gives the characteristics in this class of cases. Rickets in the human species does not ordinarily appear before the latter half of the first year, and is most frequent during the rapid growth period of the first two years. It may occur at any later age, however, and in the adult it is usually designated as osteomalacia.

According to Ruffer ('21), rickets has existed in Egypt since 2,000 B.C., and probably much earlier. Deformity of the spine and legs (probably rachitic in origin) was described by Soranus as prevalent among Roman children of the first century, A.D. In most civilized countries today rickets is still a very potent factor in stunting growth, producing deformity and lowering resistance to infection (Findlay and Ferguson '18). Kissel ('97) noted a variable degree of rickets in 80 per cent of 2,530 children examined at Moscow; and Schmorl ('09a) found evidence of either active or healed rickets in 345 (89.4 per cent) of 385 children under 5 years of age autopsied at Dresden. Increased frequency of rickets during and since the world war has been reported by numerous observers.

The **external appearance** of the body in rickets is shown in Fig. 43. The well-known characteristic features were recognized by Whistler (1645) and Glisson (1650), and described by many later observers. They include an enlarged cranium, deformed thorax (with enlarged costochondral joints often forming a "rickety rosary"), distended abdomen ("pot belly"), enlarged wrist, knee and ankle joints, with variable curvature of the lower limbs. Most of the deformities are the mechanical result

of the softening of the skeleton, as will be discussed later. Seibold ('27) described three typical stages in the development of the disorder.

In more recent descriptions of human rickets, Engel ('20, '20a) found that in German children of 2-5 years, rickets has become increasingly prevalent since 1917. Growth is much retarded in severe cases. According to data cited from Baginsky by Wohlaer ('11), body length is not much affected by rickets in the first year, but retardation becomes progressively evident in the second and third years. The body, though dwarfed, may be well proportioned and nearly normal in form; but the musculature is scanty and there is marked deformity of the limbs and thorax in severe cases, resulting in a prodigious number of crippled dwarfs. Looser ('20) stated that late rickets (or osteomalacia) is characterized by a general inhibition of body growth, with retardation in the development of the sexual organs and secondary sex characters. Well marked deformities of the trunk and limbs are characteristic, as described by Jenner ('95), Comby ('01), Vincent ('04), Wohlaer ('11) and others.

In **experimental rickets** of animals, the reported effects on the growth of the body as a whole are somewhat contradictory. Thus in puppies E. Voit ('80), Miwa and Stöltzner ('98) and Quest ('06) found continued growth without emaciation in rickets caused by calcium-poor meat diet, and Lipschütz ('10) noted that the general growth is not much retarded in rickets caused by phosphorus deficiency. This is confirmed by the more recent experiments of Mellanby ('21), with deficiency in vitamin A, etc. On the other hand, Sherman and Pappenheimer ('21) and McCollum, Simmonds, Kinney, Shipley and Park ('22) found growth retarded or suppressed in young rats with experimental rickets. Jackson and Carleton ('23) noted that in such rats the weight appears normal for body length, but that loss in body weight may be masked by increase in intestinal contents. Nevertheless, in animals, as in man, rapid growth appears most favorable for the development of rickets (at least during the latent period). General malnutrition (total inanition) appears distinctly unfavorable to the development of rickets, so that starvation, like sunlight, may even serve as a preventive or healing factor (Sweet '21; Jundell '22; McCollum, Simmonds, Shipley and Park '22).

Elliot, Crichton and Orr ('22) state that during rickets in pigs the growth rate appears to be retarded less in the head than in the rest of the body, so the head often appears unusually large in the later stages.

Stoeltzner ('09) and Mellanby ('21) have pointed out that rickets presents an apparent exception to the "law of the minimum," since the absence of an essential factor in the diet may result in distortion of skeletal growth, without suppression of growth in the body as a whole.

**Vitamin Deficiencies.**—As early as 1881, Lunin found that mice are unable to live long on an apparently adequate synthetic diet of proteins, fats, carbohydrates, salts and water. Since the addition of milk gave good results, he concluded that other (unidentified) substances indispensable for nutrition must be present in the milk. Similar experiments with better results were made by Röhmann ('03, '08, '16), probably because his artificial diets were not sufficiently purified. Hopkins ('06, '12) experimented upon rats with artificial purified

diets, confirming and extending the results of Lunin. His curves of body weight (see Fig. 44) indicate clearly the presence in milk of elusive "accessory factors," of which minute quantities are essential for growth. Osborne and Mendel ('11, '12) and McCollum and Davis ('13) similarly found that although maintenance of adult rats and growth in the young may be obtained for a time upon isolated and purified food substances, nutritive decline and failure inevitably follow, unless certain essential factors (designated as "vitamines" by Funk) are added to the diet. Billard ('22) noted a dropsical condition and subnormal growth in frog tadpoles on vitamin-free diet.

It is impossible here to review the results of the numerous investigations upon this phase of nutrition, which especially during the past decade have clari-

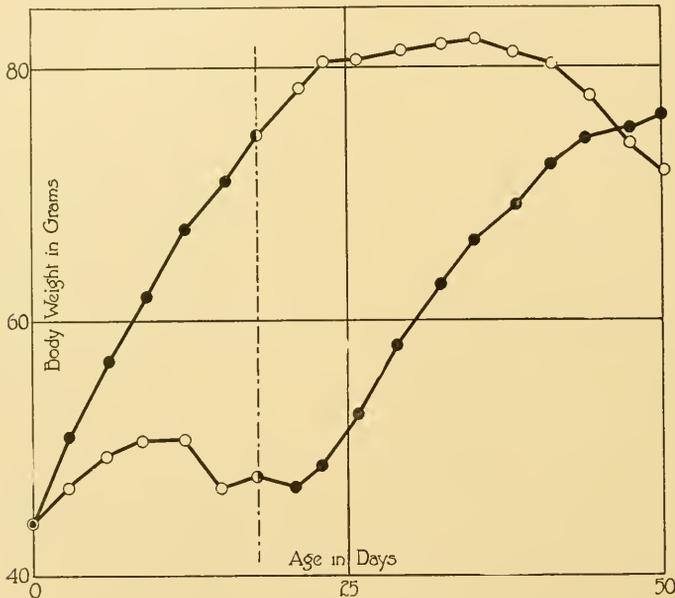


FIG. 44.—Chart showing the effects of vitamin deficiency upon growth in body weight of rats. The lower curve (up to the 18th day) shows the average retardation of growth (in 8 male rats) upon a vitamin-free dietary; the upper curve, for 8 similar rats, with addition of 3 c.c. of milk daily to the diet. On the 18th day, the milk was transferred from one set to the other, with marked effect upon the growth in each case. (Hopkins '12; Med. Res. Comm. '19.)

fied the relations of partial inanition to growth and have placed the etiology of several "deficiency diseases" upon a fairly substantial basis. The present status of the vitamin question was discussed in the symposium by McCollum, Mendel, Sherman, Shipley, Holt and Hess ('22), and the literature is reviewed in detail by the report of the Medical Research Council (by Hopkins *et al.*, 1919) and in the works by Langstein and Edelstein ('17), Stepp ('17), Aron ('20), McCarrison ('21), Funk ('22), Ellis and Macleod ('22), Sherman and Smith ('22), McCollum ('22), Mellanby ('22) and others. The following vitamins are now generally recognized: "fat-soluble A" or vitamin A, with which is usually closely associated the antirachitic factor or "fourth vitamin;" "water-soluble B" or

vitamin B ("antineuritic"); and the antiscorbutic "water-soluble C" or vitamin C. A fifth, or "vitamin X," has recently been discovered by Evans.

The chemical nature and the exact physiological functions of the vitamins are still uncertain. Hopkins concluded that they are catalytic, stimulative agents, possibly affecting both external and internal secretions. Similar views have been advanced by various workers. Chick ('20) emphasizes the greater need for vitamins *when metabolism is accelerated* (by work, low temperature, growth, pregnancy, lactation, etc.), which is very suggestive. McCarrison ('21) believes that in the absence or inadequacy of vitamins, there results a disturbance of metabolism, so that the other dietary constituents cannot be properly utilized in the various organs. Abderhalden ('22) concludes that the vitamins promote the oxidative processes in the cells of the body.

As many investigators have observed, there are marked differences among species as to the effects of vitamin deficiency, which will be mentioned later. Thus Hess ('22) states that:

"In relation to the antiscorbutic vitamin, man reacts as does the guinea pig; in respect to vitamin B, he reacts like the pigeon or fowl; and in respect to vitamin A (fat soluble factor), he resembles the rat. The rabbit, for reasons entirely unexplained, withstands deprivation of any vitamin with comparative impunity, and therefore is not employed in any biologic test for these factors. Furthermore, a diet which leads to a definite avitaminosis in one animal, leads to a quite different one in another animal. For example, a diet of polished rice brings about polyneuritis in the fowl or in the pigeon or in the rat, but induces scurvy in the guinea pig." Sugiura and Benedict ('23) have raised pigeons from hatching to maturity on diets deficient in both vitamins A and C.

The effects of vitamin deficiency upon the various individual organs of the body will be considered in the appropriate later chapters, but some more general effects upon the body as a whole may now be considered.

McCullum and Simmonds ('17, '18) observed that, since vitamins (A and B) are not synthesized in the body, they must be present in the diet or (after exhaustion of the amounts previously stored in the body) they will be absent from the milk of nursing rats, with consequent failure of growth in the young. It seems inappropriate to speak of any single "growth vitamin," since all appear (in most species) to be necessary for optimum growth. Funk, however, claims that the growth-promoting factor in vitamin B may be separated as a distinct "vitamin D" (*cf.* Funk and Paton, '22). Evans and Bishop ('22a, '23a, '23b) distinguish a "fertility conferring factor X," in the absence of which the placentae of rats are abnormal and the embryos invariably resorbed.

**Vitamin A.**—We have previously noted that the earlier failures to obtain growth upon diets free from fats and lipoids were probably due chiefly to the elimination of the closely associated "fat-soluble A" (*cf.* Stepp '22). The term was introduced by McCullum and Davis ('15, '17), who had previously ('13, '14) noted failure of continued growth in rats upon diets free from this factor. Osborne and Mendel ('13, '17a, '21) and Hess, McCann and Pappenheimer ('21) obtained similar results in rats, and Mackay ('21) likewise found that kittens on a diet deficient in vitamin A cease growth and become emaciated.

The effects of deficiency in vitamins A and B upon the growth curves of young rats are shown in Fig. 45.

When young animals are placed on diets deficient in vitamin A, there is a variable latent period during which growth continues (though at a retarded rate), probably by the aid of the vitamin stored in the fats and lipoids of the body. Evans and Bishop ('22) found that the body storage of vitamin A in young rats is apparently exhausted in 4-100 days. Osborne and Mendel ('21) hold that for growth of rats vitamin A is much less important than vitamin B; and especially for nutrition in adults (Mendel '20). Shipley, Park, McCollum and Simmonds ('21) found that in young rats on diets deficient in phosphorus and vitamin A, the arrested growth was resumed upon the addition of vitamin A (see also Fig. 45). Korenchevsky ('23) found that diets deficient in vitamin A, or calcium, or both, when fed to the male rat only, have no

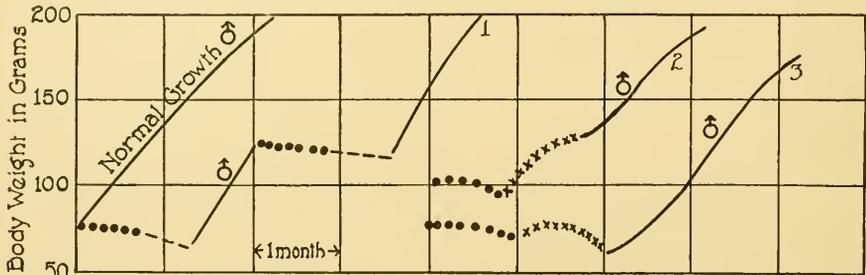


FIG. 45.—Chart showing growth curves of young rats fed on diet deficient in both vitamins A and B. The curves represented by dots (....) show the inability of the rats to grow when both vitamins, A and B, are absent from the diet. When A alone is added, *e.g.*, in butter fat, (curves marked ---), there is no improvement; but upon adding both A and B (curves marked —), excellent growth follows. When vitamin B alone is added, there is sometimes slight growth (curves marked xxxx), probably due to unexhausted reserve stores of A, but growth failure eventually follows. (Drummond; *Med. Res. Comm.* '19.)

apparent effect on the offspring. When such diets are fed to the pregnant female, still-births are more frequent. Even though the newborn may appear normal, they are unusually susceptible to rachitoid disorders later, especially when the deficient diet of the mother is continued during lactation.

The relation of vitamin A to the cause of rickets was mentioned above in connection with mineral deficiencies. The characteristic ocular lesions (xerophthalmia) produced by deficiency of vitamin A will be discussed in Chapter XIII.

**Vitamin B. Polyneuritis and Beriberi.**—The importance of vitamin B in the production of polyneuritis in animals (especially birds) and of human beriberi became evident through the work of Eijkman ('97) and numerous later investigators. For review of various other theories of beriberi, see Vedder ('13, '23) and Vaughan ('23). Nagayo ('23) claims that human beriberi, although it may involve a deficiency of vitamin B as one factor, is a disorder distinct from experimental polyneuritis and more closely resembles the infantile "Mehlnährschaden." The marked atrophy of the body in experimental polyneuritis does not occur in human beriberi. The failure of growth in young animals on diets deficient in vitamin B was demonstrated by Funk and Macallum ('15), Osborne and Mendel ('17a), Abderhalden ('19) and Shipley, McCollum and

Simmonds ('21) in rats; by Drummond ('16) in chicks; and by Emmett and Allen ('19) and Emmett, Allen and Sturtevant ('20) in frog tadpoles (see also Fig. 45).

Although Eijkman ('97) observed that in some cases there was no emaciation in the body of adult chickens, even at death from polyneuritis, this appears to be exceptional. Marked loss in body weight during polyneuritis in chicks and pigeons was noted by Tasawa ('15) and others. The loss in body weight on diets deficient in vitamin B is so marked (frequently 40 per cent) and constant that many investigators believe it is due to the associated deficient food-intake (incomplete total inanition). This view is shared by Karr ('20), Simonnet ('20), Lumiere ('20a, '20b), McCarrison ('21), Hoffman ('22), and others. For example, Novaro ('20), in substantial agreement with Findley ('20), found that in pigeons on polished rice diet the body weight, temperature, heat loss and food-intake remain constant for 7-13 days. Then they decline in the following order: heat loss; food-intake; body weight; temperature. The body weight was found to decrease in polyneuritis even more rapidly than in fasting (total inanition).

Hoffman ('22) found that polyneuritic pigeons on polished rice diet, modified so as to be deficient only in vitamin B, nevertheless lose weight as during total inanition. In both cases, recovery was made upon refeeding with adequate diet. Gotta ('23), however, modified the diet so as to produce polyneuritis with but slight loss in body weight.

**Vitamin C. Scurbutus.**—The historical development of our knowledge of scurvý has recently been reviewed by Hess ('20) and Vaughan ('23). It was perhaps the first human disorder to be recognized as a definite deficiency disease, due to the lack of fresh vegetables or antiscorbic fruit juices in the diet (Ronsseus, 1564; Kramer, 1720). More exact knowledge dates from the recent experimental production of scurvý in the guinea pig by Holst and Frölich ('07, '12). The essential factor was designated as the "water-soluble C" vitamin by Drummond ('19). Emmett and Peacock ('22) find that the requirement of chicks for vitamin C is much less than for A and B. The rat even thrives upon diets devoid of vitamin C, possibly because it may be synthesized in the body of this animal (Parsons '20).

As to the changes in body weight, Holst and Frölich found, during experimental scurvý in young guinea pigs, usually stationary weight for 1-2 weeks, followed by rapid loss, averaging 30-40 per cent, rarely reaching 50-60 per cent. Dogs were found susceptible, but negative results were obtained on mice, rats and cats. Similar results were noted by more recent investigators. Findlay ('21b) found that rabbits deprived of vitamin C gradually lose weight and die without signs of scurvý, although the offspring born during this period may show hemorrhages in the joints and viscera. The weights of Bessesen ('23) for scorbutic guinea pigs are shown in Table 12. For curves by Chick and Hume ('17) showing loss of body weight in the guinea pig during scurvý, see Fig. 46. Growth may continue during the first 2 or 3 weeks, but a later marked decline is constant. Cohen and Mendel ('18) likewise found that scorbutic symptoms (tender and swollen joints) often appear while the guinea pigs still

have a good appetite and are growing rapidly, so that (general) inanition plays little or no part at this stage. During the last 10 days, however, the loss in body weight corresponds to that in starvation. Besesen ('23) found an average loss of 16 per cent in beginning scurvy, and 37 per cent at death (Table 12). Recovery is possible, even in extreme stages, upon the addition of antiscorbutics to the diet (Fig. 46).

Hess ('15, '16, '20, '23) has studied especially the effects of scurvy upon children. The body weight usually becomes stationary, and growth in length

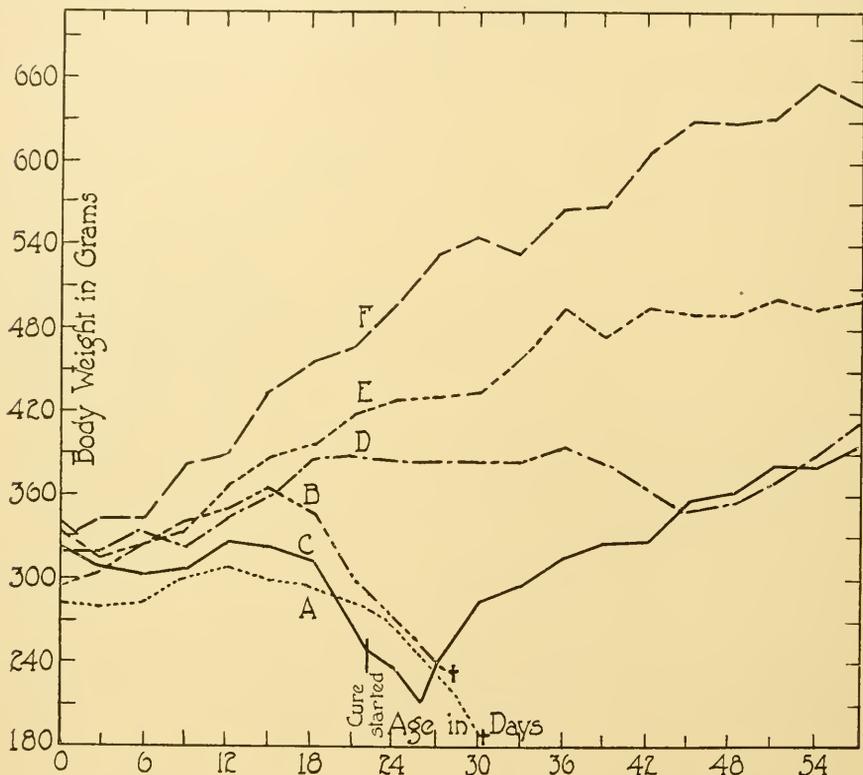


FIG. 46.—Chart showing growth curves of guinea pigs as affected by vitamin C. Curve A shows growth on typical scurvy diet of oats, bran and water (deficient in vitamin C). Curve B shows better growth for a time on oats and bran plus autoclaved milk, but eventual decline and death from scurvy. Curve C shows growth curve on diet of oats, bran and water, resulting in scurvy; but cured by adding vitamin C (orange juice and autoclaved milk) to the diet. Curve D shows the growth on the scurvy diet (oats, bran and water) plus 5 c.c. of orange juice daily; autoclaved milk added on the 56th day. Curve E shows optimum growth on diet of oats, bran and cabbage leaves; and Curve F on diet of oats, bran, autoclaved milk and 3 c.c. of orange juice daily. (Med. Res. Comm. Report '19; from Chick & Hume '17.)

is also greatly retarded (in contrast with the effects of chronic general inanition). The symptoms may be obscure in latent cases. Rapid improvement in growth is obtained by addition of vitamin C in the form of orange juice, a result also noted by Chick and Dalyell ('21) and others.

**Water Deficiency (Aqueous Inanition).**—The period of toleration of thirst varies greatly in man, as noted by Rowntree ('22), the recorded duration ranging

from 36-72 hours for travelers lost in a desert to 18 days in the case of Viterbi (an Italian political prisoner) on total inanition. As previously stated, the period of duration during inanition is greatly extended when water is available. Marriott ('23) states that during the development of anhydremia the loss in body weight is more rapid than that observed in any other condition, reaching 10-25 per cent in one or two days. He also cites the observations by King and McGee as to the effects of desert thirst on man.

Rosenfeld ('86) held that Oertel's obesity cure, which involves a restriction of the liquids in the diet, is dangerous on account of producing lesions in the kidneys, heart and nervous system.

Among lower animals, Falck and Scheffer ('54) observed a duration of 4 weeks in the dog on dry biscuit; while Pernice and Scagliosi ('95a) noted death after 11 days in a dog on dry bread, and after 8-10 days in young chicks on dry maize. Bowin ('80) found that both dogs and rabbits die in about 23 days on dry diet. Nothwang ('91) observed death from thirst in pigeons at an average of  $4\frac{1}{2}$  days. Kudo ('21) kept adult albino rats on dry diet 6-7 days, while on total inanition one survived 11 days. With variable amounts of liquid (milk) added to the diet, the duration period was correspondingly lengthened.

The loss in body weight observed during thirst is also variable, but is usually marked, with great emaciation, as in total inanition. According to Lorenzen ('87) a relatively dry diet is very effective in reducing the amount of fat in man, a principle used in the "reducing" diet of Oertel and others. As previously mentioned, Prochownick's diet (for reducing fetal size) is low in water content as well as in carbohydrates.

Chossat ('43) noted a loss of 35 per cent in the body weight of frogs subjected to evaporation. The losses recorded before death on dry diet in other animals are as follows: Schuchardt ('47), 44 per cent in pigeons; Falck and Scheffer ('54), 20 per cent in a dog; Bowin ('80), 50 per cent in rabbits, somewhat less in dogs; Skoritschenko ('83), very irregular loss in rabbits; Pernice and Scagliosi ('95a), 24 per cent in a dog, 34-41 per cent in young chicks; Maurel ('04, '04a), 30 per cent in adult guinea pigs; Kudo ('21), 36 to 51 per cent average in adult albino rats (Table 9).

The importance of water in growth has been emphasized by Davenport ('97, '99). It is frequently stated that the water content of living organisms can be modified experimentally to only a very limited extent; but this is not supported by the experiments of Hall ('22), who subjected various animals to exsiccation in a dry chamber, without food (excepting the mice, which were fed dry corn and oats). Subsequent recovery was obtained in all cases by giving water. The periods of exsiccation and the losses in body weight and in water content are shown in the accompanying table (p. 116).

In human infants, O. and W. Heubner ('10) stated that lack of water in the diet may cause inhibition of growth, at least in weight. Similarly, Meyer ('13) found that upon a diet of concentrated "Eiweissmilch," the growth of healthy infants was retarded, with prompt recovery upon the addition of merely *aqua destillata*. Meier ('21) noted that the lack of water in breast-fed infants

may cause a disturbance resembling alimentary toxicosis, and recalls the related "dessication fever" and "inanition fever" of the newborn. Utheim ('22) has recently reviewed the evidence that the weight of the body fluctuates according to its water content; and that the latter is greatly influenced by the diet. The dehydration produced by diarrhea is well known.

EFFECTS OF EXSICCATION (HALL '22)

Species	Per cent exsiccated of		Time required
	Body weight	Water content	
Earthworm ( <i>Allobophora chloroticus</i> ).....	69.6	83	105 min.
Leech ( <i>Placobdella parasitica</i> ).....	70.3	92	450 min.
Meal worm ( <i>Tenebrio molitor</i> ).....	52.6	105	1,084 hrs.
Newt ( <i>Ambystoma punctatum</i> ).....	47.0	...	116 hrs.
Frog ( <i>Rana pipiens</i> ).....	41.0	50	33 hrs.
Turtle ( <i>Chrysemys marginata</i> ).....	33.1	...	288 hrs.
Chameleon ( <i>Anolis carolinensis</i> ).....	46.3	...	186 hrs.
Horned toad ( <i>Phrynosoma cornutum</i> ).....	33.8	...	119 hrs.
Lizard ( <i>Sceloporus spinosus</i> ).....	47.8	...	86 hrs.
Wood mouse ( <i>Peromyscus leucopus</i> ).....	30.7	...	77 hrs.
Meadow mouse ( <i>Microtus pennsylvanicus</i> ).....	32.1	...	68 hrs.
House mouse ( <i>Mus musculus</i> ).....	24.2	34	270 hrs.

Spiegler ('01) found that young puppies are very sensitive to a dietary water deficit, which causes inanition and general retardation in growth. Kudo ('21a) held albino rats one month old at constant body weight for several weeks by a restricted amount of liquid (milk) in a diet otherwise adequate for growth. The rats show a progressive tolerance of thirst, so that less liquid milk is required daily for maintenance as the experiment proceeds. The tail becomes elongated, while the body length remains constant (thus differing from the results of Jackson and Stewart by underfeeding).

The results of Kudo's thirst experiments upon the various organ weights (see Tables 9 and 10) resemble somewhat those of underfeeding experiments or total inanition on the same species, though certain differences occur. The general resemblance may be due in part to insufficient food-intake during thirst, which has also been observed by Straub ('99) in dogs, and by Maurel ('04, '04a) in guinea pigs. On the whole, we may conclude that with aqueous inanition (dry diet) the length of life and loss in body weight usually do not differ much from those previously noted during total inanition (*cf.* Table 1).

Although oxygen is not strictly a food-stuff, the effects of its deficiency are of interest for comparison. J. Loeb ('96) observed that the resistance of developing ova to lack of oxygen varies greatly in different species. Eggs of the fish *Ctenolabrus* are injured almost immediately when deprived of oxygen, and the segmenting cells tend to fuse into a syncytial mass. The eggs of *Fundulus*, on the contrary, are very resistant to lack of oxygen.

## CHAPTER VI

### EFFECTS ON THE INTEGUMENT, ADIPOSE TISSUE AND MAMMARY GLAND

The present chapter includes the effects of inanition upon the skin and appendages, including the mammary gland. In connection with the *tela subcutanea*, the effects upon adipose tissue in general are also noted.

The effects of inanition on the skin and appendages are of interest in dermatology, and especially in relation to the diagnosis of the various deficiency diseases (pellagra, malnutritional edema, scurvy, etc.). Atrophy of the skin is likewise characteristic in many other disorders involving general malnutrition. The effects on the mammary gland are of obvious importance in pediatrics. After a summary of the more important effects the changes will be considered in detail under (A) total inanition, or on water alone, and (B) partial inanition.

#### SUMMARY OF EFFECTS ON THE SKIN AND APPENDAGES

These effects will be summarized for both total inanition and partial inanition including the deficiency disorders.

**Changes in Weight.**—In adults, aside from the *tela subcutanea*, the loss in weight of the integument during inanition is usually relatively less than in the body as a whole, although nearly equal in the rat and frog. In the newborn rat, the skin may increase in weight while the body is held stationary; but the growth impulse soon decreases to a minimum, later increasing in experiments begun toward the adult stage. The loss in weight of the skin is promptly regained upon refeeding.

The **general appearance** of the skin during total inanition is variable, thickening and roughening of the hair coat being frequent. The *epidermis* becomes somewhat atrophic, but mitoses persist in reduced number in the deeper epithelial cells. In the *corium*, the pigment is generally reduced in amount. The *healing of skin-wounds* is slow and imperfect during inanition and hibernation.

The ***tela subcutanea*** during inanition loses heavily in weight (up to 90 per cent or more), chiefly through atrophy of the *adipose tissue*. The rate of loss varies in different regions, however, and in some cases fat may persist in considerable quantities, even at death from starvation. Flemming established three histological types of adipose atrophy; simple, serous and proliferative; to which may be added gelatinous or mucoid atrophy, occurring chiefly in adipose bone marrow. Hibernating animals subsist chiefly upon fat stored in the so-called hibernating gland. In general, the ordinary neutral fats of the body appear to be easily mobilized, while the lipoidal fats contain phospholipins which are relatively resistant to starvation. The atrophic adipose tissue is easily restored to normal upon adequate refeeding.

The **mammary gland** undergoes marked atrophy during inanition in the adult female, and retarded development of the gland occurs in the malnourished young. Histologically the atrophy of the adult gland cells is confined to the cytoplasm, with prompt recovery upon adequate refeeding. During total (incomplete) inanition, lactation is persistent, although reduced in amount, with variable changes in the chemical composition of the milk. During partial inanition, the effects vary according to the type of deficiency.

During **partial inanition**, the changes in the skin also are variable, according to the type of the deficiency. *Protein* deficiency occasions marked cutaneous disturbances, as, for example, in the edema so frequently characteristic of famine and similar chronic malnutritional conditions. In *pellagra* (primarily due to protein deficiency), the skin lesions are very marked and characteristic, with variable inflammatory changes in the acute stage, and atrophic changes in the chronic stage. *Iodin* deficiency causes a myxedema, probably secondary to thyroid lesions. During *ricketts* (due to calcium-phosphorus and vitamin deficiency), the skin is variably atrophic. In other *vitamin deficiencies*, retarded growth or abnormal structure frequently occurs in the skin and appendages. Cutaneous hemorrhages, and occasionally edema, are found in scurvy. *Aqueous inanition* (water deficiency) causes a cutaneous loss of weight somewhat similar to that during total inanition, accompanied by variable structural changes.

#### (A) EFFECTS OF TOTAL INANITION, OR ON WATER ALONE

**Changes in Weight of the Integument.**—If the tela subcutanea is excluded, the loss in the weight of the skin proper, including hair, nails, etc., in adult animals during inanition is usually relatively less than that in the body as a whole. Thus in pigeons with average loss of 40.4 per cent in body weight, Chossat ('43) found a loss of only 33.3 per cent in the skin, not including the feathers (in which there was no loss in weight). Pfeiffer ('87) found but little loss in the weight of the skin in the rabbit, aside from subcutaneous fat. In 3 rabbits with loss of 35-41 per cent in body weight, Weiske ('97) noted a loss only 22-25 per cent in the skin. Voit ('94, '05, '05a) in the dog noted a loss of 32 per cent in the body and of 20 per cent in the skin. In the fat-free skin, the loss is relatively less than in the fat-free body. Sedlmair ('99) in starved cats found the loss in weight of the skin relatively somewhat less than that of the body. In adult albino rats, Jackson ('15) observed that in acute inanition the body weight lost 33 per cent in weight, the skin 31 per cent; in chronic inanition, the body lost 36 per cent, the skin 39 per cent.

The course of the loss in weight of the skin in the adult guinea pig at successive stages of total inanition was noted by Lazareff ('95). With losses in body weight of 10, 20, 30 and 36 per cent, the corresponding average losses in weight of the skin were 1.97, 8.17, 12.71 and 17.94 per cent. Thus it appears that the loss is relatively slight in the earlier stages, becoming progressively greater but attaining a maximum percentage only half that in the body as a whole. On the other hand, in frogs (*Rana pipiens*) with progressive loss in body weight up to 50 or 60 per cent, Ott ('24) found relatively a still greater loss in weight of

the integument in the male, although somewhat less in the female (Table 6). The percentage of dry substance remained nearly constant.

**In the young**, the changes in the weight of the integument differ from those in the adult. Manassein ('68, '69) in rabbits on total inanition at age of about 3 weeks obtained an average loss of about 35 per cent in body weight and of 40 per cent in skin weight; at the age of 3 months, body loss was 33 per cent, skin 19 per cent; in adults, body loss was 39 per cent, skin 27 per cent. Aron ('10, '11) concluded that in underfed puppies the skin increases slightly in relative weight. Trowbridge *et al.* ('18) likewise observed a slight increase in the weight of the integument of yearling steers held nearly at maintenance (constant body weight) by underfeeding; while in those losing about 17 per cent in body weight the hide lost only 3-6 per cent.

In albino rats held at maintenance by underfeeding for various periods beginning at 3 weeks of age or later, Jackson ('15a) found a marked loss (36 per cent) in the weight of the integument in the rats beginning at 3 weeks of age (Table 4), with smaller losses in those beginning later. Stewart ('18, '19) in still younger rats observed the greatest loss (48 per cent) in those underfed from birth to 10 weeks; in those underfed from birth to 3 weeks there was no loss of weight in the integument; and in those held at birth weight by underfeeding 16 days there was an actual *increase* of 25 per cent in the weight of the integument. This appeared to be normal developmental growth, and not merely an increase in weight due to edema. A smaller relative increase (10 per cent) was found by Barry ('20, '21) in the skin of newborn rats which had been stunted prenatally by severe underfeeding of the pregnant mother.

These results (shown in Table 4) demonstrate clearly that the dystrophic growth of the integument varies greatly according to age. In the prenatal and newborn rats, the tendency to increase in weight of the skin during subnutrition appears greatest, but the growth impulse (in underfed animals) rapidly decreases to a minimum, the greatest losses occurring at body weights of 15-25 g. Later the growth impulse again increases, so that the losses become relatively less, up to the adult stage, where the loss is nearly proportional to that of the body. There are also differences according to the intensity of the underfeeding and probably according to the type of inanition (to be considered later).

For the human species, data as to changes in the weight of the integument during inanition are scarce. Ohlmüller ('82) noted that in a normal infant of 56 days, the body weight was 4,195.5 g., the skin weight 1,291.67 g., or 31.16 per cent; while in an atrophic infant of 56 days, the body weight was 2,381.2 g., the skin weight 290.55 g., or 12.21 per cent. It is evident that the tela subcutanea was here included with the skin proper, however, for Ohlmüller remarks that the enormous loss was due to the adipose content. A few data upon the weight of the integument, without tela subcutanea, as observed by me in autopsies of atrophic infants are given in Table 3. Lack of norms for comparison makes it difficult to draw any conclusions, however.

**Recovery in Weight of Skin upon Refeeding.**—In albino rats held at maintenance by underfeeding from 3-12 weeks of age, Stewart ('16) found that upon full refeeding the integument rapidly recovers the marked

loss in weight, reaching its normal proportionate weight within two weeks. In albino rats underfed from birth to 3 weeks (with retarded body weight of 10 g.) or to 10 weeks (15 g.), and then fully re-fed to body weight of 25, 50 and 75 g., Jackson and Stewart ('19) obtained nearly normal weight (or above) for the integument in all except one group re-fed to 25 g., which was sub-normal (Table 7). In rats similarly underfed for longer periods (from 3 weeks to nearly a year of age), and then re-fed until permanent dwarfed size was reached, although the body weight was markedly below normal adult, the weight of the skin was but slightly below that normal for corresponding body weight (Table 8).

**General Appearance.**—The integument varies in appearance during inanition. Tiedemann ('36) and Falck ('81) noted that in starvation the human skin is atrophic, lax, dry, shrunken and pale. A somewhat similar description for atrophic infants is given by Bourgeois ('55), Vincent ('04), Birk ('11), Lesage ('11), Nobécourt ('16), Nicolaëff ('23) and others. According to Thiercelin ('04) and Rosenstern ('11) the skin of such infants may be at first eczematous, later pale or cyanotic. In the adult man studied by Meyer ('17) the skin was dry, rough, and discolored for several days before death. In this case there were no folds, excepting the volar and plantar regions. As a result of war famine, there is a notable increase in the occurrence of skin infections (Rubner '19, Richet and Mignard '19, Vandervelde and Cantineau '19, Ivanovsky, '23), probably due to lessened immunity. The frequent occurrence of edema during famine has already been mentioned, and this, of course, may alter greatly the appearance of the skin.

The **hairs** in dogs during starvation remain firmly attached, according to Falck ('75), or become easily detached, according to Bich ('95). An increased growth in thickness of the hair coat in underfed cattle was observed by Weiske ('75) and Van Ewing and Wells ('14). Thickening and roughening of the hair coat were also found in underfed mice by Judson ('16) and Thompson and Mendel ('18); and in underfed horses by Moehl ('22). Trowbridge, Moulton and Haigh ('18) observed that poorly nourished steers shed their hair very late in the season. Irregularities in the hair coat also occur during various forms of partial inanition, to be mentioned later. Porter ('89) noted that absence of pigment is characteristic of the famine-stricken, and that in women the black hair may become yellowish, devoid of pigment. In the emaciated victims of the Russian famine, Ivanovsky ('23) stated that "the hair grew more slowly, fell out prematurely and tended to rapidly become gray. Growth of the nails on hands and feet was retarded, and the teeth readily decayed. The eyes became limpid as with aged people; the skin lost its elasticity and became wrinkled."

**Epidermis.**—Cunningham ('80) found fatty degeneration of the deeper epidermal cells, and also atrophic changes in the dermis, in starved larvae of *Bufo melanostictus* and *Rana tigrina*. Among the victims of the Indian famine, Porter ('89) observed that fatty degeneration of the cuticle may give rise to the "famine skin," a harsh, dry, patchy scurf also described by Donovan in the Irish famine of 1847. The vitality of the skin appears too low to throw off the dead epithelium.

Rabl ('85) noted many mitoses in the epidermis of *Salamandra atra* starved 5-7 months. In the epidermis cells (chiefly in the deeper layer) of both young and adult rabbits, Morpurgo ('88, '89, '89a) likewise found mitoses persistent even in extreme starvation, though reduced in number. Mitoses were also found in the peripheral portion of a sebaceous gland in an adult rabbit after death from starvation. In the epidermis cells of starved larvae of *Triton taeniatus* and *Triton alpestris*, Schultze ('88) observed irregular and lobulated nuclei, with reduced amount of chromatin. "Die Masse des Chromatins der Mitosen bei den Hungerlarven—ich sah immer noch spärliche—ist, wie ich in Uebereinstimmung mit den von Rabl für *Salamandra atra* gemachten Angaben finde, dieselbe wie bei den gut genährten Thieren."

In a lizard starved 6 days, Konstantinovitch ('03) found a thinning not only in the basal, Malpighian layer, but also in the layer of pigmented cells. In *Diemyctylus viridescens* starved for various periods, Morgulis ('11) described a marked atrophy of the epidermis, the decrease in the nucleus being much less than that in the cytoplasm of the cells. Persistent mitosis was also noted.

Ruzicka ('17) found that in adult *Triton cristatus* and *Triton taeniatus* ecdysis during fasting occurs twice as frequently as in full-fed controls. Although fasting apparently causes an acceleration of metabolism (in agreement with Child's theory), it does not result in rejuvenation of skin structure. The skin in the fasting adults becomes thinner, but differs in structure from that in normal larvae; the nuclei become chromatin poor, Leydig cells are absent, and keratinisation is accelerated (though absent in the larval skin, even during fasting). "Es sind also auch die Hungerreduktion als eine Alterserscheinung anzufassen; der absolute Hunger bewirkt schliesslich einen den künstlichen Seneszenz analogen Zustand."

**Corium.**—Some of the observations above mentioned included the dermis as well as the epidermis. Samuel ('85) observed that in fasting pigeons growth continued four days at a retarded rate in the papillae which produce the large wing feathers. This retarded growth was correlated with a diminished blood supply to the papillae. Harms ('09a) described a degeneration produced in the digital glands of *Rana fusca* and *Rana esculenta* during inanition. There is no phagocytosis. The duct resists degeneration longest. Regeneration of the gland occurs upon refeeding. Tornier ('07) noted a disappearance of pigment in the skin of underfed salamander tadpoles. Kammerer ('13) in similar experiments on *Salamandra maculosa* found that the richly-fed became yellow, the underfed variably spotted, chiefly black. He admits, however, that in all cases the pigment is reduced in amount by inanition, the black pigment of the chromatophores being more resistant than the yellow. Weber ('14) explains the "Hungermelanismus" of frogs as due, not to pigment formation, but merely to expansion of the chromatophores. The integument becomes green again upon refeeding. Ruzicka ('17) found the skin pigment greatly increased in adult fasting *Triton cristatus* and *Triton taeniatus*.

**Healing of Skin Wounds.**—Collard de Martigny (1828) noted that skin wounds in animals during starvation heal poorly and form an imperfect cicatrix. He explained this as due to the anemia. The process was studied in detail by

Chudnovski ('90) in skin wounds on starved rabbits. He found that the regeneration of the epidermis cells occurs as in well-nourished animals, but more slowly. The number of mitotic figures is diminished and their form may be abnormal. The epithelial cell nuclei are poor in chromatin and may undergo chromatolysis. Granulation tissue is absent or diminished in amount, and the infiltration of multinucleated cells (found in wounds of well-nourished animals) is feeble or absent. Rous and McMaster ('24) state that in albino rats on water alone following laparotomy the abdominal wound heals slowly but by first intention.

According to Valentin ('58) in the hibernating marmot no appreciable amount of regeneration occurs in skin wounds. Hansemann ('98) states that no mitoses ordinarily occur in the skin of the hibernating marmot or hedgehog; but in a few hibernating hedgehogs, which were killed 1-14 days after incisions were made on the snout, immigration of leucocytes occurred, and cell-divisions appeared in both epithelium and connective tissue.

**Tela Subcutanea.**—The most conspicuous changes during inanition are not in the skin proper, but in the underlying tela subcutanea. This is because in well-nourished individuals it is very largely composed of adipose tissue, which is known to be rapidly depleted by inanition. The atrophy of this layer produces the characteristic looseness and folds of the skin during starvation. On account of the progressive character of this atrophy, the thickness of the skin folds may be used as a convenient index of the stage of inanition, especially in infants, according to Batkin ('15), Marfan ('21), Peiser ('21), Gerber ('21), Käding ('22), Nicolaëff ('23) and Hille ('23). In a starved girl of 19 years, Schultzen ('62, '63) noted that the adipose panniculus had disappeared from the trunk, but was still evident in the extremities. Likewise in infantile atrophy, the subcutaneous fat does not disappear at a uniform rate over the whole body. Marfan ('21) describes the panniculus adiposus as becoming thin and finally disappearing altogether in the various regions in the following manner:

“Ce processus de destruction de la graisse commence par le ventre et finit par la face. Il atteint successivement les régions suivantes: (1) l'abdomen; (2) le tronc (d'abord la poitrine, puis le dos, puis les lombes); (3) les membres (d'abord les supérieurs, puis les inférieurs, puis les fesses); (4) la face (d'abord le front, puis les joues et le menton). On constate parfois quelques dérogations à cet ordre, mais elles sont très rares.”

The histological changes in the adipose tissue of the tela subcutanea of atrophic infants are shown in Figs. 47-49.

In extreme stages of inanition, the ordinary adipose tissue of the tela subcutanea (and elsewhere) is usually almost completely depleted, so as to lose 90 per cent or more in weight. Observations were made by Chossat ('43) in pigeons; Bidder and Schmidt ('52) in the cat; Falck ('75) in dogs; Ohlmüller ('82), DeTommasi ('94), Klose ('13) and others in the human body. Nevertheless, small areas of subcutaneous fat may be macroscopically visible, even after death from starvation, as noted by Falck ('75) in the dog; Meyer ('17) and others in man. In some cases the fat may persist in considerable amount (Fowler '70; Jewett '75; Voelkel '86; Hartman '00), indicating that death from starvation

is not due to exhaustion of nutritive material. The persistence of the human "sucking pad" (*corpus adiposum buccae*) during general emaciation has been noted, not only during infancy (Ranke '84; Lehndorff '07; Scammon '19) but

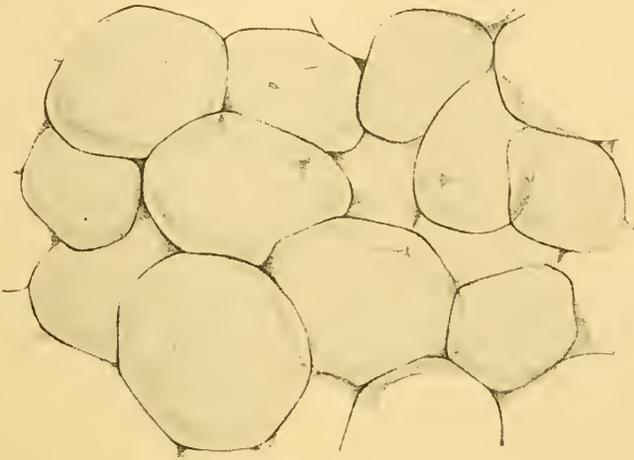


FIG. 47.—Normal adipose tissue, with large, polyhedral fat cells, from the tela subcutanea of a newborn infant.  $\times 400$ . (Parrot '77.)

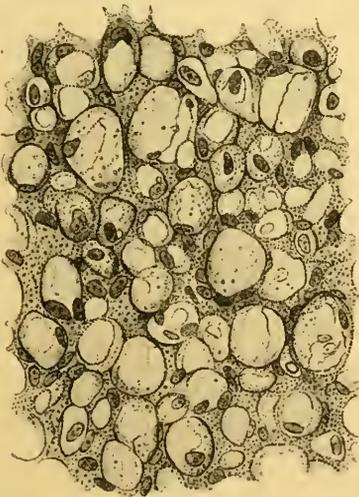


FIG. 48.—Adipose tissue from the tela subcutanea of an emaciated, athreptic infant. Adipose cells unequally atrophied; some still contain a moderate amount of fat in droplets of variable size. Cell nuclei and granular cytoplasm evident.  $\times 400$ . (Parrot '77.)

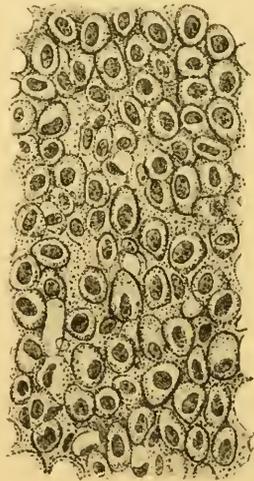


FIG. 49.—Adipose tissue from the tela subcutanea of an extremely emaciated, athreptic infant. The atrophic adipose cells have been almost completely depleted of fat, and are closely packed so as to resemble the Malpighian layer of the epidermis.  $\times 400$ . (Parrot '77.)

even in the adult (Gehewe '52). Beneke ('05) stated that the cells of a lipoma differ from ordinary fat cells in that they do not atrophy in general emaciation of the body. In cases of malnutritional edema (due chiefly to partial inanition,

however) the tela subcutanea may fail to show the usual decrease in weight, on account of the replacement of the fat by water.

**Adipose Tissue in General.**—In considering the behavior of fat in the body during inanition, we must distinguish the ordinary fat of adipose tissue from the lipoidal fat which occurs especially in epithelial cells of glands, and elsewhere. As pointed out by Nikolaides ('99), Carini ('01), Traina ('04), and Dietrich ('10), the ordinary fat is easily mobilized during inanition, hence called "wandering" or "usable" fat; while the lipoidal fat is usually "sessile" or "permanent" in character. The ordinary neutral fats appear to be readily resorbed, while the lipoidal fats contain lecithin and other phospholipins, which are more resistant to inanition. Aschoff ('09) described the relations of the various types of fat in various forms of fatty metamorphosis ("degeneration").

Bichat (1801, 1812) long ago described the metamorphosis of adipose tissue, which assumes a gelatinous aspect and consistency in the epicardial region and in the adipose bone marrow during phthisis and similar chronic diseases involving emaciation.

Virchow ('50) added further histological details of the process:

"Bei allgemeiner Abmagerung ist nichts gewöhnlicher als dass das Fettgewebe unter dem Pericardium, im Nierenhilus sich wieder in deutliches Schleimgewebe umbildet. Das Fett schwindet aus den Zellen, diese verkleinern sich, in die Zwischensubstanz tritt eine schlüpfrige, gallertige Flüssigkeit, welche die schönsten Mucin-Reactionen gibt."

Gurlt (cited by Schwann, 1839) discovered "dass bei abgemagerten Personen die gewöhnlichen Fettzellen mit Serum gefüllt sind." Similarly, Czajecwiz ('66) described the process in young and adult rabbits as follows:

"Bei Nahrungsentziehung wird der Fetttropfen in der Zelle resorbiert, seine Stelle grösstenteils durch eine sehr feinkörnige Flüssigkeit ersetzt; bei längerem Hungern schwindet das Fett gänzlich und es bleiben die Formelemente des Bindegewebes in Form von grossen, schönen, runden, mit seröser Flüssigkeit gefüllten und mit deutlicher Membran und mit einem oder mehreren Kernen versehenen Zellen zurück."

On refeeding, the fat cells were found resume their normal structure.

Toldt ('70) described the fat cells in emaciated animals as decreasing in size and approaching the primitive "Protoblasten" in appearance.

Flemming ('71, '71a, '76) studied the inanition atrophy of adipose tissue in young and old animals, including the fish, frog, rabbit, guinea pig, rat, cat, dog and man. He concluded that the "serumhaltige Fettzelle" of previous observers is not the final form of the atrophic fat cell, but merely an (inconstant) intermediate stage. This may explain the contradictory observations by previous investigators. Flemming described 3 types of fat cell atrophy as follows:

1. *Simple or Normal Atrophy.*—The fat droplet gradually decreases, with formation of secondary droplets and granules, the cell finally reverting to the ordinary connective tissue cell of variable form.

2. *Serous Atrophy.*—In this case the fat droplet is replaced by a serous droplet or droplets, sometimes with small fatty granules also. Ultimately the serous content disappears, and the cells assume the same final form as in (1).

3. *Proliferative Atrophy*.—In this case the nuclei of the fat cells proliferate, which may occur with either simple or serous atrophy.

Flemming considered the simple atrophy more characteristic of chronic malnutrition and old age, serous atrophy arising in acute inanition and proliferative atrophy in either acute or chronic inanition. His classification, with more or less modification, has since been generally followed. Hammar ('95) has shown a variation according to the type of adipose tissue, to be considered later (under hibernation). Further details in the process of adipose atrophy are also given by Poljakoff ('88, '95), Metzner ('90), Lindemann ('99), Pasini ('03), Bell (cited by Waters '08), Schidachi ('08) (with extensive review of the literature), Mönckeberg ('12), Matsuoka ('15), and Lubarsch ('21a). Metzner

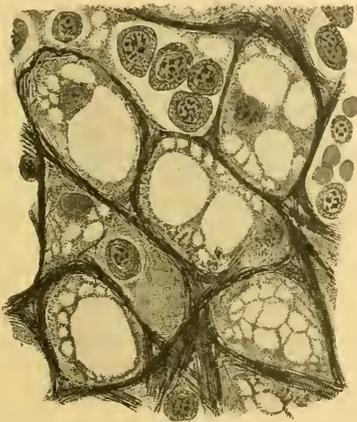


FIG. 50.—Normal bone marrow from the tibia of a young adult rabbit, showing the fibrous reticulum, large fat cells (containing fat droplets of variable size), and a few marrow cells and erythrocytes.  $\times 500$ . (Jackson '04.)

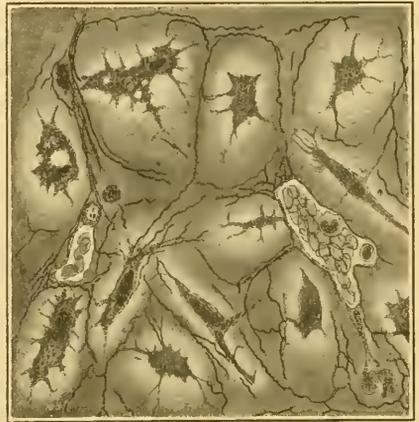


FIG. 51.—Gelatinous marrow from the tibia of a starved rabbit. The fat cells have assumed a shrunken stellate form. The fat has disappeared, excepting a few small granules in two of the cells. The stroma presents a gelatinous, amorphous mass with lighter staining areas around each cell. The reticulum fibers are present in reduced number, and the blood vessels are evident.  $\times 500$ . (Jackson '04.)

('90) described fuchsinophile (Altmann) granules in atrophic fat cells, which probably correspond to the lipoidal fat granules mentioned by subsequent observers (*cf.* Cramer '20).

Herter ('97) described the replacement of the subcutaneous fat and adipose bone marrow by a gelatinous substance in pigs during fat starvation.

The mucoid (or "gelatinous") atrophy of Bichat and Virchow is indeed especially characteristic in the adipose bone marrow during inanition. Neumann ('68), Feigl ('72), and Hoyer ('73) described in starved animals the transformation of the marrow fat cells into a network of branching cells lying in a hyalin, mucin-containing ground substance. Fenger ('73), Ricklin ('79), Geelmuyden ('86), and Helly ('06) described a similar involution of the adipose marrow in various human cachexias. Further details were added by Bizzozero ('69,

'89, '89a), Bizzozero and Torre ('81) and Denys ('87) in birds, and by Herter ('98) in the pig. According to L. Neumann ('82), this description applies only to chronic inanition; in acute inanition the cells do not become stellate. Geelmuyden ('86) found gelatinous marrow in the bones of frogs after the winter fast, and cited numerous observations on the same in human long bones in diseases with emaciation (*cf.* Dickson '08). A review of the literature, with description of the histological changes in the bone marrow of rabbits and pigeons during inanition and refeeding was given by Jackson ('04). He concluded that:

"Beim hungernden Thier entsteht Gallertmark, indem das Fett verschwindet, und die Zellen ihre ursprüngliche Reticulumform wieder annehmen. Die Reticulumfasern liegen dann meistentheils zwischen den Zellen in der reichlichen gallertigen Grundsubstanz, theilweise aber auch innerhalb der Zellen oder unmittelbar neben ihnen" (*cf.* Figs. 50 and 51).

**During hibernation** the changes in adipose tissue have received much attention, since it has been shown that during hibernation the organism subsists chiefly at the expense of its stored fat. Valentin ('57) found that in a marmot hibernating 44 days, with loss of 8 per cent in body weight, the ordinary adipose tissue had lost 19 per cent and the "hibernating gland" ("Winterschlagdrüse") 27 per cent. In 3 other marmots at the end of hibernation (average 166 days), with loss of 35 per cent in body weight, the ordinary adipose tissue had lost 99 per cent and the "hibernating gland" 68 per cent. Valentin ('58), Afanassiew ('77), Ehrmann ('83), Carlier ('03), Hansemann ('02) and others have shown that the so-called "hibernating gland" is composed essentially of adipose tissue, whose cells during hibernation undergo simple or serous atrophy similar to that found in adipose tissue in general during inanition.

The subject of **adipose involution** during inanition was exhaustively investigated by Hammar ('95) who described in the albino rat two types of fat, white and brown. The "white fat" corresponds to the usual description of adipose tissue; during inanition it is reduced to remnants of fibrous connective tissue (never gelatinous) in the subcutaneous, subserous and intermuscular localities. The "brown fat," which corresponds in general to what has been described as the "hibernating gland" in many animals, has a different structure, each cell containing a spheroidal nucleus and numerous fat droplets of variable size. During inanition the decrease in the weight of the "brown fat" is much less marked than that of the "white fat," and its structural involution is also different. It remains lobular in form, the color becoming dark reddish brown from blood-vascular congestion. The fat cells are reduced in size, and form a syncytium filling the intervascular spaces. The fat droplets are decreased in size and number, or completely absent. The cytoplasm usually becomes coarsely granular, sometimes vacuolated, the nuclei unchanged. Apparently the cells may undergo either simple or serous atrophy. Hammar's results were in general confirmed by Auerbach ('02) for various species of rodents and insectivora, including hibernating and non-hibernating forms, and by Rasmussen ('22, '23) in the American woodchuck (*Marmota monax rufescens*). Changes in the hibernating gland of the woodchuck appear slower than in other species; but subsequent to hibernation and before food is plentiful it decreases rapidly

with ultimate loss of about 75 per cent of the initial weight (body weight loss about 40 per cent). Although the fat cells of the gland decrease from  $30\mu$  to  $10\mu$  in average diameter, the spheroidal nucleus undergoes a slight *increase* in size.

**Mammary Gland.**—The only quantitative data available concerning the effects of inanition upon the weight of the mammary gland during inanition are those of Manassein ('69) which are quoted in the accompanying table.

EFFECTS OF INANITION ON WEIGHT OF MAMMARY GLANDS IN THE RABBIT  
(from Manassein '69, Table XI).

Age	Parity	Length of inanition	Body weight		Mammary glands	
			Initial, grams	Final, grams	Weight, grams	Per cent of body
Normal controls						
11 mo.....	virgin	.....	1,338.5	1,338.5	3.90	0.29
5 mo.....	virgin	.....	1,430.5	1,430.5	13.05	0.91
5 mo.....	virgin	.....	1,445.0	1,445.0	18.60	1.29
Adult.....	unknown	.....	1,361.6	1,361.6	10.42	0.76
14½ mo.....	had borne	.....	1,475.5	1,475.5	7.97	0.54
Adult.....	had borne	.....	1,624.9	1,624.9	13.91	0.86
After total inanition						
14½ mo.....	had borne	460 hrs.	1,471.3	895.7	4.61	0.50
After inanition on water only						
5 mo.....	virgin	313 hrs.	1,437.5	849.7	3.16	0.37
5 mo.....	virgin	390 hrs.	1,428.7	742.0	1.99	0.27
5 mo.....	virgin	454 hrs.	1,577.2	896.3	4.68	0.52
Adult.....	had borne <sup>1</sup>	156 hrs.	1,540.3	969.5	1.81	0.186
16 mo.....	had borne	378 hrs.	1,564.6	885.0	11.52	1.30
16 mo.....	had borne	423 hrs.	1,660.0	906.6	8.73	0.96
16 mo.....	had borne	1,105 hrs.	1,761.3	743.0	3.90	0.52
Refed for 1-4 months after inanition						
14⅔ mo.....	had borne	463 hrs.	1,518.7(-43.2%)	1,532.0	11.88	0.77
11 mo.....	had borne	411 hrs.	1,517.9(-36.9%)	1,782.7	18.9	1.06
4½ mo.....	pregnant	266 hrs.	1,207.9(-36.9%)	1,547.4	39.7	2.56
4⅔ mo.....	3 hrs. post partum	324 hrs.	1,240.5(-43.2%)	1,502.0	31.7	2.11

<sup>1</sup> Nursed 1 rabbit during inanition period.

From the data in this table it appears that there is marked variation in the normal weight of the mammary glands in the rabbit, the average being 0.76 per cent of the body weight (range 0.29-1.29). After inanition, the range is equally great (0.186-1.30 per cent), but the average is only 0.58 per cent, indicating that the weights of the mammary gland have decreased relatively more than the body weights. Those refed show a prompt recovery in the weight of the mammary gland, with hypertrophy (as might be expected) in those becoming pregnant. Unfortunately it is uncertain to what extent the weight changes in the gland during inanition are due to loss in the associated fat, rather than to atrophy of the glandular parenchyma.

In an adult female dog subjected to total inanition for 60 days (see Fig. 33), Falck ('75) noted that the mammary glands were entirely atrophied, the nipples elongated and inelastic. A marked reduction in the amount of milk secretion, with chemical changes including an increased fat content, were observed during starvation in sheep by Barbèra ('00) and Barbèra and Bicei ('00a); likewise in goats by Lusk ('01, '17). The effects of underfeeding on milk production in cattle have been studied by Eckles and Palmer ('16) and Moehl ('22), who found that normal secretion may continue for a time in spite of a considerable degree of underfeeding. Ultimately there is a decreased flow, with variable changes in chemical composition. Data for human milk secretion, and for changes during partial inanition, are mentioned later.

The histological changes during total inanition in the active mammary gland of 11 rabbits and 13 guinea pigs were investigated by Meynier ('06, '08). He found that in spite of the marked atrophy of the gland, secretion might still continue, within certain limits, sufficient to maintain the nursing young alive. The atrophy of the gland cells is confined almost entirely to the cytoplasm, and in prolonged inanition there is a marked fatty infiltration. On proper refeeding, this fat decreases in amount, and the gland tends to resume its normal functional structure. Cell division was not observed in the epithelial cells during either inanition or refeeding.

The effects of inanition upon the mammary gland in young albino rats underfed for various periods were studied by Myers ('19), who found that the development of the mammary glands is thereby retarded, roughly in proportion to the retardation of body weight. When such stunted rats are refed, however, the development of the mammary glands for some time lags behind that in normal rats of corresponding body weight, although later they recover the normal condition.

**Human Mammary Gland.**—The atrophy of the mammary gland in the adult human female during starvation has often been observed (Bright '77; Falck '81), the girl of 19 years described by Schultzen ('62, '63) apparently forming the only exception. In the autopsies during the Indian famine, Porter ('89) states that the mammary glands "had shrivelled to such a degree in the emaciated women that their position was only ascertainable by the presence of the nipple. No gland could be seen or felt."

The accounts concerning the effects of war famine upon the milk secretion of nursing mothers are somewhat variable. Thus during the siege of Paris

in 1870, according to Decaisne ('71), in some cases (12 out of 43 studied) young and vigorous women, in spite of malnutrition, were able to continue milk secretion sufficient to maintain their nursing infants. Similarly, during the recent war, Tschirch ('16), Steinhardt ('17) and Landé ('19) found the ability to nurse their offspring was not reduced in German women. Opitz ('18) and Momm ('20) found the milk reduced in amount, but unchanged in chemical composition. As Lusk ('21) remarks: "All this confirms the biological principle of the sacrifice of the mother for the welfare of the offspring." This principle has its limitations, however, and in some localities the results were less favorable, doubtless depending upon the character and degree of the inanition. Ruge ('16), for example, found that malnutrition of the mother causes marked decrease in both quantity and quality of the milk secreted. Loenne ('18) likewise noted a decreased capacity for lactation, which, according to Kütting ('21) resulted in a greater postnatal loss of weight in the newborn. Brüning ('18) ascribed the prolongation of the time required to recover the postnatal loss of weight to a deterioration in the quality, rather than in the quantity, of the maternal milk. In 16 of Decaisne's cases (above mentioned) there was practically no milk secreted, and three-fourths of the infants died of inanition.

It is well known that an extreme degree of atrophy of the mammary glands is also commonly found in various diseases involving marked emaciation, such as tuberculosis and cancer, as well as in certain types of partial inanition to be mentioned later.

#### (B) CHANGES IN THE INTEGUMENT DURING PARTIAL INANITION

Under this heading will be considered the structural changes in the integument upon diets deficient in protein (including malnutritional edema and pellagra), salts (including rickets,) vitamins (including scurvy), and water.

**Protein Deficiency.**—Osborne and Mendel ('11) noted certain changes in the hair coat of young albino rats whose growth was retarded by diets incomplete in proteins. Similar changes were observed by Wheeler ('13) in young mice on inadequate protein diets. Evvard ('12) found that maize-fed pregnant sows give birth to many weakling pigs, with the skin lighter, anemic and deficient in hair development. He ascribed this to calcium deficiency; but experiments later (Evvard, Cox and Guernsey '14) indicated that the protein deficiency is the most important factor in the maize diet. (Osborne has shown that zein is deficient especially in tryptophan and lysin.) Skin lesions were observed also in rats on the maize diet by Abderhalden ('19), and by several investigators attempting to produce experimental pellagra in animals by maize diets (cited by Marie '08, '10). Osborne and Mendel ('16a) observed that with corn-gluten food (deficient in tryptophan and lysin) young chicks were stunted in growth and the body remained covered with down, as at the beginning of the experiment. However, a few feathers continued growth which had already begun. In another experiment ('16b), in a young rat held at maintenance by a diet lacking lysin, a patch of hair on the animal's back was dyed red at the beginning of the experiment. This color remained unchanged for 6 months; then lysin was

added to the diet and the color soon disappeared, on account of the resumption of growth in the hairs as in other parts of the body. Drummond ('16), however, noted continued growth in beak and feathers of chickens held at constant body weight (100-150 g.) by rice diet (mixed deficiency) for periods of 20-80 days. Zuntz ('20) concluded that the growth of the epidermal structures (including hair and nails) may be restricted by lack of cystin, and he obtained increased growth of hair in sheep and man by addition of hydrolized horn to the diet. The literature on alopecia in animals on various artificial diets is reviewed by Brüning ('14a).

**Malnutritional Edema.**—As already mentioned, cutaneous edema (with or without general anasarca and ascites) may be produced experimentally in rats by diets deficient in protein or fats, and similar deficiencies may be responsible for the edemic cachexia found in domestic animals and in conditions of human famine. Many authors, however, consider that "famine edema" and allied conditions are due to general inanition rather than to any specific deficiency. Cutaneous edema is usually associated with atrophy of the adipose tissue. Cramer ('23) found that in young rats on a diet deficient in tryptophan: "The hair falls out in patches after 6 or 7 weeks of this diet, and after another 8 or 10 days there is an extensive oedematous condition extending over parts of the trunk and stretching the skin." This cutaneous myxedema was ascribed to hypothyroidism, due to extensive lesions in the thyroid gland.

**Cutaneous Lesions in Pellagra.**—As previously mentioned, the exact etiology of pellagra is yet somewhat uncertain, although it seems probable that protein deficiency in the diet is at least an important factor. The cutaneous lesions are variable according to the stage and severity of the disease, and are sometimes absent ("pellagra sine pellagra"). While space does not permit the review in detail of numerous observations on the cutaneous pathology in pellagra, the more recent papers by Griffini ('70), Raymond ('89), Babes and Sion ('01), v. Veress ('06), Gurd ('11), Roberts ('12), Fiocco ('12), Raubitschek ('15) and MacNeal ('21) may be cited. It is of interest to note that in some preliminary therapeutic trials by Goldberger and Tanner ('22), the dermal lesions in 2 cases reacted favorably to cystin, and in a third case to cystin and tryptophan.

In general, the human skin in pellagra shows an acute stage of erythema (similar to that in sunburn), followed by a chronic stage of atrophy and pigmentation. The pigmentation usually affects the areas exposed to the sun, and appears in patches symmetrically disposed on both sides of the body.

The histological changes in the acute (erythematous) stage usually involve inflammatory phenomena, with more or less edema in both epidermis and dermis. The epidermis undergoes proliferation and desquamation, with degeneration changes frequently forming blebs in the stratum germinativum (Malpighian layer). The dermis shows congestion, with marked fibrosis and pigmentation. Later the acute symptoms subside and a chronic condition of general atrophy in all layers of the skin gradually supervenes. This atrophy resembles that characteristic of old age, with hyalin degeneration and sclerosis in the blood vessels. Marked cutaneous edema may be present, but this "wet form" appears less frequently.

According to Marie ('08 '10), there is found in pellagra a precocious tendency to alopecia, with sclerosis and pigmentation of the ectodermic structures.

**Deficiency in Salts.**—Von Hoesslin ('82) gives some weights of the skin in dogs on nearly iron-free diet, but unfortunately normal controls are lacking. Roughening of the hair coat was observed in puppies by Quest ('06) with calcium-poor diet, and by Masslow ('13) with phosphorus-poor diet. Babcock ('05) found in cows on low salt rations during lactation no decrease in the milk yield for a considerable period of time, and a slight increase in fat content of the milk. Meigs ('22) reviewed the effects of partial inanition upon lactation, concluding that a marked deficit of calcium or phosphorus may not affect the amount of secretion for a long time, whereas a serious shortage of protein, fat or carbohydrate causes an immediate reduction.

In **rickets** the skin may be affected in children (Cheadle and Poynton '07). In rats subjected to experimental rickets, by deficiency in phosphorus or calcium and antirachitic vitamin, the skin becomes emaciated, and the hair coat frequently appears rough and uneven (McCollum, Simmonds, Shipley and Park '21; Shipley, Park, McCollum and Simmonds '21; McCollum, Simmonds, Kinney, Shipley and Park '22). Jackson and Carleton ('23) found a markedly subnormal weight of the integument in rachitic rats, even when the body weight appeared normal (Table 11).

Smith ('17) and Hart and Steenbock ('18a) found that a deficiency of **iodin** in the diet of pregnant sows results in the birth of weak, hairless pigs, with edematous skin and undeveloped hoofs. This condition, which is ascribed to malfunction of the enlarged fetal thyroid gland, may also occur in sheep, and occasionally in cattle and horses.

**Vitamin Deficiency.**—Funk and Macallum ('14) found the feathers and beak apparently normal in a chick whose growth was suppressed for several months by a diet of unpolished rice and cod liver oil. In chicks and pigeons on polished rice diet with experimental polyneuritis, Tasawa ('15) found the skin atrophic, thin and dry; the fat in the subcutaneous tissue and elsewhere greatly reduced in amount. In the so-called "wet" beriberi of man (due to deficiency of vitamin B) edema and anemia of the skin are characteristic.

According to Emmett and Allen ('20) and Funk ('22), lack of vitamin A in the diet of young rats produces a coarse and sparse hair coat. Cramer ('20) claims that if rats are deprived of vitamins for 25 days, the lipoids disappear from the "brown fat" (as well as from the suprarenal cortex); hence he proposes to call this type of adipose tissue the "lipoid gland" or "cholesterin gland."

The experiments of McCollum and Simmonds ('18) indicate that vitamins (A and B) are not synthesized in the mammary gland by the nursing mother rat; therefore if vitamins are absent from the diet they are lacking also in the milk, and the young fail to grow properly.

**Scurvy.**—The skin undergoes characteristic changes in scurvy, which is caused by a deficiency in vitamin C. Holst and Frölich ('07, '12) discovered that scurvy can be produced in young guinea pigs by a diet of oats or other cereals with water. The characteristic cutaneous hemorrhages occur; likewise subcutaneous edema, but only occasionally. Petechiae in the follicles of the

vibrissae appear constant, however. Bessesen ('23) found the integument usually subnormal in weight (Table 12).

The extensive literature on human scurvy has recently been reviewed by Hess ('20) who notes that the skin is usually pale or livid and dotted with numerous petechiae. These are variable in size and most frequently located on the lower extremities. There may also be larger superficial hemorrhages, with color varying from reddish in the more recent to blue, green or brown in the older lesions. Emaciation and edema may occur, the latter most frequently localized in the regions of the ankles or eyes. According to Sato and Nambu ('08) and Comrie ('20), cutaneous hemorrhages, often associated with sclerosis and marked edema, occur especially in the lower extremities.

That the regions of the sweat glands and especially of the hair follicles are particularly susceptible to the petechial hemorrhages was observed by Lasègue and Legroux ('71), and confirmed by Aschoff and Koch ('19), Bierich ('19) and Wiltshire ('19). Wiltshire also described a peculiar "hyperkeratosis" of the affected follicles, each presenting a hard swelling, of pin-head size, due to the accumulation of epithelial débris at the mouth of the follicle. The hairs become atrophic, and may be broken off and regenerated. A similar hyperkeratosis is said to occur in other malnutritional states.

**Water Deficiency.**—Tiedemann ('36) stated that in man during extreme thirst the skin becomes dry and hot. Schuchardt ('47) found no apparent loss in the skin of pigeons with loss of 44 per cent in body weight on a dry barley diet. Scheffer ('52) and Falck and Scheffer ('54) in a dog which lost 20.7 per cent in body weight during 28 days on dry biscuit, noted an apparent loss of 28 per cent in the weight of the skin. Bowin ('80) observed that in dogs on a dry diet the skin becomes roughened and the hairs are easily detached. Pernice and Scagliosi ('95a), in chicks fed dry maize only, noted that the comb, at first red, becomes pale and later cyanotic. At autopsy the skin is dark reddish or nearly black (from passive congestion), and the fat has almost disappeared. As shown in Table 9, Kudo ('21) found that in adult albino rats on dry diets (acute or chronic thirst), the relative loss in the weight of the integument is slightly less than that of the whole body, as found in total inanition. As shown in Table 10, Kudo ('21a) noted that in young albino rats (about 4 weeks old) which were held at nearly constant body weight by a dry diet for various periods (1-13 weeks), the integument usually loses slightly in weight (7.5-14) per cent. This slight loss appears early and is not progressive in the longer experiments. The skin becomes somewhat roughened, but the hair is not easily detached (as it is in adult rats). Dryness and desquamation were observed on the plantar surfaces. The claws become much elongated, especially in the longer test periods.

According to Tobler and Bessau ('14) the loss of turgor in the skin of malnourished infants with diarrhea is due to the withdrawal of water from the skin. Marriott ('23) states that during anhydremia the skin becomes gray, wrinkled and dry, and loses its elasticity. There is marked stagnation in the peripheral circulation.

## CHAPTER VII

### EFFECTS ON THE SKELETON

It has long been recognized that the skeleton loses little or nothing during general inanition, the wasting of other parts of the emaciated body giving rise to the characteristic appearance expressed by the phrase "reduced to a skeleton" (see Fig. 33). During certain types of partial inanition (rickets and scurvy), however, the skeleton is markedly affected. After a brief summary, the effects of inanition upon the skeleton will be considered under (*A*) total inanition, or on water only, and (*B*) partial inanition.

#### SUMMARY OF EFFECTS ON THE SKELETON

During **total inanition** (or on water alone) there is but slight loss in the weight of the skeleton in adults, since the solids lost are largely replaced by water. In the young, during incomplete inanition there is even a persistent skeletal growth, variable in amount according to circumstances.

Histologically there is but little change in the adult bony tissue during total inanition, aside from resorption tending to osteoporosis in chronic conditions. Degenerative changes may occur in the cartilage cells, and especially in the adipose bone marrow, which undergoes mucoid atrophy (as described in Chapter VI). There is also an atrophy of the red marrow, with degenerative changes in the hemopoietic cells. Bone fractures heal poorly during inanition; but regeneration and restitution of normal skeletal structure occur upon appropriate refeeding, if the preceding inanition is not too prolonged or severe.

**Protein Deficiency**, including pellagra, tends to produce in adults a skeletal condition of osteoporosis, somewhat similar to that in chronic total inanition. In young animals on incomplete protein diets there appears to be less tendency to persistent dystrophic skeletal growth, but more perfect recovery upon refeeding after long periods of suppressed growth.

**Calcium and Phosphorus.**—The skeleton serves as a storehouse of reserve mineral supply, and is especially sensitive to a dietary deficiency in salts of calcium or phosphorus. A deficiency in calcium or phosphorus alone apparently produces skeletal softening grossly resembling rickets, but histologically presenting a "pseudorachitic osteoporosis" of variable extent and character.

True **rickets** apparently involves an accessory factor ("fourth vitamin") and also a relative deficiency in calcium or phosphorus. The fresh weight of the skeleton is not much affected, but there is marked softening (with consequent deformities) and the dry weight is greatly reduced. Histologically rickets is characterized, in the region of enchondral ossification, by an increased width and irregularity of the proliferative cartilage zone, a failure of the pro-

visional calcification, and an intensified vascular invasion from the marrow and perichondrium. A characteristic, irregular "metaphysis" zone is thereby produced, composed of excessive osteoid substance (uncalcified bone), which replaces the cartilage, apparently by metaplasia. Subperiosteal osteoid is also formed. The bone marrow becomes atrophic and variably fibroid in character. Cessation of osteogenesis, together with continued absorption in the spongiosa and cortical bone, may produce a variable degree of osteoporosis. Recovery is possible upon appropriate diet, but severe rickets causes permanent dwarfing and deformity. In late or adult rickets (osteomalacia) there is much decalcification of bone (halisteresis), and the enchondral ossification changes are absent.

**Scurvy**, caused by lack of vitamin C, is characterized by a general hemorrhagic tendency, inhibited osteogenesis and marked atrophy of the osseous tissue. The skeleton is fragile and brittle, with a histological structure quite different from that in rickets. In the young (infantile scurvy or Barlow's disease), the proliferative cartilage zone is widened, as in rickets, but the provisional calcification takes place. The normal invasion and replacement of this cartilage by osteogenic marrow tissue fails to occur, however, and the accumulation of calcified trabeculae forms a wide, weakened zone, which easily fractures, causing hemorrhages and an irregular swollen area ("Trümmerfeld"). The adjacent marrow undergoes a fibroid degeneration, related to that in rickets and other forms of inanition, but with characteristic multiple hemorrhages. Atrophy of the osteogenic tissue, together with continued absorption in both spongiosa and cortex, results in osteoporosis which is more constant and pronounced than in rickets. Except in the most extreme stages, recovery is possible upon appropriate diet.

Fetal scurvy is produced when pregnant guinea pigs are placed upon scorbutic diet, but the occurrence of fetal rickets is doubtful. There are marked differences among species in the susceptibility to scurvy and rickets, as found also in other dietary deficiencies.

**Aqueous inanition**, with dry diets, occasions skeletal changes apparently similar to those found in total inanition. This is probably due in part to the lessened food-intake on dry diets.

#### (A) EFFECTS OF TOTAL INANITION, OR ON WATER ONLY

**Weight Changes in Adults.**—Actual weights of the skeleton in mammals subjected to various degrees of inanition, in comparison with those of normal controls, indicate little or no loss, according to observations on pigeons by Chossat ('43) and Lukjanow ('89); on the cat by Bidder and Schmidt ('52); on dogs by Falck ('54, '75) and Schöndorff ('97); on hibernating marmots by Valentin ('57); on various mammals by Bourgeois ('70), C. Voit ('66, '94), and E. Voit ('05a); on rabbits by Gusmita ('93), Pfeiffer ('87), Weiske ('97) and Sedlmair ('99); on the femur of guinea pigs by Lazareff ('95); on albino rats by Jackson ('15); and on man according to Rokitansky ('54) and Cohnheim ('89). Where apparent loss in weight of the skeleton occurs, it is almost always

less than 10 per cent, usually below 5 per cent, which is very slight in comparison with the corresponding loss in body weight.

The nearly stationary weight of the skeleton during starvation, despite the loss of calcium phosphate and marrow fat, is possible because the substances lost are largely replaced by water, the specific gravity of which is higher than that of the fat (*cf.* Wellman '08, Jackson '15, Lusk '17).

In the skeleton of amphibia, however, the destructive effect of starvation may be much greater. Harms ('09), Kammerer ('12) and Nussbaum ('14) found in fasting Triton and Proteus a marked shrinkage in the length of the vertebral column, but no weights of the skeleton were recorded. Ott ('24) found that during hibernation and subsequent inanition in the leopard frog (*Rana pipiens*), the ligamentous skeleton in general showed no loss in weight, but rather a slight increase (Table 6). In the group with loss of 60 per cent in body weight, however, there was an apparent decrease of 12 per cent in the weight of the skeleton. There was a marked and progressive decrease in dry substance.

**Weight Changes in the Young.**—The earlier observations upon the skeleton in malnourished young children by Bouchaud ('64), Ohlmüller ('82) and Herter ('08) indicated merely that the skeleton, though retarded in growth, fails to lose in weight and (as in adults) becomes relatively heavier in proportion to body weight. Later it became apparent, as already stated in Chapter IV, that in young individuals subjected to underfeeding, certain dystrophic growth changes may occur, chief among which is a persistent growth of the skeleton. This was observed by Camerer ('05), Variot ('07a, etc.), Stolte ('13), Jackson ('22), and others in the human infant; by Waters ('08), Falke ('10), Trowbridge, Moulton and Haigh ('18, '19) and Moulton, Trowbridge and Haigh ('21) in calves; by Aron ('10, '11, '13) in puppies and rats; by Jackson ('15a), Jackson and Stewart ('18), Barry ('20, '21) and Stewart ('16a, '18, '19) in the albino rat (see p. 89; Table 4); by Thompson and Mendel ('18) in the mouse; and by Podhradsky ('23) in young fasting tadpoles of *Rana fusca*. Further data upon the weight of the ligamentous skeleton in atrophic infants are given in Table 3.

That such dystrophic skeletal growth does not invariably occur in malnourished young, however, is indicated by the observations of Tschirwinsky ('10) on lambs, and by Lascoux ('08), Freund ('09), Lesage ('11), Waser ('20) and others on atrophic children, as mentioned in Chapter IV. The skeletal growth is doubtless affected by the amount and character of the insufficient diet, and apparently varies also according to age (Birk '11; Lust '13). The age factor appears most clearly in the work of Jackson, Stewart and Barry (Table 4), which indicates that in the albino rat the persistent growth tendency of the skeleton in undernourished rats is relatively strongest after the weaning period (3 weeks of age), being less in older as well as in younger stages; and not evident in the fetus.

**Structural Changes in the Adult Bone.**—Various observers have noted that the bones tend to become weakened and brittle during conditions of prolonged inanition (*cf.* v. Recklinghausen '10), but in most cases it appears probable that these changes are primarily due to certain specific (especially mineral) deficiencies, which will be mentioned later. This applies especially to the various

forms of "Hungerosteopathie" (osteoporosis and osteomalacia) frequently observed during periods of famine (by Chelmonski '21; Dalyell and Chick '21; Koepchen '19; Schlesinger '19; Richet and Mignard '19; Sauer '20; Simon '21; Szenes '21; Seeliger '23; Nicolaeff '23) and to similar skeletal disorders in malnourished animals (by Theiler *et al.*, '12, '20; Gans '15; Hedinger '20). It is also possible, as will appear later, that some of the effects of inanition upon the skeleton may be indirect, through injury to some of the endocrine glands (parathyroid, etc.) which are concerned in calcium metabolism. (Cf. Stefko '23a.)

Gusmita ('93) found apparent dilation of the Haversian canals and enlargement of the lacunae in the bones of a starved dog; aside from this no data appear as to the effect of total inanition upon osseous tissue.

**Changes in Adult Marrow.**—The changes in the adipose bone marrow during inanition were described in the preceding chapter, p. 125. It undergoes mucoid atrophy, with the absorption of the fat and metamorphosis of the fat cells, which return to their primitive stellate form and become embedded in an abundant gelatinous or mucoid intercellular substance. Hyperemia usually occurs. The reticulum fibers, which are observed in the adipose marrow, appear still quite distinctly in the atrophic mucoid marrow (Jackson '04) (Figs. 50, 51). Kölliker ('89) described a transformation of yellow (adipose) marrow into red (lymphoid) marrow through inanition. The formation of gelatinous marrow in the long bones of various mammals was reviewed by Ricklin ('79) and Ackerknecht ('12).

The red or lymphoid marrow may also undergo mucoid atrophy, depending upon the relative abundance of adipose cells present (Denys '87; Roger and Josué '00; Traina '04; Jackson '04; Dickson '08; Dantschakoff '09; Meyer '17; Jolly '20; Stefko '23). The various stages in the marrow changes during inanition were described by Solts ('94), in fasting dogs with loss of 13–52 per cent in body weight. There is hyperemia in the early stages, followed by mucoid degeneration in the middle stages. Some of the fat cells become stellate; some are destroyed. Other marrow cells, including the giant cells, undergo vacuolar degeneration and final necrobiosis. Capillary thromboses and hemorrhages may occur. Traina ('04) likewise found the bone marrow nearly normal in fasting rabbits up to about 10 per cent loss in body weight. At 10–20 per cent loss, the fat disappears from the adipose marrow cells (in the long bones, first at the ends). The fat may be replaced by serous fluid, with undiminished cell volume; or the fat cells may form a branched reticulum, enclosing marrow cells of normal or diminished size. Interstitial gelatinous substance appears, and the cells, including the megakaryocytes, undergo degenerative changes. At death from starvation, small fat droplets may still be found in the fat cells, also in the leukocytes and even free in the blood vessels. Altmann's granules become more numerous and distinct in the marrow cells. The observations of Opie ('04) on the eosinophiles in the bone marrow of fasting guinea pigs are stated in Chapter XV. The changes in the marrow cells during inanition have been reviewed by Helly ('06).

Although the lymphoid tissue is generally found to undergo atrophy with disappearance of the lymphocytes in the bone marrow as elsewhere during

inaition (Jolly '20), a proliferation of leukocytes was found by Sanfelice ('89) and of marrow cells in fasting rabbits by Roger and Josué ('00). Dantschakoff ('09), however, described in the marrow of fasting birds (chick and duck) a general rarefaction of cells with progressive decrease in hemopoiesis. Foa ('99) described the degenerative changes in the megakaryocytes of fasting rabbits. A decrease in the blood-forming elements in human red marrow during malnutrition was described by Dickson ('08). Lossen ('10) found that in the red bone marrow of fasting rabbits there is a marked decrease in the number of erythroblasts but a relative increase in the number of lymphocytes and myelocytes. Similar changes were observed in human cachexias. Ikeda ('22) observed in the bone marrow of fasting rabbits at first a transient proliferation of the myeloid and (slightly) the erythroblastic elements; later the process becomes normal, but in protracted inaition atrophy of the myeloid tissue occurs. Stefko ('23) concludes from an extensive study of material from 50 necropsies that inaition stimulates the formation of myelocytes in the bone marrow, thereby affecting also the blood picture.

**Hibernation.**—Some observations have also been made on the bone marrow during hibernation. According to Pappenheim ('01), in hibernating spermo-philis, the red marrow of the ribs shows only slight changes; but the adipose marrow of the long bones undergoes atrophy proportional to the emaciation of the body. On awakening, this marrow also becomes red. Beretta ('02) noted frequent mitoses in the erythroblasts and leucocytes of the femur marrow in the hibernating hedgehog (*Erinaceus europaeus*).

**Cartilage.**—The cartilage during inaition has been studied most frequently with reference to its fat content. Manassein ('68, '69) observed in the costal, articular and laryngeal cartilage cells of rabbits a variable number of highly refractive (fatty?) granules, which persisted during starvation. Similarly a persistence of the fat in the cartilage cells during inaition was found by Sacerdotti ('98, '98-'99, '00) in starving rabbits; and by Bell ('09) in underfed cattle. Rabe ('10) noted an increase in the size of the fat droplets of the cartilage cells in the rabbit's ear during starvation, with a gradual decrease in glycogen content.

Structural changes in the vertebral column of *Triton taeniatus* after several months of starvation were described by Harms ('09). Degenerative changes affect first the marrow, with complete disappearance of the fat, enlargement and disintegration of the marrow cell nuclei. Later the cartilage cells are similarly affected, with vacuolar degeneration, nuclear enlargement and karyorrhesis. Ultimately the intervertebral disks become completely fibrous. Podhradsky ('23) noted ultimate resorption of the caudal chorda dorsalis in fasting tadpoles of *Rana fusca*.

Degenerative changes were found also by Meyer ('17) in the cartilage cells of the epiglottis and trachea in a man who had starved to death. The greatest degeneration appears in the interior of the cartilage, although surface cells are also affected. The nuclei are pycnotic or absent; and often entire cells have disappeared, leaving empty lacunae.

**Skeletal Changes in the Young.**—The dystrophic growth changes in undernourished young children and animals, with dissociation of growth in height and

weight due to persistent growth of the skeleton, have already been considered. Certain further details as to structural changes will now be mentioned.

A thorough histological study of the zone of enchondral ossification (upper femur, etc.) in the full term fetus of rabbits subjected to total inanition for 2-8 days was made by Diatschenko ('97, '99). No data as to the effects of the maternal inanition upon the fetal body are given, but marked and progressive changes were found in the zone of ossification. The cartilage showed no changes except in this zone, although some increase in the number of osteoblasts beneath the neighboring periosteum was evident. The hyperplastic zone (columns of flattened cartilage cells) increases from 0.6 to 0.8 mm. in width. The hypertrophic zone becomes indistinct, but the atrophic zone (of regressive cartilage cells) increases from 0.12 to 0.23 mm. in thickness. The atrophic cartilage cells are markedly shrunken, in rounded, strongly calcified capsules, separated by thickened septa.

The bony trabeculae in the adjacent marrow zone become slightly thickened and covered by osteoblasts 2 or 3 layers deep, instead of the normal single layer. The nuclei of the cartilage cells and the osteoblasts in the region stain feebly, giving a characteristic light zone in stained preparations, which increases progressively in width during the period of inanition.

The newly formed bone laid down upon the trabeculae and walls of the medullary spaces may present a somewhat thickened osteoid (uncalcified) layer, but never the irregular osteoid masses characteristic of rickets. The progressive changes produced in the fetal ossification zone are designated by Diatschenko as "*chondrodystrophia foetalis ex inanitione*" and resemble somewhat those of syphilitic osteochondritis. They differ from those in rickets especially in the increased width of the atrophic cartilage zone and in the intensity of calcification.

In a radiographic study of the skeleton in the hands and feet of children retarded in growth by malnutrition, Variot ('05a, '06, '06a, '07d) found the centers of ossification appearing nearly normal according to the height. Thus the process of ossification is somewhat in advance of that in normal infants of the same body weight, but is behind the normal for corresponding age. A similar condition was found by Jackson ('15a) in the skeleton of young albino rats held at maintenance by underfeeding from 3 weeks to 10 weeks of age. The persistent growth of the skeleton involves the normal appearance and union of the various epiphyses, corresponding to the size or weight of the skeleton. Unpublished observations upon sections of the lower end of the femur in these rats by Dr. F. P. Silvernale, in the Institute of Anatomy, University of Minnesota, show an apparently normal process of ossification, with no indication of the dystrophic changes observed by Diatschenko ('97, '99) in the rabbit fetus.

In the cranium of athreptic infants, a depression of the fontanelles with a tendency of the bones to overlap, so as to produce ridges at the sutural borders, was noted by Tardieu ('80), Thiercelin ('04) and others. This may be due to cranial overgrowth exceeding that of the brain, or to decreased intracranial fluid. Dystrophic structural changes in the cranium of athreptic infants, according to Lesage ('14), may involve a "soft atrophy," with retarded ossifi-

cation of the fontanelles and sutures, similar to the craniotabes of syphilis or rickets. In "congenital spasmodic atrophy," on the contrary, Lesage and Cleret ('14) described the head as small and the cranium hard, an intense osseous hyperplasia sometimes filling the fontanelles and sutures with a dense bony tissue. Zuntz ('19) noted that the hardness of the skull is not modified in the fetus of rats during maternal starvation. Nicolaëff ('23) found osteoporosis, especially of the vertebrae and cranial vault, in famine-stricken children.

**Recovery upon Refeeding.**—As previously noted, a recovery of normal body weight is possible, if the inanition has not exceeded certain limits in length or severity. If the normal size as well as the weight of the body is to be recovered in the young, the subsequent growth of the skeleton is necessary. Aron ('11, '13) found that puppies and young rats underfed for long periods do not regain normal size upon full refeeding. This was confirmed by Jackson and Stewart ('18, '20) in underfed young rats. If the underfeeding period is not too severe or prolonged, however, and if not begun at too early an age, perfect recovery was found possible (Stewart '16). The weight of the skeleton (ligamentous, cartilaginous and dry) at various stages of recovery was studied by Jackson and Stewart ('19).

In children refed after prolonged inanition, Goldstein ('22) observed that the increase in weight begins quickly while increase in length (skeletal growth) does not appear until after a stationary period.

As to histological structure, Solts ('94) refed 2 dogs and 3 puppies after inanition, finding that the bone marrow regains normal structure. The mucoid substance gradually disappears and the necrotic cells are absorbed. Many mitoses occur in the marrow cells, and nucleated red cells become abundant. Jackson ('04) similarly found that the bone marrow in a pigeon, richly fed for 3 weeks after a severe underfeeding period of 16 days, showed disappearance of the gelatinous bone marrow with complete recovery of normal structure.

Bourgeois ('70) found that during inanition in animals the formation of a callus and the consolidation of fractures is difficult or impossible. The effect of inanition upon regeneration of bone was studied also by Trifiliev ('01) in fractures of the radius in starved and normal rabbits. The callus was found less voluminous and the process of repair delayed several days in the test rabbits in comparison with the controls. Hammer ('20) noted a similar effect as a result of human malnourishment during the war famine. "Wir haben nämlich seit längerer Zeit beobachten können, dass einzelne Frakturen eine auffallend geringe Neigung zur Heilung zeigen die in einer verzögerten Kallusbildung ihre unmittelbare Ursache hat, eine Beobachtung die auch anderwärts gemacht worden ist, worauf neben anderen (Eisler, Rupp, Tietzke) vor allen Melchior mehrfach hingewiesen hat." Hammer concludes that this inhibition of the regenerative capacity of the bone, which may exist in the absence of clinical symptoms, is not due to dietary deficiency of calcium or phosphorus, and is probably an indirect result of the effects of inanition upon the endocrine glands. A delay up to 8 or 10 months in the healing of fractures during the Russian famine was recorded by Abel ('23).

## (B) EFFECTS OF PARTIAL INANITION

The effects of partial inanition on the skeleton will include deficiencies of protein (with pellagra), of salts (calcium, phosphorus and rickets), of vitamins (A, B and C) and of water. The effects on skeletal growth were summarized by Jackson ('21).

**Protein Deficiency.**—As already mentioned in Chapter V, Osborne and Mendel ('11, etc.) found that on various incomplete protein diets young albino rats remain unchanged in size for long periods, after which they are capable of complete recovery upon adequate refeeding. In both respects these results indicate that the skeleton reacts differently in protein deficiency in comparison with general underfeeding. Schulz ('12) found no increase of length in puppies fed farinaceous gruels (mixed deficiency), with full recovery upon later refeeding, excepting the very young puppies, which remained permanently stunted. Brüning ('14, '14a) noted no persistent skeletal growth in young rats on one-sided carbohydrate diet with stationary body weight. Mendel and Judson ('16), however, found persistent growth of the skeleton in mice on diets with protein or salt deficiency, as well as in simple underfeeding.

Evvard, Cox and Guernsey ('14) noted defective bone development in the offspring of pregnant swine fed on maize (deficient in both protein and calcium). Osteoporosis and osteomalacia have often been observed in cases of human malnutrition, involving deficiency in protein as well as in calcium and phosphorus (Alwens '19). On milled rice diet (deficient in protein, salts and vitamins), fragility of the bones and atrophy of the bone marrow were found in animals by McCarrison ('21) and others. Regenerative activity in the bone marrow of dogs on rice diet was noted by Brucco ('20).

While the chemical data are too numerous to be mentioned here, it may be noted that Klose ('13), in an infant with alimentary edema (mixed deficiency), found that the skeleton shows a marked increase in water content, with decrease in fat, protein and ash. Similar data are given by Aron ('10, '11, '13, '13a) for underfed puppies.

According to Findlay and Mackenzie ('22), dietary deficiency of protein in rats causes patchy hemorrhagic areas in the bone marrow of the femur.

In **pellagra** (assumed to be due chiefly to protein deficiency), fragilitas ossium was noted frequently, especially in the ribs, by Fraenkel ('69-'70), Lombroso ('92), Tuczek ('93), Marie ('08, '10), Raubitschek ('15) and Harris ('19). Roberts ('12) presented X-ray figures showing rarefaction of the spongiosa and cortical layer in the bones of the hands.

In rats on **lipoid-free** ration with retarded growth of body, Hatai ('15) found the weight and length of the long bones normal for the body length, but the tail length slightly above normal.

**Salt Deficiency.**—In human experiments with complete dietary deficiency of inorganic salts, Munk ('93) concluded from urinary analysis that there is a loss of calcium phosphate from the skeleton (*cf.* Forster '76; Wellman '08; Lusk '17). Lötsch ('12) described in cattle on salt-poor diet a skeletal disorder resembling human rickets and osteomalacia. Forbes ('19) has studied the

relation of minerals to the growth and structure of the body, and especially of the skeleton. "The readiness with which minerals may be deposited in the bones, the lack of a definite upper limit of such a deposit, and the readiness with which these minerals may be withdrawn constitute the skeleton a true store of mineral nutriment." McClendon ('22b) states that in a normal white rat weighing about 70 g. the skeleton contains 82 per cent of the phosphorus and 96 per cent of the calcium in the body.

In most of the earlier experiments, the mineral deficiencies were complicated by other (especially vitamin) deficiencies, so their interpretation is often uncertain.

**Calcium Deficiency.**—It is difficult to consider the effects of calcium deficiency aside from the question of rickets. Some of the more general effects of calcium deficiency upon the skeleton will be mentioned now, leaving those papers dealing more specifically with rickets for later consideration.

Chossat ('42) observed that on diet of wheat (calcium-poor) and water, adult pigeons die before 10 months with a diarrhea and skeletal lesions ascribed to the calcium deficiency and prevented by addition of calcium carbonate to the diet. The bones, especially the femur and sternum, become very porous, softened and fragile, so as to fracture easily. Similar results were obtained by Friedleben ('60), Milne-Edwards ('61) (with loss of  $\frac{1}{3}$  in weight of the skeleton), C. Voit ('81) and numerous more recent workers. E. Voit ('77) found that in pigeons on calcium-poor diet the bones more actively used in movements and support retain their calcium content longer, while the inactive (*e.g.*, skull and sternum) become porous and thin. The negative results of Weiske ('71, '74) and Weiske and Wildt ('73) with goats, rabbits and lambs on calcium-poor diets were ascribed by later investigators to starvation (total inanition) since the animals refused the food. Numerous more recent workers have investigated the histological changes in the skeleton of various animals on different calcium-poor diets, and have described, in addition to the resorptive changes associated with osteoporosis, variable other lesions more or less closely related to those of rickets (to be mentioned later).

According to Kellner ('16) fragility of the bones occurs also in the large domestic animals on calcium-poor diets. The relation between malnutritional and senile osteoporosis has been emphasized by Alwens ('19) and others. Rubner ('20a), however, states that the bone lesions occurring during the war famine were not curable by calcium alone. McClendon ('22a) found that low calcium diet produced osteoporosis in young rats, with marked reduction in the thickness of the wall in the shafts of the long bones.

Dibbelt ('11) cites evidence indicating that there is a "physiological osteoporosis" in the skeleton of the human infant and in the young of other animals. He ascribed this to the relative poverty of calcium in the milk, a condition which favors bone resorption. Wieland ('13) also reviewed the evidence for "physiological osteoporosis," but found no proof of a universal calcium-deficit in the nursing's milk. In the case of the human infant, it is difficult to exclude the possibility of latent rickets, scurvy or similar disorders due to dietary deficiencies.

Albrecht ('13) found that in pregnant cows on calcium-poor diet the skeleton of the fetus develops normally, the necessary calcium being withdrawn from the maternal skeleton. Eppard, Cox and Guernsey ('14) noted imperfect development of the skeleton in pigs from sows fed maize diet during pregnancy, but ascribed this to deficiency of protein rather than of calcium.

**Phosphorus Deficiency.**—Not many experiments have been made with diets deficient in phosphates, aside from those to be mentioned later in connection with rickets. Weiske ('71) and Weiske and Wildt ('73) fed phosphorus-poor diets to adult goats and young lambs, but found no apparent effect on the skeleton. Later investigators (Roloff, E. Voit) explained these negative results as due chiefly to the failure of the animals to eat the diet, with resultant general starvation. Hart, McCollum and Fuller ('09, '09a) found that low-phosphorus diet causes osteoporosis in pigs, but made no histological examination. Heubner ('10), Lipschütz ('10, '11a) and Schmorl ('13) fed puppies diets poor in phosphorus, and found the skeletal changes more like those of scurvy than of rickets. It is probable that these diets involved also deficiency in vitamin C (to be considered later).

**Rachitis.**—Some of the gross deformities resulting from human rickets as described by Whistler (1645) and Glisson (1650) were mentioned in Chapter V. Vincent ('04) states that the enlargement of the costochondral joints ("rickety rosary") is one of the earliest and most striking changes, found by Holt in 142 out of 144 cases. Vincent claims this is absent in all other diseases, but it occurs also in scurvy. "Pigeon breast" is frequent, with lateral compression of the thorax, and a deep longitudinal groove on each side of the protuberant sternum and costal cartilages. A deep transverse furrow ("Harrison's sulcus") may occur at the lower end of the sternum, or there may be a funnel-shaped depression in the ensiform region. Spinal deformity is common—usually kyphosis, more rarely scoliosis or lordosis. Deformities of the clavicle, pelvis and limbs (especially the lower) may also occur, and the epiphyses, especially of the wrists and ankles, are enlarged. The skull is also especially affected, with arrested growth of the facial region but enlargement of the cranium (Figs. 43 and 52). Regnault ('99) claimed that the enlargement of the rachitic cranium is apparent, rather than real. The forehead is square and projects forward, with frontal and parietal eminences thickened, vertex and occipital region flattened. Thin spots ("craniotabes" of Elsässer) may occur, perhaps due partly to pressure atrophy. The cranial sutures are usually open and the closure of the fontanelles delayed. The changes in the individual bones were described fully by Seibold (1827), Beylard ('52), Comby ('01), Jenner ('95), and more recently with excellent illustrations (including X-ray) and review of the literature by Wohlaer ('11). Kauffman ('22) and Kauffman, Creekmur and Schultz ('23) claim that the changes in the temporal bones in otosclerosis may represent a form of late or adult rickets.

These gross changes, which are chiefly the mechanical result of the softened skeleton, have recently been described for human rickets with further details by Cheadle and Poynton ('07), Lesage ('11), Peckham ('20), Engel ('20), Maass ('21), Schmidt ('21), Brusa ('21), Park and Howland ('21), Marfan ('22) and

Pfaundler ('22). Some of these changes are shown in Figs. 43 and 52. Similar lesions have been described by numerous investigators in various animals, especially puppies and rats, during experimental rickets.

Although it is often stated that the growth of the skeleton is retarded during rickets, but few data are available upon the fresh weight of the skeleton to support this view. Trousseau and Lasègue ('50) noted a dry weight of only 1 kilogram in the skeleton of a rachitic dwarf of 8 years, the normal weight being

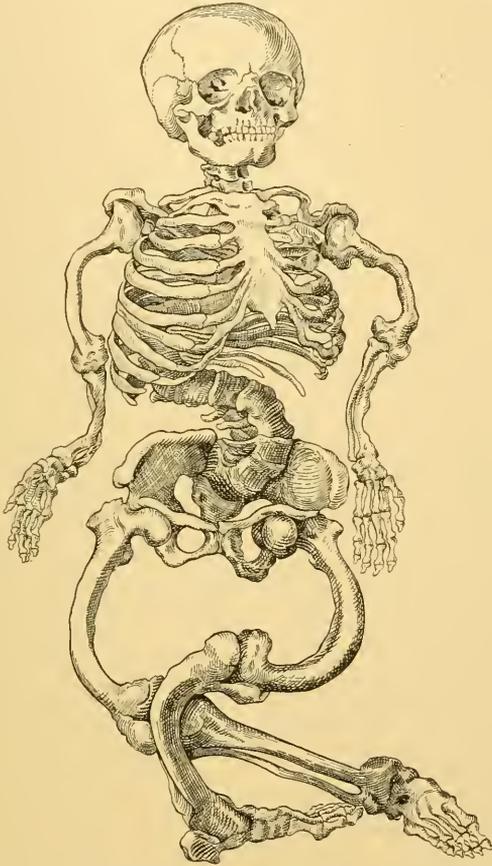


FIG. 52.—The skeleton of a female dwarf, aged 42 years, 4 feet and 2 inches in height; showing extreme deformities as a result of rickets during early life. The lateral curvature of the humeri is probably due to the use of crutches. (Seibold, 1827.)

7 or 8 kilograms. Friedleben ('60) confirmed Virchow's ('54) finding of continued growth (especially subperiosteal) of bone during human rickets and concluded: "Von Bedeutung ist es, dass der Gesamtknochen beträchtlich massenhafter und dicker erscheint, als der normale, was einestheils von der lockeren porösen Beschaffenheit der frischem Auflagerungsschichten, andernteils von einer beträchtlichen Zunahme des Wassergehalts herrührt." Especially in late rickets, however, the skeleton may share in the general retardation in growth of the body as a whole, as stated in Chapter V. Wohlauer ('11) stated that in

comparison with the norms of Wilms and Sick, the centers of ossification in rachitic children usually appear normal in time, but are delayed in severe cases. Jenner ('95) emphasized the arrested growth of the bones in rickets. Lehnerdt ('10) concluded that in infantile rickets the skeletal mass is usually normal or even increased. Voit ('80) and Dibbelt ('09) found the weight of the fresh bones and cartilages normal or above in puppies with rickets produced by calcium-poor diet (extracted meat plus fat). Jackson and Carleton ('23) likewise found nearly normal weights, in proportion to body weight, for both the ligamentous and cartilaginous skeleton in rats with experimental rickets (Table 11). In nearly all cases, however, there was found a marked, but variable, decrease in the *dry* weight of the skeleton—a conclusion supported by a large number of observations in the literature on rickets in man and other mammals. Owing to this loss (chiefly of calcium phosphate) the dry content of the bones during rickets may decrease from about 65 per cent down to 30 per cent or less, depending upon the stage and severity of the lesion.

As previously mentioned, the experiments on diets deficient in calcium and in phosphorus have been made chiefly to determine the cause of rickets. As early as 1839, Guérin noted that the bones in puppies on a meat diet become softened and deformed, and he made the diagnosis of rickets produced by lack of calcium phosphate. Roloff ('66, '75) confirmed these results, finding softening of the long bones, scapulae, pelvic bones, vertebrae, etc. The epiphyseal joints become enlarged, forming a "rickety rosary" along the costochondral junctions. The bones become lighter (due to osteoporosis) and the thorax elongated dorsoventrally. The condition develops most readily in young, rapidly growing puppies. Although no histological examination was made, it was diagnosed as rickets, due to lack of calcium. The addition of calcium salts to the diet prevented the disease, but non-calcium salts (including phosphates) did not. Friedleben ('60) recognized clearly that the osteoporosis produced in pigeons by mineral-poor diets differs fundamentally from true rickets.

The first production of experimental rickets in which the histological structure was carefully studied was apparently that of Wegner ('72). He found that the addition of small doses of phosphorus to the ordinary diet stimulates osteogenesis in young animals (calf, rabbit, chicken). A salt-extracted grain diet in young chickens makes the bones soft, thin and brittle (confirming Chossat '42). The addition of phosphorus to this diet was found to produce rickets.

"Aeussert interessant ist es, dass unter dem gleichzeitigen Einfluss der Phosphorfütterung und der Entziehung anorganischer Substanzen, namentlich des Kalkes, der Wachstumsmodus der Knochen eine Aenderung erfährt, die auf das vollkommenste dem entspricht, was wir beim Menschen als Rachitis zu bezeichnen gewöhnt sind (Taf. 1, Fig. 34). Man sieht bei einem Vergleich mit dem daneben stehenden normalen Knochen an dem Beispiel gewählten oberen Ende der Tibia eines jungen Huhnes die ausserordentliche hohe, von zahlreichen weiten Markräumen durchzogene gallertig, durchscheinende gewucherte Knorpelmasse; in sie greift sehr unregelmässig in wellig-hügeligen Linien ein die Zone der Kalkinfiltration, die übrigens an sich sehr unvollkommen ist. An der Stelle, wo sich ausgebildete, weitmaschige spongiöse

Knochensubstanz bilden sollte, existirt ein ganz ungewöhnlich dichtes osteoides Gewebe; die mikroskopische Untersuchung weist dann noch des Genaueren nach, wie alle diese Vorgänge auf das bunteste durch einander gehen, kurz wir haben die Rachitis, wie sie im Buche steht."

Wegner stated that his work confirms the theory that rickets is due to two factors: (1) insufficient supply of inorganic salts (due to defective intake or excessive excretion); and (2) a constitutional stimulus upon the osteogenic tissue.

Lehmann ('78) and E. Voit ('77, '80) produced experimental rickets in puppies. Voit stated: "Ich will es unternehmen, jeden jungen Hund grosser Rasse in 3-4 Wochen durch Fütterung mit kalkarmen Muskelfleisch und reinem Fett ohne Abmagerung hochgradig rachitisch zu machen." Voit ('80) based his diagnosis upon the characteristic softening and deformity of the various bones, with broadening of the epiphyseal cartilage and marked histological irregularities in the process of ossification.

While it was early recognized that rickets involves an abnormal widening of the epiphyseal cartilage and a disturbance of the normal process of enchondral ossification (Rufz '34; Guerin '39; Beylard '52; Friedleben '60) the exact histology of this disorder was somewhat neglected until comparatively recent times. Meyer ('49) described the structure of rachitic bone as similar to that decalcified by acids. A detailed and accurate histological description was given by Broca ('52), whose excellent work has usually been overlooked by later investigators. He recognized that the "spongoid tissue" described by Guerin in human rickets is essentially an uncalcified osteoid layer, a transition between the epiphyseal cartilage and the calcified diaphyseal bone, normally present in small amount, but accumulating in large quantity when the ossification process is interrupted in rickets.

The existence of osteoid substance (uncalcified bone) in rickets was also recognized by Friedleben ('60), Wegner ('72), Kassowitz ('82-'85) and others, but its significance was not fully appreciated until later. Pommer ('85) emphasized the formation of excessive osteoid substance as a cardinal point in true rickets. This distinguishes it from **osteoporosis**, which is due merely to excessive absorption of already formed bone. **Halisteresis**, or decalcification of formed bone, is less frequent, but may occur (as was noted by Broca), especially in adults. The gross appearance and consistency of bone may be very similar in rickets and osteoporosis, and the two conditions may be coincident. **Osteomalacia** is now generally considered as a form of late rickets arising after growth has ceased, and hence not involving the phenomena in the zone of enchondral ossification (Pommer '85; Wild '01; Schmorl '05; Looser '05, '08, '09, '20; Schmidt '09; Ribbert '09; Stoeltzner '09; v. Recklinghausen '10; Boehme '19; Higier '22; Korenchevsky '22; Maxwell '23; *et al.*). This view was held long ago by Beylard ('52) and others.

It is impracticable to mention here the large number of papers (chiefly German) dealing with the histology of rickets, which appeared in the pre-vitamin epoch, chiefly between 1885 and 1910. Detailed reviews of this literature will be found in the works of Rievel ('07), Schmorl ('09b), Lehnerdt ('10), and v. Recklinghausen ('10). The chemical phases of rickets are reviewed by

Schabad ('10). The essential structural features which were established for rickets may be summarized briefly as follows (Schmidt '21, p. 204):

“Die anatomische Grundlage dieser Veränderungen ist sehr kompliziert. Sie besteht erstens im Auftreten osteoider Substanz in einer das normale Mass in Dicken- und Flächenausdehnung weit überschreitender Menge, und oft in einer mit starker Hyperämie verbundenen, übermässigen knochenbildenden Tätigkeit des Periostes und Endostes, welche zu Verdickung und Verdichtung der Knochen führt; zweitens in einer Störung der enchondralen Ossifikation, nämlich in übermässiger Proliferation, mangelnder Verkalkung und unregelmässiger Vaskularisierung und Ossifikation des Knorpels.”

Associated with the endosteal proliferation, especially in the long bones, the marrow may be extensively replaced by a fibrous connective tissue. Primary lesions in the marrow have been described by Marfan and Baudouin ('09), Marfan, Baudouin and Feuillé ('09), confirmed by Hutinel and Tixier ('09). There is apparently an early stage of proliferation in the various types of marrow cells, followed later by their regression and replacement by fibrous marrow. Networks of osteoid trabeculae may be formed in this fibrous marrow, or may arise by decalcification of pre-existing bone (halisteresis). The decalcified, osteoid structures may later be resorbed through the activity of the osteoclasts (Morpurgo '09), giving rise to a variable degree of osteoporosis.

In the region of enchondral ossification, the proliferative zone of the epiphyseal cartilage becomes abnormally wide. According to Pommer ('85), Schmorl ('06) and Heubner ('06), this is due not to increased proliferation of the cartilage, but to lack of its removal as occurs in the normally succeeding stages in the ossification process. Provisional calcification fails to occur in the adjacent zone. Schmorl ('09) considers this defective calcification of the cartilage primarily responsible for the further irregularities in the process of ossification. The vascularization of the cartilage is excessive, with vessels coming not only from the marrow, but also (largely) from the adjacent perichondrium or periosteum. Kassowitz ('78, '82-'85, '12) has long maintained that this hyperemia is inflammatory in character and of primary importance in rachitis. Owing to the irregular invasion of the cartilage, the normally even plane of ossification is replaced by a wide irregular “spongoid zone” or “metaphysis,” composed of cartilaginous masses of variable size, intermingled with osteoid substance (uncalcified bone) and vascular marrow. This occasions the widening of the zone between the epiphysis and diaphysis, as seen by the Roentgen-rays or in gross preparations.

According to Strelzoff ('73), Kassowitz ('82-'85), Schmidt ('09), and Wohlaer ('11), the osteoid substance (at least in part) is formed by direct metaplasia of the persistent cartilage. Although this metaplasia theory is doubted by Schmorl ('06, '09), it has recently been supported by McCollum and his co-workers. Ribbert ('13) described necrosis of the cartilage cells, which he considered evidence of a toxic agent in rickets. Simultaneous with the formation of the osteoid metaphysis, osteoid substance is also deposited under the periosteum of the bone. The osteoblasts become surrounded by matrix, as normally, but the latter fails to become calcified.

The various stages in the **process of healing** in the rachitic skeleton have been described by various authors, including Schmorl ('06, '09), Marfan and Baudouin ('09), Wohlaer ('11) and Schmidt ('21) for man; by Mellanby ('21) in puppies; and by Pappenheimer ('22) for rats. Calcification appears in the metaphysis near the zone of proliferative cartilage, and the normal process of enchondral ossification ensues. Several layers may appear, indicating alternating stages of recrudescence and healing. The abnormal osteoid structures become calcified, but later may be largely resorbed. A correction of minor deformities is possible. Extensive deformities cannot be corrected, however, and permanent dwarfing frequently results. Entire destruction of the epiphyseal cartilage (a rare occurrence) necessarily precludes the possibility of further growth in length of the long bones.

Whether the histological features above mentioned as characteristic for human rickets are to be found in the somewhat similar disorders experimentally produced in the lower animals is a question which has been much disputed. Mouriquand ('23) claims that in human rickets the hyperemia and proliferation of the bone marrow entail a decalcifying chondromyelitis which is not apparent in experimental rickets in rats. There is no doubt, as Heubner ('06) and others have shown, that many of the typical changes in the zone of enchondral ossification in rickets can be produced in puppies by feeding calcium-poor or phosphorus-poor food. Hypertrophy of the proliferating cartilage, vascular invasion of the cartilage and absence of calcification in this zone can be thus produced. As to the crucial point, the production of osteoid tissue, but few investigators have been successful until quite recently. Absence of excess osteoid tissue, with increased absorption producing merely "pseudorachitic osteoporosis" were found in experiments with calcium-poor diets (chiefly in puppies fed horse-meat plus lard) by Korssakow ('92), Reimers and Boye ('05), Miwa and Stoeltzner ('98), Stoeltzner ('99, '08), Aron and Sebauer ('08), Dibbelt ('09), Götting ('09), and Schabad ('10).

Stilling and von Mehring ('89) found that the puppies from a bitch fed calcium-poor diet (horseflesh plus fat) showed no bone changes, but the mother after continuing on the diet 126 days showed softening of the vertebral column and pelvic skeleton. Histological examination of the affected bones revealed active resorption, with bony trabeculae, covered by layers of osteoid, as in human puerperal osteomalacia.

Dibbelt ('10) fed a calcium-poor diet (rice and horseflesh, plus sodium and potassium chloride) to an adult dog during pregnancy. A resected rib showed considerable decalcification (halisteresis) of bone, with many osteoclasts, Howship's lacunae, etc., indicating an active resorption comparable to that in puerperal osteomalacia. Her 6 puppies appeared normal at birth; but 2 of the puppies continued nursing the calcium-poor milk of the mother (still on the calcium-poor diet). Although they increased normally in body weight, they developed marked skeletal lesions, so that they were scarcely able to crawl within a few weeks. One of the puppies was then fed horseflesh plus calcium phosphate, and improved rapidly. The other was fed horseflesh only and became worse. A resected rib (on the third day of the sixth week) showed

retarded ossification and deficient bony tissue, but no osteoid substance. The proliferative zone of the cartilage was greatly increased in breadth. The primary marrow spaces were filled with vascular fibrous tissue and few marrow cells. Osteoclasts were present, but not abnormal in abundance. Korenchevsky and Carr ('23) likewise found young rats much more susceptible to rickets when the mother was fed during pregnancy or lactation on diets deficient in calcium or vitamin A.

Stoeltzner and Salge ('01) confirmed Wegner's ('72) experiments resulting in the production of osteoid tissue of puppies by adding phosphorus to the calcium-poor diet, but they still designated this as "pseudorachitische Osteoporese" rather than true rickets.

Stoeltzner ('08), Lehnerdt ('09, '10) and Shipley, Park, McCollum, Simmonds and Kinney ('22) found that strontium cannot successfully replace calcium in preventing rachitoid lesions in puppies fed a calcium-poor diet. It

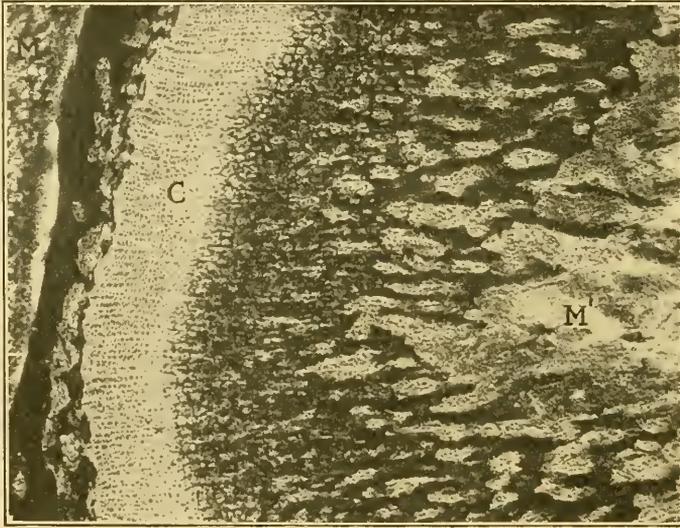


FIG. 53.—From a photograph of a portion of a section of the upper extremity of the tibia in a normal young albino rat about 1 month old, body weight 36 g. C, epiphyseal cartilage; to the left of which is a vertical black band, representing calcified bone of the epiphysis. To the left of this, a small part of the epiphyseal marrow (M) is visible. To the right of the epiphyseal cartilage is a wide zone of enchondral ossification, with a network of ossified trabeculae, finer next to the cartilage, and becoming progressively coarser toward the marrow cavity (M') of the diaphysis. Prepared by von Kossa's silver method (calcified tissue black). X50. (Preparation by O. J. Morehead.)

appears that strontium, like calcium and phosphorus, may stimulate the formation of osteoid substance, which (in the absence or malassimilation of the salts necessary for calcification) may persist in excessive amounts. The identity of the lesions with those of human rickets is questionable, however. In genuine rickets, the osteoid tissue appears incapable of calcification, even in the presence of calcium salts, whereas in "pseudorickets" the osteoid tissue (if present) becomes calcified as soon as the necessary salts are supplied.

Lipschütz ('10, '11, '11a) observed that puppies on a phosphorus-poor diet develop bone lesions resembling those of scurvy, in connection with which they will be discussed later.

As noted in the discussion of the etiology of rickets in Chapter V, the more recent work on experimental rickets has recognized a vitamin factor. Elliot, Crichton, and Orr ('22), however, produced rickets (with excess osteoid) in pigs on diets of oatmeal and bran, in spite of abundance of vitamins A, B and C, but preventable by the addition of calcium salts. Mellanby ('19, '21) has especially emphasized the importance of vitamin A, or an allied antirachitic factor, though recognizing also other factors. By various deficient diets, he has produced in puppies skeletal lesions which appear in all respects essentially identical with those of human rickets. Similar success has been obtained with experimental rickets in rats by Korenchevsky ('21, '22, '22a), Sherman and Pappen-

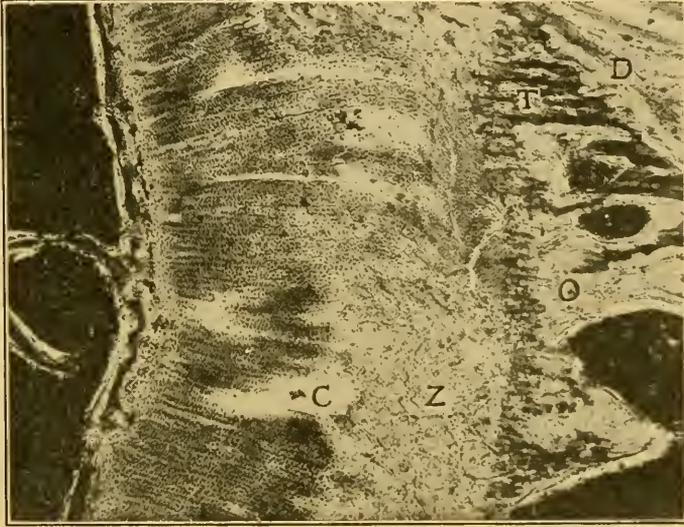


FIG. 54.—From a photograph of a portion of a section of the upper extremity of the tibia. Albino rat (McCl 14.2) had been placed on a phosphorus-poor diet (white flour, 93 per cent; spinach, 1 per cent; NaCl, 2 per cent; lime, 2 per cent; yeast 2 per cent) for 1 month, beginning at 3 weeks of age, resulting in severe rickets. Final body weight, 31 grams. Compare with Fig. 53, and note the great hypertrophy of the epiphyseal cartilage (C), to the left of which is a thin black band, representing the remnant of calcified bone layer of the epiphysis, surrounded by a light band of uncalcified osteoid tissue. (The epiphyseal marrow cavity appears black.) To the right of the epiphyseal cartilage, the zone of enchondral ossification is replaced by a wide irregular zone (Z), representing the "metaphysis," composed of osteoid tissue, invading marrow, and remnants of cartilage. The calcified bony trabeculae (shown in Fig. 53) have nearly disappeared, but some remnants (T) are still visible. Around and between the slender calcified trabeculae are relatively wide bands of uncalcified, osteoid tissue (O). The dark area below and to the right represents marrow of the diaphysis. Von Kossa's silver method (calcified tissue black).  $\times 50$ . (Preparation by O. J. Morehead.)

heimer ('21), Pappenheimer, McCann, Tucker and Hess ('21), McCollum, Simmonds, Shipley, and Park ('21, '21a, '22), McCollum, Simmonds, Parsons, Shipley and Park ('21), Shipley, Park, McCollum and Simmonds ('21, '21a, '22), McCollum, Simmonds, Kinney, Shipley and Park ('22), Park, Shipley, McCollum and Simmonds ('22), McCollum ('22), Shipley ('22), Hess ('22), Jobling, Pappenheimer and Hess, ('22), and Pappenheimer, McCann and Tucker ('22).

The characteristic histological changes produced in the bones of young albino rats by experimental rickets are shown in Figs. 53 and 54.

As previously noted, the work of McCollum and his co-workers strongly indicates that at least two factors are concerned in the production of rickets: (1) a "fourth vitamin" or organic factor which is closely associated with vitamin A and promotes calcium deposition; and (2) a dietary deficiency of

either calcium or phosphorus. Thus there is apparently a low-calcium rickets and a low-phosphorus rickets, each of which may produce the essential lesions, including the osteoid substance. There are minor differences in the histological details, which vary much according to the stage and severity of the disease, but the low-phosphorus rickets appears morphologically to resemble more closely the ordinary human rickets. As noted above, however, most investigators have obtained osteoporosis, rather than rickets, on low calcium diets.

**Vitamin Deficiency.**—The probability of a “fourth vitamin” factor in rickets was mentioned above. Skeletal changes in other vitamin deficiencies will now be considered. In young rats on a vitamin-free diet (polished rice with salt), Ishido ('23) found in the bone marrow of the femur and tibia numerous fat cells, which did not occur in rats exposed to ultraviolet light, or in full-fed controls.

**Vitamin A.**—Herter ('97) noted mucoid degeneration of the bone marrow, and also bloody synovial fluid in the knee-joints, in pigs during fat starvation, involving deficiency in vitamin A. Tozer ('18, '20, '21) found that the changes in the costochondral junctions of guinea pigs on a diet deficient in vitamin A, but otherwise adequate, closely resemble those of mild experimental scurvy in these animals. Mackay ('21) and Tozer ('21a) obtained similar results in kittens on a diet deficient in vitamin A, but otherwise adequate. Hess, McCann and Pappénheimer ('21) likewise obtained no rickets in young rats on diets deficient merely in vitamin A, although histological examination showed retarded osteogenesis. Emmett and Peacock ('22) noted enlarged knee-joints and beading of the ribs in chicks on a diet deficient in vitamin A, but give no histological data. Findlay and Mackenzie ('22) found that diets deficient in vitamin A cause gelatinous degeneration of the marrow in the femur of the rat. Shipley, Park, McCollum and Simmonds ('21) observed that diets deficient in vitamin A, but otherwise complete, produce merely osteoporosis in the bones of rats.

**Vitamin B.**—But few changes have been observed in the skeleton during beriberi or polyneuritis, due to deficiency in vitamin B. Shipley, McCollum and Simmonds ('21) found that under these conditions rats show no gross deformity of the skeleton, but histologically present lesions essentially identical with those seen in guinea pigs with scurvy. These changes include osteoporosis; thin epiphyseal cartilage with strongly calcified zone of provisional calcification; no zone of osteoid; marrow congested and hemorrhagic, sometimes showing reticulum only. Findlay and Mackenzie ('22) likewise found that diets deficient in vitamin B produce hemorrhagic congestion in the bone marrow of the femur in the rat. Findlay ('21) noted atrophy of the skeleton in avian beriberi.

**Vitamin C. Scorbutus.**—Although scurvy has doubtless occurred in the human race at various intervals since ancient times, it was not clearly recognized and differentiated as a distinct deficiency disease until about the 17th century. Fragility of the bones in scurvy was noted by Gideon Harvey (1675). The classical treatise by Lind (1772) mentioned briefly the gross skeletal lesions, including the occasional separation of the epiphyses in young patients. Since that time, a voluminous literature on scurvy has accumulated, which has recently been well summarized by Hess ('20) and Höjer ('24).

The skeletal changes in human adult scurvy have been described recently by Aschoff and Koch ('19), Bierich ('19) and Comrie ('20). In children, scurvy was long confused with rickets. Infantile scurvy was first clearly demonstrated by Barlow ('83, '94) and is therefore commonly known as Barlow's disease. At that time but little was known of the essential histological changes in the skeleton during infantile scurvy, the details of which have since been thoroughly investigated by numerous workers. Naegeli ('97) was the first to give a detailed description of these changes, which have been confirmed and extended by Schmorl ('99, '01, '07), Schödel and Nauwerk ('00), Jacobsthal ('00), Looser ('05), Erdheim ('18), and others. Fraenkel ('04, '06, '08,) has studied especially the skeletal changes as shown by the Röntgen-rays, including the so-called "white line." The pathology and pathogenesis of scurvy have also been

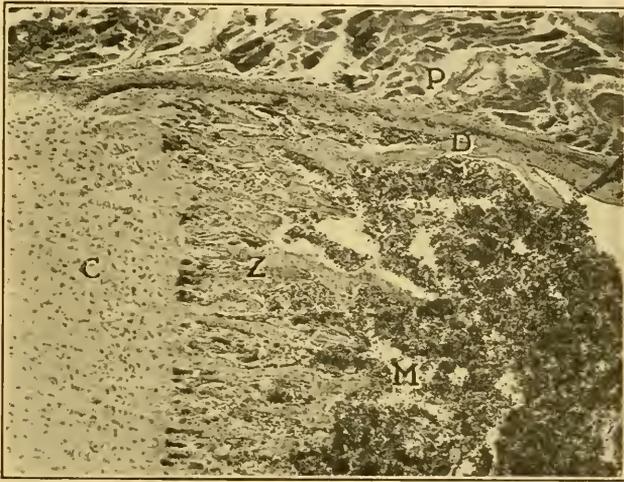


FIG. 55.—From a photograph of a portion of a section through the costochondral joint of a normal guinea pig; body weight 236 g. C, costal cartilage; Z, zone of enchondral ossification (bony and calcified cartilaginous trabeculae, and invading marrow); M, costal marrow; D, bone of costal diaphysis; P, costal periosteum and adjacent intercostal muscle. Zenker fixation; hematoxylin-eosin stain.  $\times 40$ . (Preparation by Everett Rowles.)

reviewed by Vincent ('04), Lesage ('11), Schmidt ('21) and especially by Hess ('20). Höjer's ('24) recent monograph is excellent.

The gross skeletal lesions include osteoporosis, with fragility and thinning of the cortex in the shaft of the long bones, and frequent occurrence of fractures in severe cases. Enlargement of the costochondral joints occurs, and has frequently been mistaken for rickets (*cf.* Hess '20; Hess and Unger '20). The general hemorrhagic condition in scurvy is manifested in the skeleton by frequent subperiosteal and marrow hemorrhages. The bone marrow undergoes changes, becoming more fibrous or gelatinous in appearance, especially at the ends of the long bones. Hemorrhages and fractures with enlarged calluses are most frequent in pre-adult cases at the junction of the diaphysis with the epiphyseal cartilage.

The microscopic changes in the skeleton have been studied in detail, especially during infantile scurvy. Although there is much variation in different

bones, and in different individuals according to age and to the stage and intensity of the disorder, the structural changes in general involve a *fibroid and*

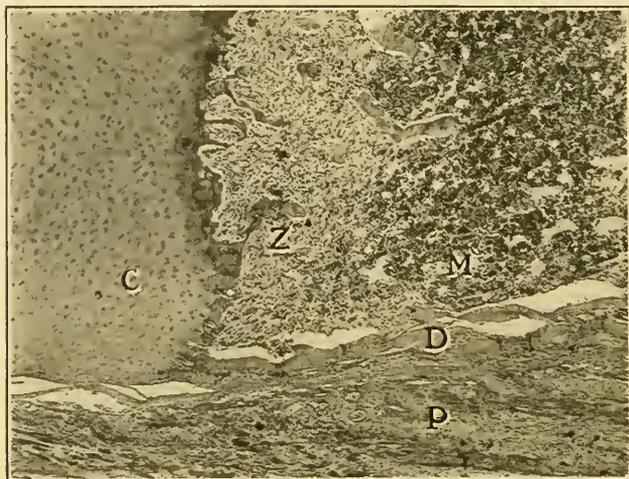


FIG. 56.—From a photograph of a portion of a section through the costochondral joint of a young guinea pig on a diet of oats and milk-powder for 10 days; body weight reduced from 273 g. to 212 g. Incipient scurvy. *C*, costal cartilage; *Z*, zone of enchondral ossification, largely replaced by fibroid marrow; *M*, more nearly normal costal marrow; *D*, bone of costal diaphysis; *P*, adjacent periosteum and (atrophic) muscle. Zenker fixation, hematoxylin-eosin stain.  $\times 40$ . (Preparation by Everett Rowles.)

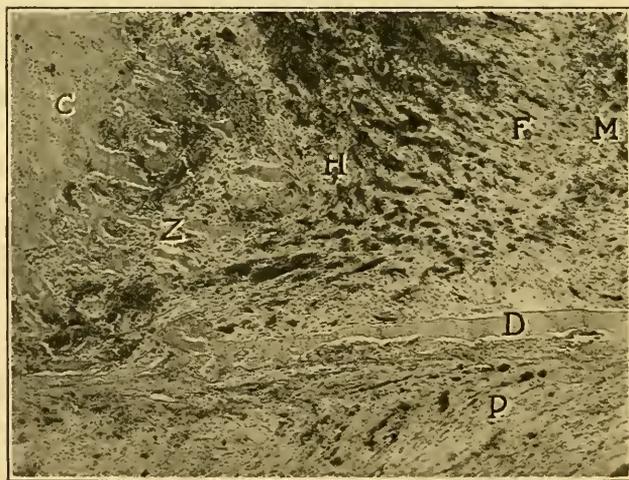


FIG. 57.—From a photograph of a portion of the enlarged costochondral junction of a young guinea pig; body weight reduced from 254 g. to 169 g. in 21 days on a diet of oats and milk-powder, with death from scurvy. *C*, costal cartilage; *Z*, irregular zone of enchondral ossification; *H*, zone of fibroid marrow with distended blood vessels and hemorrhages; *F*, zone of non-hemorrhagic fibroid marrow; *M*, more nearly normal marrow; *D*, bone of costal diaphysis; *P*, adjacent periosteum, hemorrhagic, with markedly atrophic muscle.  $\times 40$ . (Preparation by Everett Rowles.)

*hemorrhagic degeneration of the marrow, with associated inhibition of osteogenesis and atrophy of the preexisting bone.*

In a typical section through an area of enchondral ossification (*e.g.*, a costochondral joint), as shown by Figs. 55-57, the structure of the cartilage appears abnormal. The zone of proliferation is usually increased in thickness, and the normally columnar arrangement of the cells becomes very irregular. The provisional calcification of the cartilage matrix occurs. But since this zone is not (as normally) invaded and replaced by the osteogenic tissue from the marrow, the calcified trabeculae do not become covered with bone, but form a widened and weak layer which easily fractures. The consequent hemorrhages, with partial organization and resorption from the adjacent marrow and periosteum, result in the very irregular and variable structure of this swollen area ("Trümmerfeld" of Fraenkel).

Adjacent to this "Trümmerfeld," the bone marrow presents a fibroreticular structure with a gelatinous ground substance and few marrow cells ("Gerüstmark" of Schödel and Nauwerk). Scattered through the marrow of this region multiple hemorrhages frequently occur. The marrow in the remainder of the shaft is more nearly normal. The interspersed bony trabeculae appear variably thinned, due to failure of bony apposition, combined with continued resorption. Schmorl ('07) opposed Looser's theory that the rachitic bone changes are secondary to the marrow hemorrhages.

Osteogenesis is also retarded or entirely inhibited in the periosteum, with primary atrophy of the osteoblasts. Resorption continues, however, although the osteoclasts are not abnormal in number. The entire bone, both cortex and spongiosa, therefore becomes progressively osteoporotic. The bony tissue is normally calcified, but greatly reduced in amount. Bahrtdt and Edelstein ('13) and others have found that the fat content of the bones in infantile scurvy may be nearly unchanged, although the calcium and phosphorus content is greatly reduced.

The histological changes in the skeleton of scorbutic adults appear very similar to those in children, excepting the intensive changes in the cartilage at the junction with the marrow. It may be noted that in children a coincidence of rickets and scurvy is not infrequent, as in the case described by Ingier ('13). Such complications, as also the changes during recovery from scurvy, may produce very puzzling structural conditions.

**Experimental Scurvy.**—Bartenstein ('05), Frölich ('12), and others found that young guinea pigs fed on raw or sterilized milk diet develop skeletal lesions (including microscopic) which have a remarkable similarity to those of infantile scurvy, excepting the absence of hemorrhagic tendency. Lipschütz ('10) obtained similar results in puppies fed a phosphorus-poor diet of rice and egg albumin, supplemented by salt mixtures. The addition of casein, lecithin, nucleins and phosphates gave normal structure in controls. Schmorl ('13) obtained in puppies on phosphorus-poor diet skeletal lesions even more closely resembling human scurvy, with occasional small hemorrhages in the subchondral zone. The more typical hemorrhagic condition was absent, however, and Schmorl concluded that the disorder is not identical with human scurvy.

A new epoch in experimental scurvy began with the work of Holst and Frölich ('07, '12). They found that by means of various diets (cereals or bread)

it is easy to produce in young guinea pigs a disorder which in every essential respect corresponds to that found in human infantile scurvy. They worked out the gross and microscopic changes (including the skeletal) with great care. They also compared the lesions with those found during ordinary starvation (water only), in which the mucoid degeneration of the marrow is similar, but the other changes (hemorrhage, etc.) different. For details, see Höjer ('24).

The results of Holst and Frölich in guinea pig scurvy have been confirmed and extended by Jackson and Moore ('16), Chick, Hume and Skelton ('18), Tozer ('18), and others. Howe ('21) obtained softened skull bones and enlarged joints in guinea pigs on vitamin-poor diets, but the relation to scurvy is uncertain.

Ingier ('13, '15) made an extensive study of the effect of a scorbutic diet upon the fetus in pregnant guinea pigs. There are marked individual variations, but the skeletal changes appear greatest in the earlier fetal stages. The earlier fetuses usually die showing marked evidence of inhibited growth. Fetuses from later periods of pregnancy are born alive with comparatively slight skeletal changes. The pregnant mothers also suffer severely, especially in the earlier stages of gestation.

Experimental scurvy, in all essential respects apparently identical with human scurvy, was also produced by K. Hart ('12) in young monkeys fed on condensed milk. The entire skeleton is affected in typical fashion, although there are marked individual variations. These results on the monkey were fully confirmed by C. Hart and Lessing ('13) and by Talbot, Todd and Peterson ('13). In both cases, they confirmed Fraenkel as to the constancy of the "white line," which appears on the X-ray negative in the area of increased density at the junction of the epiphysis and diaphysis. (Hess doubts the diagnostic value of this sign.) More recently, Harden and Zilva ('19a) have also produced typical scurvy in monkeys, and noted the histological changes in the costochondral joints.

In contrast with the striking success in producing experimental scurvy in the guinea pig and monkey, the results in other species of animals have been largely negative. Holst and Frölich failed with the rat, mouse and cat. McClendon, Cole, Engstrand and Middlekauff ('19) fed oats to a rabbit for 9 months, resulting merely in fragility of the bones. Findlay ('21b) likewise obtained merely loss in weight, excepting the offspring (above mentioned). As noted by Hess ('20), other evidence indicates that birds, pigs and cattle likewise show little or no susceptibility to scurvy. These are striking examples of the marked nutritional differences between species.

**Aqueous Inanition.**—Schuchardt ('47) found an apparent loss of 7 per cent in the bones of pigeons with loss of 44 per cent in body weight on a dry barley diet. Falck and Scheffer ('54) noted an apparent loss of 5.3 per cent in the ligamentous skeleton of a dog fed dry biscuit 4 weeks with loss of 20 per cent in body weight. In adult albino rats, Kudo ('21) observed in the acute thirst series (body loss 36.1 per cent) an average loss of 4.3 per cent in the ligamentous skeleton and of 11.8 per cent in the cartilaginous skeleton. In the chronic thirst series (body loss 52.4 per cent) the relations were reversed, the ligamentous skeleton losing 10.3 per cent and the cartilaginous 5.0 per cent (Table 9). In

experiments with young rats held at nearly constant body weight by dry diet for periods of 1-13 weeks, Kudo ('21a) found in general a progressive increase in skeletal weight, reaching a maximum average of about 40 per cent increase in the ligamentous skeleton, 58 per cent in the cartilaginous skeleton, and 32 per cent in the humerus and femur alone (Table 10).

The only data for structural changes in the skeleton during aqueous inanition are apparently those by Pernice and Scagliosi ('95a). In a dog which died after 11 days on dry bread, with body loss of 24 per cent, the bones were noted as showing a moderate stasis hyperemia. Three young chicks were fed dry maize and lost 34-41 per cent in body weight in 8-10 days. At autopsy, no change was noted in the periosteum and osseous tissue, but the marrow appeared dark red in color. Microscopically cells of the cartilage in the lingual region appeared markedly atrophic, with zigzag borders and poorly stained nuclei. In some cases, the entire cell had degenerated into an amorphous granular mass.

So far as known, the skeletal changes, both in weight and structure, during aqueous inanition are thus similar to those found during total inanition or on water alone (Table 4). This is perhaps due, at least in part, to the invariable lessening of the food intake on a dry diet, which would naturally produce under-nourishment.

## CHAPTER VIII

### EFFECTS ON THE TEETH

Like the skeleton, the teeth appear very resistant to inanition in general, though especially susceptible to rickets and scurvy. After a brief summary, the effects of inanition upon the teeth will be considered under (A) total inanition, or on water only; and (B) partial inanition.

#### SUMMARY OF EFFECTS ON THE TEETH

In **total inanition**, or on water alone, the teeth in adults show no appreciable change in weight or structure, but there are slight changes in chemical composition, especially in chronic (incomplete) inanition. In the young, such inanition may delay the process of dentition, but persistent growth and development of the teeth (as of the skeleton) occur in young rats held at constant body weight by underfeeding.

The effects of **partial inanition** have been studied chiefly in rickets and scurvy. In both human and animal *rickets* there is delayed and abnormal dentition. Both enamel and dentine may be defective and imperfectly calcified. Caries and lesions of the peridental membrane are frequent; but the dental defects are not closely correlated with the skeletal lesions, and are exceedingly variable in both human and animal rickets.

In *scurvy*, the gums are markedly congested and swollen in about 80 per cent of the adult human cases, but apparently in a much smaller proportion of guinea pigs. The alveolar bone and peridental membrane undergo necrosis, with consequent loosening of the teeth, and ulcerations or pyorrhea may occur (more rarely in animals). Congestion and hemorrhage appear very early in the dental pulp (guinea pig), with consequent pulpar degeneration and fibrosis, and possibly osteodentine formation. Scorbutic changes may affect the teeth before eruption, even in the fetus. Recovery of normal structure in the teeth is possible upon antiscorbutic diet, unless extreme degeneration has occurred.

#### (A) EFFECTS OF TOTAL INANITION OR ON WATER ALONE

Comparatively few observations have been made upon the teeth during simple inanition. Weiske ('97) noted that in 4 adult rabbits 7-11 days on distilled water alone, with loss of 35-41 per cent in body weight, there is a slight decrease in the organic content of the teeth, with corresponding relative increase in the inorganic content. Trowbridge, Moulton and Haigh ('18), in connection with an elaborate study of the changes in seven yearling steers subjected to various planes of prolonged underfeeding, found an apparent increase in the weight of the teeth, even with stationary or decreasing body weight. The

chemical composition of the teeth is also changed, with an increase in water content and a decrease in nitrogen and ash.

Talbot ('09) and others have pointed out the importance of malnutrition in connection with defective teeth of children. Sill ('09), for example, in 1,000 school children 6-12 years of age in the Jewish quarters of East Side, New York City, found 40 per cent malnourished, more or less anemic and under weight; while 86 per cent had dental caries. He believes that dental caries is a causative factor in malnutrition. It might, however, be an effect, rather than a cause; or possibly a "vicious circle," malnutrition producing defective teeth, which in turn tend to prevent an adequate food-intake. Emerson ('22), however, found no increase in caries among malnourished children.

Tschirwinsky ('10) observed that in underfed lambs there is a delay in the replacement of the temporary with the permanent incisors. Jackson ('15a) found that in albino rats held at constant body weight by underfeeding from 3-10 weeks of age, there is a progressive development of the teeth, the formation and eruption of the third molars proceeding in spite of the stationary body weight. This was confirmed by Stewart ('18). Similarly Boas ('23) finds that among poor children the eruption of the permanent teeth is not retarded, as is the general body development. It therefore appears that the teeth share with the skeleton the persistent tendency to growth during incomplete total inanition (general underfeeding).

Bean ('14) and others have suggested the relative development of the teeth (appearance and replacement of the deciduous teeth) as a method of determining the "physiological age" of children. This would appear to be a more convenient index than the height or skeletal epiphyses, but unfortunately there has not been as yet a sufficient investigation of the correlation of dentition with skeletal and other changes during retardation of growth in malnourished children. This is necessary before it can be determined how reliable is the stage of dentition as an index of "physiological" (or better "anatomical") age, in comparison with "chronological" age.

#### (B) EFFECTS OF PARTIAL INANITION

King ('18) incidentally noted the frequent occurrence of defective teeth in rats suffering from malnutrition on diets which apparently contained relatively too much starch and too little protein.

**Mineral Deficiency.**—Aside from observations in connection with rickets, not much is known as to the effects of dietary mineral deficiencies upon the structure of the teeth. Miller ('87) found a very slight apparent decrease in calcium content in the teeth of adult dogs after 13 weeks on a calcium-poor diet. The deficit is restored by refeeding on a diet rich in calcium. Leonard ('20) observed imperfect formation of enamel in many infants 6 months to 3 years of age. This was ascribed to malnutrition from diets lacking in essential salts and vitamins, but did not appear in the permanent teeth of the older children.

**Rachitis.**—Irregularity of the teeth in rickets was noted even by Whistler (1645) and Glisson (1650). An abnormal delay in the eruption of the teeth in

rachitic children has frequently been observed (Seibold '27; Woronichin '76; Jenner '95) and is one of the well-known clinical symptoms of rickets.

Comby ('01) described the rachitic changes observed by himself and others in the jaws and teeth. Eruption is retarded and pronounced deformities occur, though fortunately rarely. "Ces dents sont malades dans leur germe; elles sortent noirâtres, fendillées, insuffisamment revêtues d'émail; au lieu de se développer normalement, elles tombent en poussière, et les racines seules persistent au milieu des gencives tuméfiées, fongueuses et saignantes." The permanent teeth are usually good, though delayed in appearance.

The work of Veve ('02) was inaccessible.

In his comprehensive work on rickets, Wohlauer ('11) gave a detailed account of the changes in the jaws and teeth, which are frequent and important. The mandible becomes deformed, with the alveolar process slanting obliquely inward (Fleischmann). The maxilla is bent inward at the attachment of the zygomatic process, while the alveolar process is pressed outward. These deformities of the jaws, which are caused primarily by tension of the attached muscles upon the softened bones, naturally disturb the normal position of the teeth and give rise to various degrees of malocclusion.

The dentition is delayed, and the teeth appear at extended intervals and in abnormal sequence (Baginsky). Moreover the teeth show various abnormalities in form. They may or may not be attacked by caries, depending upon the time at which the rickets appears. If dentition occurs at the florid stage of rickets, the teeth are markedly affected; but not if the dentition is completed before the onset of rickets. The same principle applies to the permanent teeth, according to Wohlauer.

According to Burchard and Inglis ('08), Hopewell-Smith has described an imperfect development of enamel during rickets, the first formed enamel containing numerous spaces, probably filled with soft tissue. Wells ('19) found delayed dentition in 32 out of 42 consecutive cases. There are frequently no teeth erupted at the end of the first year; sometimes none up to 18 months. The developmental process may be arrested, and there is a striking tendency to early caries. The enamel may be completely destroyed even before the tooth is fully erupted.

According to Pfaundler ('22), in addition to the delay in dentition, the following peculiarities of the teeth may occur in rachitic children: "The individual teeth appear at unusually long intervals; erupt asymmetrically and in atypical order. Particularly in the upper jaw, they are frequently small, soft, easily broken and discolored by caries, to which they are peculiarly liable. They are often frightfully misshaped and foreshortened. There is occasionally an excessive formation of enamel. The temporary teeth show striped or circular erosions at neck and root. The permanent teeth, the germs of which are also affected, show these erosions at the crown."

Marfan ('22) and Ruden ('22) have recently likewise described delayed dentition, abnormal development of the teeth, and malformation of the jaws as a result of rickets in children. Park ('23a) holds that with proper diet during pregnancy and by the use of sunlight and cod liver oil during infancy "more

could be accomplished in regard to the eradication of caries of the teeth than in all other ways put together, and that rickets would be abolished from the earth."

In **experimental rickets** in puppies, Voit ('80) noted that the teeth are small and poorly developed. In spontaneous rickets in white rats, Weichselbaum and Erdheim ('09) found imperfect calcification of the dentine, especially of the youngest layer (adjacent to the odontoblasts), which was penetrated by vascular loops. The rickety teeth are very transparent to the X-rays. They cited similar observations by Fleischmann ('07) in human teeth during rickets.

M. Mellanby ('18, '20, '21) has described a general hypoplasia of the teeth in puppies with rickets caused by diets deficient especially in vitamin A. The following defects are noted: (1) delayed shedding of the deciduous teeth; (2) delayed eruption of the permanent teeth; (3) irregular position and overlapping, especially of the incisors; (4) enamel defective or partially absent; (5) general softening of the teeth, due to low calcium content. The dental defects appear independent of oral sepsis or other complications.

In experimental rickets of young rats, Shipley, Park, McCollum and Simmonds ('21) observed that the incisor teeth are frequently loose, fragile and sometimes fractured. The conditions were studied more in detail by McCollum, Simmonds, Kinney and Grieves ('22), who found the greatest percentage of oral defects in the rats fed diets deficient in protein, calcium and vitamin A. The next highest incidence occurred in rats on diets low in calcium; and a still lower percentage occurred on diets low in both calcium and vitamin A. No caries-like lesions, pulp exposure, osteodentine, or defects in the attaching tissue or maxilla occurred in the stock rats on complete diet. They conclude that severe oral disease may result from relatively defective diets, where the disturbance appears out of all proportion to the cause. The diet is thus of primary importance in determining the quality of the teeth and their vitality in resisting invasion by microorganisms.

A further report by Grieves ('22) places the rats studied in 3 groups. In group 1 (on low calcium diet causing a pseudorachitic condition with excess osteoid), 22 per cent of the rats show caries-like defects and 3.65 per cent of their molars are involved. In 41 per cent of these rats, attaching-tissue defects occur, involving also the molars. Diets affecting the bones do not always affect the tooth attachments, however.

In group 2 (diets low in calcium and vitamin A), 31 per cent of the rats show caries-like defects and 5.21 per cent of their molars are involved. Twenty per cent of these rats show attaching-tissue defects. But many definitely rachitic rats show little or no dental defects; rachitis and caries-like lesions are rarely coexistent.

In group 3 (diets high in calcium and butter fat), 17 per cent of the rats show caries-like defects and 1.71 per cent of their molars are involved. In 28 per cent of these rats, attaching-tissue defects occur, disturbing 33 per cent of their molar attachments.

The caries-like and attaching-tissue lesions are described by Grieves in detail. The variability of the lesions in the test rats resembles that found in human rickets, indicating differences in individual resistance. Endocrine and other

factors may be involved. "Until further facts are available, one can think only of the necessity for a proper Ca-P-organic factor balance in any diet as the most important in the formation and maintenance of normal bones and teeth and healthy attaching-tissues."

Marshall ('23) in puppies on diets "insufficient or improperly proportioned" in calcium and phosphorus found a marked delay in dentition and relative absence of dentine, with normal amount of enamel.

**Scorbutus.**—In *human adult scurvy*, the involvement of the gums and teeth usually forms one of the first and most conspicuous symptoms. The lesions have recently been described and illustrated in detail by Aschoff and Koch ('19). Comrie ('20) noted swollen and bleeding gums in 80 per cent and severe gingivitis or pyorrhea in about half of 600 cases. Bierich ('19) found the gingival swellings most pronounced in those with carious teeth. The lesions have recently been summarized by Hess ('20). The gums become congested and hemorrhagic. Later the teeth become loose and may fall out, and the alveolar bone undergoes necrosis. Pyorrhea may be present. The gums may become so swollen as to hide the teeth, forming foul, fungoid growths.

In *infantile scurvy* (Barlow's disease) the gingival lesions are similar but somewhat less pronounced if teeth are present; and are slight or absent before the eruption of teeth. Talbot ('19) emphasizes the susceptibility of the alveoli and periodontal membrane, rather than the teeth, to the changes produced by scurvy.

In **experimental scurvy** the dental and gingival lesions have been frequently studied. Holst and Frölich ('07, '12) in their pioneer work on experimental scurvy in the guinea pig noted loosening of the teeth, some gingival hyperemia and hemorrhages, and rarely gingival ulcerations. Only 20 per cent of the scorbutic guinea pigs show marked congestion of the gums. These results have been confirmed by Cohen and Mendel ('18) and many others. Jackson and Moore ('16) found congestion, hemorrhages and necrotic degeneration in the pulp of both incisors and molars.

The first detailed histological study of the teeth in scurvy was made by Zilva and Wells ('19). They find that in guinea pigs on scorbutic diet profound changes occur in the teeth very early (at 10 days), when only slight lesions are seen elsewhere. In the teeth the pulp undergoes a fibroid degeneration. "In complete pulpar fibrosis no cellular elements of any description occur . . . Nerves, cells, blood vessels and odontoblasts have all shared the process of fibrification and are no longer recognisable. The fine cellular connective tissue, which is but a loose mass of network in the normal state, has either become grossly hypertrophied or quite obliterated, and its place taken by a new firm fibrous structure, devoid of cells, nuclei or any regular arrangement of constituted parts . . . The irregular osteoid condition is well marked . . . In a scurvy tooth the condition persists right up to the apex of the root; the change appears to start first in the odontoblastic cells at the top of the pulp, working down toward the apex, followed by distended blood vessels and hemorrhage; then complete fibroid degeneration follows. . . In advanced cases of scurvy the teeth were apparently sound but useless, inasmuch as they had been loosened by the gradual absorption of the cement membrane of the alveolar sockets, which had

left exposed that portion below the neck." Nearly normal structure of the teeth had been recovered in a scorbutic guinea pig cured by one month on normal mixed diet. Scorbutic changes were also noted (but not in detail) in the teeth of monkeys.

Wells ('19, '21) added further data to the results of Zilva and Wells ('19). Pregnant guinea pigs were fed scorbutic diet and six in advanced stages of pregnancy aborted after 11-15 days on the diet. "Microscopical sections were made of the teeth of the mother and offspring and in every case an advanced state of scurvy could be seen." Wells ('21) states that the irregularly osteoid condition of the dentine is "probably due to the hemorrhagic condition of the dental fibrils," an explanation which appears unintelligible.

Howe ('20) confirmed the results of Zilva and Wells, finding a loosening of the teeth and a condition resembling pyorrhea in scorbutic guinea pigs. Unless the conditions are extreme, recovery follows the use of antiscorbutics. A similar disorder was produced by Howe ('21) in guinea pigs on a diet deficient in all three vitamins (A, B and C). Howe ('22) also reports loosening of teeth, excessive tartar formation, etc., in monkeys on scorbutic diet.

Robb, Medes, McClendon, Graham and Murphy ('21) in guinea pigs on scorbutic diet (equal parts of white flour and alfalfa meal) report that "The teeth of our scorbutic animals become very loose. The dropping-out-of-the-teeth indicates a loss of cementum and possibly of material from the alveolar process. The changes in the teeth proper were surprising. There was marked hyperemia of the pulp with some hemorrhage. The odontoblasts lost their tall columnar form and secreted osteodentine very rapidly. The osteodentine nearly filled the pulp cavity in some cases." Unfortunately the normal process of development in the teeth of the guinea pig is unknown; but osteodentine occurs normally in the pulp of the incisor of the rat, which suggests a possible source of error in interpretation. However, Höjer ('24) obtained similar results.

In young rats fed McCollum's rachitic diet No. 2911 (calcium-deficient), Bracco ('23) obtained no gross appearance of rickets, but microscopically the teeth showed intense congestion of the pulp and marked irregularities in the formation of dentine.

In the case of the pulpar degeneration observed by Zilva and Wells, it should be noted that the histological changes closely resemble those described by Burckhard and Inglis ('08) following traumatic thrombosis or "jugulation," which results in death of the pulp or extravasations leading to fibroid degeneration. "Inflammation of a low grade may persist in the pulp for long periods, giving rise to an increase of its fibrous tissue with atrophy of the cellular elements, producing a condition found in chronic interstitial inflammation in some other tissues—a sclerosis." Fibroid degeneration of the pulp may also occur normally in old age, and is ascribed by Hopewell-Smith to capillary thrombosis. It therefore seems probable that the scorbutic pulpar fibrosis described by Zilva and Wells is not a unique condition, but is probably secondary to the hemorrhagic condition resulting in interference with the normal blood supply to the bone and is thus related to the fibroid degeneration which occurs also in the pulp marrow.

## CHAPTER IX

### EFFECTS ON THE MUSCULATURE

The present chapter deals with the effects of inanition upon the skeletal musculature only. The cardiac muscle will be considered in connection with the heart, and smooth muscle in connection with the various organs in which it occurs. (See Index.) The marked atrophy of the musculature explains the characteristic weakness generally appearing in both total and partial inanition, as well as in various chronic diseases involving malnutrition. Under such conditions the musculature appears to serve as a storehouse of protein, fat and glycogen reserves for the exhausted organism. After a brief summary, the effects of inanition upon the musculature will be dismissed under (A) total inanition and (B) partial inanition.

#### SUMMARY OF EFFECTS ON THE MUSCULATURE

During **total inanition**, there is in adults, both human and animal, a marked loss in the *weight* of the skeletal musculature, which in general is roughly proportional to that of the entire body. The loss in the musculature is relatively greater in some species (frogs), and in general is somewhat greater in chronic (incomplete) than in acute inanition. The degree of atrophy apparently varies in different regions of the body.

In young animals (rats) held at constant body weight by underfeeding, the musculature tends to increase slightly in weight. In malnourished human infants, the musculature appears atrophic, but it is questionable whether there is much actual loss of weight except in extreme cases. The appearance of emaciation may be increased by the relative growth of the skeleton. Recovery in the musculature after inanition usually appears promptly upon adequate refeeding.

The *histological changes* in the skeletal muscle fibers involve first a simple atrophy—a decrease in size with no evident changes in structure. The ordinary (neutral) fat, both interfibrous and intrafibrous, undergoes progressive resorption, but the phosphorized lipoidal granules are very resistant to inanition. Later certain of the muscle fibers begin to show degenerative changes, with progressive loss of the characteristic striations in the myofibrillae, granular (fatty, albuminous or pigmentary) degeneration in the sarcoplasm. Waxy degeneration is rare. The nuclei are more resistant, and often undergo proliferation. A variable degree of hyperplasia (fibrosis) occurs in the interstitial connective tissue. The extent of the degeneration varies greatly, not only in different fibers of the same muscle, but also in the muscles in different regions of the body.

In hibernating animals, during the feeding period, there is a marked storage of fat in the muscle, which serves as an important storehouse of fat and protein for the organism during the subsequent fasting period. In the frog and the salmon the musculature thus contributes largely to the materials for growth of the sex glands during the fasting period. Similarly in all species the musculature during inanition is apparently consumed to supply the needs of the more essential vital organs of the body.

In the various forms of **partial inanition**, atrophy and degeneration in the skeletal musculature are frequently evident, especially in those conditions involving general emaciation of the body, such as famine edema, pellagra, etc.

In *rickets*, there is apparently a regressive dystrophy of the musculature, with a slight progressive loss of its weight (in rats). In *beriberi*, there are found the usual atrophic degenerative changes in the muscle fibers, with nuclear proliferation and interstitial fibrosis—a condition frequently resembling that of chronic myositis. In *scurvy*, the muscles share in the general hemorrhagic condition, but the fibers also independently undergo the typical atrophic degenerative changes with interstitial fibrosis.

In *aqueous inanition* (on dry diets), the skeletal musculature undergoes atrophy with loss of weight and degenerative changes in the muscle fibers resembling those in other forms of both total and partial inanition. The intermuscular connective tissue may present a round cell infiltration, as in rickets and scurvy, which does not ordinarily appear in total inanition.

#### (A) EFFECTS OF TOTAL INANITION OR ON WATER ONLY

The effects of total inanition upon the skeletal musculature and the very similar effects on water alone will be discussed (1) as to the gross changes, especially in weight, and (2) as to the histological changes involved.

**Changes in Weight of the Musculature.**—These changes may conveniently be considered separately in the adult and in the young organism, human and infrahuman.

**Adult Human.**—The atrophy of the skeletal musculature during starvation has often been observed, but quantitative data are lacking. Tiedemann ('36) stated that: "Die Leichname Verhungertes fand man in hohem Grade abgemagert, besonders waren die Muskeln sehr dünn, welk und leicht zerreibbar." Willien ('36) noted that especially the muscles of the trunk become atrophied during inanition. Rokitsky ('54) concluded that in general the atrophy of the musculature during malnutrition is relatively less than that of the blood, adipose and areolar tissues, but greater than that of the viscera, nervous system and skeleton. Falck ('81) noted that the muscles at autopsy appear "braun, klebrig, atrophirt." In a case of starvation with loss of about 40 per cent in body weight, Bright ('77) observed that the musculature throughout appeared wasted, especially that of the trunk, and entirely devoid of fat. Theile ('84) recorded the weights of the various groups of muscles in both adults and children in different conditions of nutrition. In a greatly emaciated man 31 years old, it appears that the upper extremity muscles have lost relatively less than the

lower, and the diaphragm less than either. In an emaciated (tuberculous) man of 39 years, the perineal musculature was atrophied, apparently more than that of the extremities. (The children will be mentioned later.)

**Adult Animal.**—In adult pigeons on total inanition with average loss of 40.4 per cent in body weight, Chossat ('43) found the loss in the skeletal musculature to be very slightly greater, averaging 42.3 per cent. Bidder and Schmidt ('52) in a cat with loss of 50 per cent in body weight found an apparent loss of about 67 per cent in the musculature. In various mammals, Bourgeois ('70) noted that the musculature during inanition loses slightly more (relatively) than the whole body, the loss in dry weight averaging about 45 per cent. The trunk muscles appear to lose relatively more than those of the neck and limbs, confirming Collard de Martigny (1828) and Chossat ('43).

C. Voit ('66) found during starvation in the cat a loss in the musculature relatively slightly less than that in the whole body; while Sedlmair ('99) found it slightly greater. In the dog, a relative loss in the musculature slightly greater than that in the body as a whole was found by C. Voit ('94), Kumagawa ('94), and E. Voit ('05, '05a). In the rabbit, Pfeiffer ('87) found the musculature to lose relatively somewhat less than the whole body; Weiske ('97) found the relative loss slightly greater than in the whole body; while Voit ('05) found it nearly unchanged in relative weight. Jackson ('15) in albino rats on acute inanition found an average loss of 33 per cent in body weight and of 31 per cent in the musculature; while in chronic inanition, with body loss of 36 per cent the musculature lost 41 per cent in weight (Table 4).

Gaglio ('84) noted a loss of 85 per cent in the musculature of a frog starved with loss of 56 per cent in body weight. In leopard frogs (*Rana pipiens*) with previous losses in body weight up to 50–60 per cent, Ott ('24) found that the loss in the musculature always relatively exceeds that of the body in the male. In the female, the loss in the musculature is even greater in the earlier stages of inanition, but later it more nearly corresponds to that in the body as a whole (Table 6). There is a progressive decrease in the percentage of dry substance in the musculature.

Certain special conditions of total inanition require attention. In 3 marmots hibernating an average of 166 days, with loss of 35.5 per cent in body weight, Valentin ('57) observed an average evident loss of 30.3 per cent in the musculature, the loss being apparently more rapid in the earlier part of the period. Miescher ('80, '97) found that in the fasting Rhine salmon, the sex glands develop at the expense of the musculature, which may lose over 50 per cent in weight. The superficial lateral trunk musculature is attacked (histology mentioned later), while the remaining muscles appear relatively unaffected. Changes in the weight of the fasting salmon are also given by Gillespie (Paton '98). In the Pacific salmon, Greene ('13-'19) likewise found a loss of 40–50 per cent in weight of the musculature during the fasting period of migration.

An apparently comparable condition exists in the frog, as observed by Gaule ('01), in which the musculature reaches its maximum weight during the summer feeding period (July–August). It declines to a minimum during the winter

fasting period, and is apparently sacrificed in part to serve as material in the development of the sex glands. These are conspicuous examples of dystrophic growth changes during adult inanition, certain portions of the body growing at the expense of others, as occurs so generally during chronic inanition in young organisms.

**Human Infants.**—In malnourished, athreptic infants, marked atrophy of the musculature has been observed by DeTommasi ('94), Thiercelin ('04) and many others, so that in extreme cases the emaciated body appears reduced to "skin and bones." Ohlmüller ('82) found that in an atrophic infant of 56 days the musculature formed 23.6 per cent of the body, whereas in a "normal" infant of the same age it formed 25.8 per cent. This would indicate that the musculature had relatively lost slightly more than the body as a whole, or had been more retarded in growth. Theile ('84) likewise observed the musculature of an emaciated infant apparently forming only about 17 or 18 per cent of the body, the normal at birth being 20–22 per cent. Nicolaëff ('23) found variation in the amount of atrophy in the individual muscles of famine-stricken children. The functionally active muscles of mastication (temporal, masseter) lost relatively less than the biceps brachii, which sometimes lost 50 per cent in weight.

**Young Animals.**—In nursing puppies subjected to chronic inanition by insufficient or improper diet, Quattrochi ('01) observed marked emaciation, with atrophy of the skeletal musculature. Aron ('10, '11) noted that in an underfed puppy the musculature formed only 29.3 per cent of the body weight, while in a full-fed litter-mate control it formed 50.2 per cent. Since the control was much larger, however, the comparison indicates not the loss, but merely the amount of retardation in growth. An initial control of the corresponding body weight is required to determine whether an actual loss in the musculature has occurred.

In young albino rats held at nearly constant weight by underfeeding for various periods, Jackson ('15a) found a slight increase in the weight of the musculature (Fig. 39; Table 4), a result confirmed by Stewart ('16, '18) and by Jackson and Stewart ('20). In the fetuses of rats subjected to inanition by underfeeding the pregnant mother, however, Barry ('20, '21) obtained a slight loss (or retarded growth) in the weight of the musculature.

In a thin yearling steer held at maintenance by underfeeding for several months, Trowbridge, Moulton and Haigh ('18) found that the musculature formed 44.5 per cent of the body weight, whereas in a fat control of the same age it formed only 33.1 per cent. This would apparently (though not necessarily) indicate a persistent growth of the musculature during inanition. On the other hand, Thompson and Mendel ('18) believe that in underfed albino mice the characteristic curvature of the spinal column is caused by the arrested growth of the skin and muscle, together with the persistent growth of the vertebral skeleton.

It may be noted that although there may be no actual loss in the weight of the musculature, or even a slight gain, in young organisms on chronic inanition, an appearance of emaciation may be produced by the concurrent persistent growth of the skeleton.

**Recovery upon Refeeding.**—Stewart ('16) found that in young albino rats held at maintenance for several weeks, and in which the musculature was presumably above normal in weight, approximately normal conditions are restored after the first week or two of refeeding upon adequate diet. In younger rats, underfed from birth to 6 or 10 weeks of age, Jackson and Stewart ('19) observed, upon refeeding to a body weight of 25-75 g. that the musculature lags behind and appears slightly below normal weight. Similarly in young rats refeed fully after long periods of inanition, Jackson and Stewart ('20) found in most cases a slight deficit in the weight of the musculature. However, the differences are so slight and variable that their significance is somewhat doubtful.

**Histological Changes in the Musculature.**—The histological changes also may be grouped according to those in the adult and the young, both human and infrahuman.

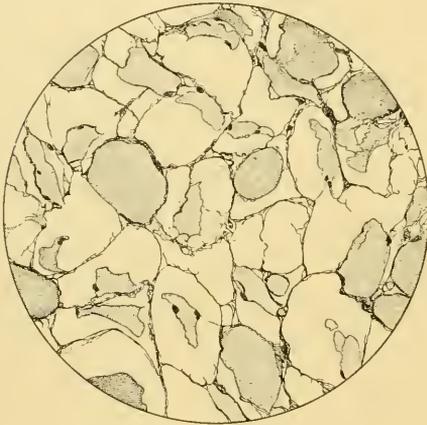


FIG. 58.—Cross section showing the histological structure of skeletal muscle in a man who died from starvation. The muscle fibers appear extremely atrophied and separated from the endomysium by extensive spaces. (Meyer '17.)

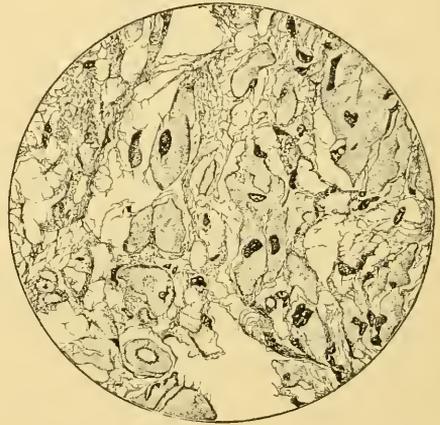


FIG. 59.—Cross section showing the histological structure of cardiac muscle in a man who died from starvation. The muscle fibers appear variably atrophic and shrunken, in places separated by extensive spaces intermingled with the connective tissue stroma. (Meyer '17.)

**Adult Human.**—Schultzen ('62, '63) described fat droplets and indistinct cross striation in the skeletal muscle fibers of a 19 year old girl who had starved to death. "Striationem transversam bene perspicuam reddere non licuit. Inter fibrillas magnae adipis guttae." Hayem ('77), in cases of starvation during and after the siege of Paris, found that the lesions in the muscle fibers appear more distinct in chronic than in acute inanition, and include: (1) simple atrophy, the cross striation remaining unaffected; (2) granular degeneration; (3) fatty degeneration; (4) pigmentary degeneration. The interstitial connective tissue tends to hyperplasia (fibrosis).

Popow ('85a) studied the changes in muscle fibers (human and animal) during starvation, noting decreased diameter, also granular, fatty and sometimes waxy degeneration. Landau ('10) noted fatty degeneration in the muscle fibers in various diseases involving general cachexia or nutritional disturbance

of the muscle tissue through interference with the circulation. In a man who died from starvation, Meyer ('17) found a marked atrophy of the skeletal muscle fibers, which in cross sections appear to have shrunken away from the endomysial sheaths (or sarcolemma?) leaving empty spaces of variable width (Fig. 58). The striations in most fibers are only faintly visible, though often well preserved. The sarcoplasm may form granular masses. The nuclei may be proliferated, sometimes forming a degenerated mass.

**Adult Animal.**—Heuman ('50) observed a decrease in the size of the pectoral muscle fibers in starved pigeons. Valentin ('58) could find no evident changes in the microscopic structure of the muscle fibers in hibernating marmots, in spite of loss in body weight up to 35 per cent. Manassein ('69, '69a) in the muscle fibers of starved rabbits found granular degeneration (albuminous or fatty), sometimes pigmented or waxy (Zenker's) degeneration. The granular degeneration was found oftenest in the recti muscles of the eye, the order of frequency in other muscles observed being: tongue, diaphragm, abdominal muscles, shoulder muscles, intercostals. Lépine ('74) noted brownish pigmentation and disappearance of fat in the muscles of starved animals. Carville and Boche-fontaine ('74, '75) found the muscles in starved dogs to be yellowish red. No decrease was noted in the diameter of the fibers, which are in most cases finely granular, many with loss of cross striation. Some fibers appear vitreous (waxy degeneration?) with spaces separating the sarcolemma. Eichhorst ('79) observed non-fatty granulation in the muscle fibers of starved pigeons and raven.

In fasting summer frogs, Sokoloff ('76) studied the degeneration (granular or waxy) in the muscle fibers, also the regeneration upon refeeding. The nerve endings in muscle appear very resistant to starvation. In the atrophic and degenerated muscle fibers of starved frogs, Gaglio ('84) found numerous fine albuminous (non-fatty) granules, with proliferation of the nuclei; also slight increase in the interstitial connective tissue.

In rabbits subjected to total complete or incomplete inanition, Ochotin ('85, '86) described the usual granular or fatty (?), occasionally waxy, degeneration in the muscle fibers of the diaphragm. Coen ('90), in the starved rabbit and kitten, found the muscle fibers mostly well preserved, some showing finely granular degeneration with loss of striation. The interstitial stroma shows congestion and a variable degree of nuclear proliferation. Morpurgo ('90) observed occasional mitoses in the skeletal muscle of adult rabbits on ample refeeding after inanition.

During inanition in the pigeon Knoll ('80) noted in the muscle fibers a reduction in the fatty interfibrillar granules, but an increase in the non-fatty. Knoll ('89) and Knoll and Hauer ('92) observed during starvation a decrease in the granulation in the dark fibers of the pectoralis major, but the greatest degree of atrophy occurs in the non-granular, light fibers. Morpurgo ('89) found the average diameter of the skeletal muscle fibers in starved pigeons reduced from  $33\mu$  to  $18.6\mu$ , indicating a loss in volume of 68 per cent.

The size of the skeletal muscle fibers under various degrees of nutrition was measured by Kunkel ('87), Schwalbe ('90), Schwalbe and Mayeda ('90), Mayeda ('90), and Halban ('94), who found the average diameter of the fibers

decreased in both human and animal malnutrition. In the fasting frog, Kunkel ('87) found a marked decrease in the diameter of the sartorius fibers, but not in their number. The large range of normal variation in the size of the muscle fibers makes comparison somewhat difficult. Frankl and Freund ('84) held that the diminution in the volume of muscle during emaciation is due only in part to decreased caliber of the atrophic fibers, the greater part of the decrease being ascribed to actual disappearance of disintegrated fibers, the interstitial connective persisting in increased amount. In the starved dog, Morpurgo ('89b) found no decrease in the number of muscle fibers, and the muscle nuclei undergo but slight atrophy.

Statkewitsch ('94) studied the microscopic changes in the muscle and other tissues during inanition in numerous animals (mammals, birds, reptiles and amphibians), giving also a detailed review of the earlier literature. He found that in general the skeletal muscle is affected earlier and more intensively than smooth muscle. "Abgesehen von einer Abnahme der Grössenverhältnisse und einer Trübung treten in den quergestreiften Muskelfasern je nach der Dauer des Hungerns Schwellung, kleinkörnige und späterhin auch grosskörnige Degeneration auf, wobei die quere, wie auch Längsstreifung nicht mehr beobachtet werden kann." The degenerative changes appear first in the cervical musculature, then (in order) in the extremity muscles, pectoralis major, heart, rectus abdominis, and finally the smooth musculature. The granules are albuminous; fatty granules (by ether or osmic tests) not being found during inanition. Zenker's (waxy) degeneration is rare (found in 1 cat and 1 dog, 6-24 hours post mortem), and pigmentary degeneration was never observed. Since the muscle fiber shrinks greatly, the nuclei *appear* more numerous, being nearly unchanged in size. In extreme stages of inanition, nuclear degeneration may occur. Very similar changes were found by Konstantinowitsch ('03) in the muscle fibers of starved rabbits, lizards and frogs; and by Beeli ('08) in cats, showing decrease in the average nuclear diameter.

Athanasiu and Dragoin ('08) found no fat in the striated muscle fibers of the summer frog, but a storage of large amounts in rows of interfibrillar granules during the winter. Similarly Miescher ('80, '97) observed fat droplets between the myofibrillae of the muscle fibers in the superficial lateral trunk muscles of the fasting salmon. Further details as to this fat storage were noted by Mahalanobis (Paton '98) and especially by Greene ('12, '12a, '13, '19) and Greene and Greene ('14). Greene finds that in the Pacific salmon at the beginning of its migratory fast the fat is stored chiefly in the muscles: (1) in the dark superficial lateral trunk muscle, chiefly as large droplets within the fibers; (2) in the great mass of pink muscle, with large quantities of fat, at first entirely interfibrillar, in droplets of variable size up to  $100\mu$ ; (3) in the smaller fin muscles, a slight amount of fat, chiefly interfibrillar. The stored fat is gradually consumed on the river journey to the spawning grounds, but it is not completely exhausted even at death. Chemical analysis indicates that the muscle also decreases markedly in protein content, with slight loss in ash and increase in water content.

Bell ('09, '10, '11, '12) made a careful study of the granules in muscle fibers during inanition, finding that in the ox the "liposomes" (fatty or lipoidal granules

staining with scarlet red, etc.) do not appear to vary much under moderate fluctuations in the degree of nutrition. In the rat and cat, however, the liposomes during starvation decrease notably in size, number and staining capacity. For the rat, this was confirmed by Bullard ('12). Krause ('11) also states that the fat droplets in muscle fibers are dependent upon the nutritive condition of the animal. In starved dogs, Morgulis, Howe and Hawk ('15) found indistinctness of the striations, but no swelling or granular degeneration of the muscle fibers.

In the muscle fibers, as previously mentioned in Chapter VI for adipose tissue, the fat is apparently of two kinds: (1) the ordinary (neutral) fat, which is easily removed by inanition; and (2) the phosphorized, lipoidal fat, which strongly resists inanition and in extreme stages becomes increased in amount by fatty degeneration or infiltration (v. Gierke, '21).

In *Amia calva* after 20 months of starvation, Smallwood ('16) found the skeletal muscle fibers in various degrees of degeneration and disintegration, which appeared to involve progressively: (1) the cross striations; (2) the sarcoplasm; and (3) the nucleus.

Moulton ('20, '20a) observed that in the skeletal muscle of underfed steers there is a marked loss of nitrogen as well as of fat, with notable decrease in the size of the muscle fibers, but no obvious change in histological structure. Thus the muscles form an important storehouse for protein, as well as for fat and glycogen.

**In the Young.**—So far as they have been observed, the changes in the structure of the muscle in young individuals appear in general similar to those in adults. Walbaum ('90) observed that in malnourished children there is a decreased content in the fatty granules of the skeletal muscles excepting the eye muscles. Moenckeberg ('12) described the atrophic and degenerative changes during malnutrition in the muscle and other tissues. Lesage and Cleret ('14) found a marked interstitial sclerosis in the muscle tissue of infants with congenital spasmodic atrophy. According to Nobécourt ('16), Variot and Ferrand studied the diameter of crural muscle fibers in malnourished infants. In the "hypotrophic" infants (with moderately retarded growth) the muscle fibers show a variable degree of diminution in diameter; but the fibers in the more severely malnourished are said to show no decrease in diameter. "La fibre striée des enfants *amaigris*, même dans le cas où cet amaigrissement est considérable et où l'enfant n'a que la moitié du poids qu'il devrait avoir pour son âge et pour sa taille, n'est presque pas diminuée de volume." This remarkable finding needs verification, although it is quite possible that in the young the muscle fibers tend to resist a decrease in volume during inanition. As was noted above, the total mass of the musculature in underfed young rats not only fails to decrease, but usually even increases slightly in amount, with nearly constant body weight.

Morpurgo ('98a) concluded that the general law of post-embryonal development in the musculature is the same as in other tissues. There is an early period of cellular differentiation, governed by heredity and independent of nutrition and function (Roux). The later growth of the muscle fibers is not governed

chiefly by heredity, but varies according to nutrition and function. During this later period, inanition causes a simple atrophy of the muscle fibers.

Changes in the *chemical composition* of the musculature during inanition have been referred to incidentally in the foregoing account, and are further described in the papers of Aeby ('75), Pfeiffer ('87), Lukianoff ('88), Aldehoff ('89), Tonninga ('93), Rubow ('05), Roger ('07), Maignon ('07), Tobler ('11), Terroine ('20), and Moulton, Trowbridge and Haigh ('22a). In general, they support the doctrine that the muscles serve as an important storehouse for reserve protein, fat and other materials, which are consumed by the organism during inanition.

### (B) EFFECTS OF PARTIAL INANITION

We have here to consider the effects upon the musculature in certain forms of partial inanition, including deficiency of protein, minerals, vitamins and water.

**Protein Deficiency.**—As mentioned in Chapter V, the edema found during human famine and allied conditions may be due to a mixed deficiency, but usually a lack of protein appears to be of primary importance. In this malnutritional edema, Budzynski and Chelchowski ('16) and others have generally observed profound atrophy and weakness of the musculature. Maase and Zondek ('17), however, ascribed the muscular atrophy in the cases of "war edema" to general inanition, and especially to deficiency of fat. In the muscles of an infant with alimentary edema, Klose ('13) found an increased water content, with reduction in fat, protein and ash.

In the "cachexia aquosa" and allied conditions in sheep and cattle on inadequate (especially low protein) diets, Hoare ('15) and Froehner and Zwick ('15) state that the muscles are emaciated, pale, flaccid and sometimes edematous. Kohman ('20) was able to produce a malnutritional edema with muscular atrophy in rats on a watery diet, low in protein and fat.

**Pellagra**, as stated in Chapter V, may be considered as primarily due to protein deficiency. In this condition, especially in advanced stages, muscular atrophy is very common. Fraenkel ('69-'70) found it in 21 out of 48 cases, the pectoralis major being especially involved. Muscular atrophy in pellagra is mentioned also by Tuczek ('93) and Marie ('08, '10); the literature on the subject is reviewed by Raubitschek ('15).

**Mineral Deficiency.**—In a puppy on an iron-poor diet, von Hoesslin ('82) observed continued growth of the body; but the muscles of the extremities showed fatty degeneration, and microscopically fat droplets appeared among the myofibrillae.

In human **rickets**, atrophy of the musculature is mentioned by Whistler (1645), Glisson (1650), Seibold (1827), Vincent ('04), Cheadle and Poynton ('07), Wohlaer ('11) and Engel ('20). Bing ('07), Stoeltzner ('09) and Banu ('21) also support the theory of a specific regressive dystrophy of the musculature in rickets, although Heubner and Comby consider the process a disuse atrophy. Jenner ('95) observed a transparent appearance and indistinct cross striation of the muscle fibers, but no fatty degeneration. Banu ('21) finds the

muscle fibers uniformly atrophied, with disappearance of the cross striations, increased distinctness of the longitudinal striations, multiplication of the muscle nuclei and increased connective tissue.

In *experimental rickets* (or pseudorickets?) of puppies, E. Voit ('80) found no significant change in the weight of the musculature. Aron and Sebauer ('08) noted that in experimental rickets in a puppy the musculature appeared less well developed than in the control, perhaps on account of lack of exercise in the former. In rachitic rats, Jackson and Carleton ('23) found a slight but progressive loss in the weight of the skeletal musculature, amounting to 12 per cent in the severely rachitic group.

**Vitamin Deficiency.**—The effects of vitamin deficiency on the muscles have been noted chiefly for vitamins B and C.

**Vitamin B. Beriberi and Polyneuritis.**—In human beriberi, Bälz ('82) found nuclear proliferation and sometimes atrophy of muscle fibers. Scheube ('94) observed parenchymatous-fatty (sometimes colloid) degeneration of the muscle fibers, some fibers being atrophic and some hypertrophic; with some increase in the number of muscle nuclei and in stroma. Rumpf and Luce ('00) stated that the muscle lesions are not those ordinarily found in simple neuritis, but indicate a myopathic process, designated as *polymyositis acuta parenchymatosa et chronica interstitialis*. Duerck ('08, '08a), however, considered the changes found in the musculature (atrophic degeneration, nuclear proliferation, etc.) as non-specific and identical with those occurring in other diseases.

Kato and Shizume ('19), McCarrison ('19) and others have described the changes in the musculature of the chick and pigeon during polyneuritis galinarum. Findlay ('21) found considerable muscular atrophy and loss of cross striation. Funk ('22) also has recently reviewed the changes found in birds with beriberi. The muscle fibers "exhibit atrophy and fatty degeneration, but the changes disappear rapidly on returning to normal nutrition."

**Vitamin C. Scorbutus.**—In human scurvy, the hemorrhagic tendency is manifested in the musculature as elsewhere. According to Sato and Nambu ('08), the muscles, especially those of the lower extremities, show hemorrhages to a variable extent. The muscles also present edema and marked atrophy, in connection with the general cachexia. Histologically, the muscle tissue exhibits a myositis, with interstitial hemorrhages, atrophy and degeneration of the muscle fibers. The changes are also described by Aschoff and Koch ('19), who found the hemorrhages frequent near the muscular attachments, and in the tendons, fascia, etc. The musculature of the legs is affected most, the arms less and the trunk least, exposure to trauma being an important factor. Comrie ('20) noted marked atrophy of the muscles, with deep-seated hemorrhages in over half of the cases. Hess ('20) has recently summarized the various changes in human and animal scurvy, including degeneration of the muscle fibers, hemorrhages and variable pigment deposits secondary thereto, and interstitial fibrosis.

In experimental scurvy of guinea pigs, Holst and Frölich ('07, '12) found intramuscular hemorrhages, especially in the neighborhood of the bones and joints, with microscopic changes similar to those in human scurvy. "Die Muskelfasern waren in grosser Verbreitung abnorm schmal und zeigten öfters

einige fettige Degeneration. Auch bestand oft ein Zerfall in unregelmässige, hyaline Klümpchen, die zum Teil nicht in derselben Weise wie in normalen Fasern gefärbt wurden. Zwischen diesen Klümpchen bestanden hier und da kleine Ansammlungen von Sarkolemmkernen. Sonst wurde aber keine Vermehrung der Zellen bzw. eine rundzellige Infiltration nachgewiesen."

In experimental scurvy of monkeys, Hart ('12) described typical intramuscular hemorrhages, and also some peculiar granules, the staining reactions of which indicated a calcium content.

Jackson and Moore ('16) stated that the degenerative lesions found in the muscles of the guinea pig in scurvy are independent of the intramuscular hemorrhages. Höjer ('24) found hemorrhages, atrophy of the muscle fibers, and necroses with calcification.

**Aqueous Inanition.**—Longet ('68) stated that the autopsy of a man after death from thirst shows disappearance of fat and marked emaciation in the musculature. Schuchardt ('47) in pigeons on dry diet with loss of 44 per cent in body weight noted an apparent loss of 37 per cent in the pectoral musculature. Nothwang ('91) in pigeons after death from thirst found the muscles apparently well preserved and dark red in color. Scheffer ('52) and Falck and Scheffer ('54) found in a dog on dry diet an apparent loss of 20 per cent in body weight and of 29 per cent in the musculature.

In histological structure, Pernice and Scagliosi ('95a) observed that in a dog subjected to a dry diet the muscle fibers are pale, poorly stainable, somewhat homogeneous in appearance, with indistinct striations. The fibrillae appear attenuated; the nuclei are numerous and some show mitosis. In chickens under similar conditions, the skeletal muscle shows occasional slight hemorrhages, with partial loss of striation. The interstitial stroma presents a round cell infiltration. As previously mentioned, this occurs also in the muscles during rickets and scurvy, but rarely in total inanition. It may represent an inflammatory reaction to toxic substances in the circulation.

The foregoing investigators found also a marked drying of the musculature which in many cases was measured by chemical analysis. Straub ('99) observed a loss of 20 per cent in the water content of the musculature in dogs subjected to aqueous inanition on a dry diet. Durig ('01) in frogs deprived of water by exsiccation found that the organs vary much in their loss in weight and in water content, the musculature losing most heavily. Similarly in dogs subjected to experimental diarrhea, with loss of 25-30 per cent in body weight, Tobler ('10) noted that the skin and musculature suffer most, losing up to 50 per cent of their water. The water content of the viscera is much less affected.

The loss of weight in the skeletal musculature of rats on a dry diet was noted by Kudo ('21, '21a), as shown in Tables 9 and 10. In adult rats in the acute thirst series with average loss of 36 per cent in body weight, the musculature lost 33 per cent; in the chronic thirst series, the body lost 52 per cent and the musculature 61 per cent. In young rats held at nearly constant body weight by a dietary deficiency of water for 1-13 weeks, there was a loss of about 5-7 per cent in the musculature of the various groups.

## CHAPTER X

### EFFECTS ON THE BRAIN

In general the brain appears relatively resistant to the effects of both total and partial inanition. Usually little or no loss in weight or changes in gross or microscopic structure are apparent. In advanced stages of starvation, however, and especially in types of partial inanition (beriberi, pellagra) involving neural or psychic disturbances, there are well-marked degenerative changes in the nerve cells. After a brief summary, the effects of inanition upon the brain will be considered under (A) total inanition, and (B) partial inanition.

#### SUMMARY OF EFFECTS OF INANITION ON THE BRAIN

The brain in general is extremely resistant to loss in weight during total inanition or on water alone. In adults, both human and infrahuman, even with a loss of 40 or 50 per cent in body weight, the loss in brain **weight** is below 10 per cent, usually below 5 per cent, and often shows no appreciable change. This is also true in general during the various forms of partial inanition; but in some cases there may be an actual increase in brain weight (with edema in pellagra, etc.) or a definite atrophy, with decreased weight (during protein deficiency, pellagra, etc.).

In atrophic infants, the brain is capable of continued growth with retarded, or even stationary, body weight. The same is true in young animals, especially in newborn subjected to prolonged underfeeding, although in some cases (acute inanition, various forms of partial inanition, and at later ages) the brain weight may remain unchanged, or even show a slight loss. In human rickets the brain appears enlarged (often hydrocephalic), but in experimental rickets in animals it is usually normal in weight. After severe underfeeding, the brain may fail to grow properly upon subsequent ample refeeding.

In **structure**, the brain during **total inanition** (or on water only) grossly appears normal, excepting a variable degree of congestion, especially in the meninges. Microscopically the white substance (medullated fibers) usually appears normal. Aside from a variable degree of hyperemia, the gray substance usually likewise shows no marked change, except in the nerve cells. Even most of these cells frequently appear normal, but there are often atrophic and degenerative changes which are extremely variable in different individuals, in different cells, and in different regions of the brain. As a rule, the changes appear well marked only in advanced stages of inanition.

These brain cell changes, which have been extensively studied in various animals, are especially evident in some of the large cells (of Betz and Purkinje, etc.), although frequently more intensive in the smaller cells. The changes

involve cell atrophy with progressive chromatolysis (of the Nissl substance), neurofibrillar degeneration, cytoplasmic vacuolation, rarely nuclear degeneration. "Steatosis" is not characteristic. Only slight changes appear in the brain cells during hibernation. In the young during inanition the normal developmental changes in the brain are largely arrested, but the degenerative changes are less conspicuous than in the adult.

In the various forms of **partial inanition**, the structural changes of the brain in general resemble those described for total inanition, including a variable degree of congestion and of atrophic degeneration in the nerve cells. The changes are especially marked in beriberi, with the associated phenomena of paralysis; likewise in insane pellagrins, frequently involving karyorrhesis and complete cell disintegration. Sclerosis due to glial proliferation is more frequent than in total inanition. Hemorrhages occur in scurvy and beriberi. In general, it may be noted that the lesions of the nerve cells during the various types of inanition are not specific in character, but closely resemble those produced by toxic and other injurious agents.

It is a remarkable fact that although the brain appears relatively resistant to the effects of inanition in general, it is, as pointed out by Clark ('23), more susceptible than any other tissue to the effects of oxygen deficiency.

#### (4) EFFECTS OF TOTAL INANITION, OR ON WATER ONLY

Under this heading will be included the effects upon the brain, human and infrahuman, adult and young, as to (1) weight and (2) structure.

1. **Effects on Brain Weight.**—In the **human adult**, it has long been known that the brain is very resistant to inanition in general (Rokitansky '54), but exact quantitative data appear relatively scanty. Von Bischoff ('64) stated that during emaciation the brain does not share the loss in body weight, at least not to the same degree.

Porter ('85-'87, '89) published average weights of the adult brain found in autopsies upon victims of the Madras famine of 1877-78, as shown in the accompanying table.

BRAIN WEIGHTS IN VICTIMS OF THE MADRAS FAMINE (PORTER '89)

Condition of body	Men		Women	
	No. of cases	Weight, ounces	No. of cases	Weight, ounces
Plump (normal).....	9	43.8	8	39.33
Dropsical.....	24	42.35	19	39.2
Emaciated.....	195	41.06	130	37.0
Atrophic (greatly emaciated).....	4	39.5	4	36.0

This table would indicate in the extreme cases an apparent loss of about 9.8 per cent in the brain weight of the men, and 8.1 per cent for the women. All of these

had probably lost over 40 per cent in body weight. Porter concluded that the brain wastes like other tissues, but to a lesser extent, "and no doubt to this is due the effusion of serum into the subdural and subarachnoid cavities so frequently found in these cases." The relatively slight loss in the dropsical cases was ascribed to edema in the brain substance.

Marchand ('02) found no significant difference in brain weight as the result of inanition. Matiegka ('04), however, in adults from 20 to 59 years of age, obtained average brain weights as shown in the accompanying table.

AVERAGE BRAIN WEIGHT IN DIFFERENT CONDITIONS OF NUTRITION (MATIEGKA '04)

Nutritional condition	21 Men, grams	38 Women, grams
Good.....	1428.6	1261.0
Medium.....	1392.0	1208.0
Poor.....	1324.2	1190.3

Comparing the extremes, Matiegka's data would indicate a loss in brain weight of about 7.3 per cent for the men, and of 5.6 per cent for the women.

Krieger ('20) similarly compared the brain weights in several groups of emaciated adults with various norms, as indicated in the accompanying table. The apparent loss in body weight, estimated by comparing with Gärtner's norm for body length, ranged from 36-48 per cent in the various groups. The loss in brain weight was estimated by comparison with the norms of (1) Marshall, based on age and height; (2) Bischoff, based on body weight; and (3) Marchand, based on age and height.

AVERAGE BRAIN WEIGHT IN VARIOUS CONDITIONS OF EMACIATION IN ADULTS. ALL MALES, EXCEPT AS INDICATED IN GROUP I. FROM AUTOPSIES IN THE PATHOLOGICAL INSTITUTE, JENA (KRIEGER '20)

Group	No. of cases	Observed brain weight, grams	Percentage deviation of brain weight from the norm of		
			Marshall	Bischoff	Marchand
I. Insane. No chronic organic disease					
{ male.....	6	1,326	-0.37	-0.52	-5.6
{ fem.....	4	1,216	-0.16	+6.2	-3.6
II. Chronic diarrhea.....	5	1,346	-1.02	-0.22	-4.1
III. Malignant growths.....	19	1,357	+0.8	-1.2	-3.4
IV. Chronic general infections.....	23	1,365	+0.36	-0.65	-2.8
V. Tuberculosis.....	25	1,347	-0.18	-0.18	-4.0
VI. Various cases in the aged.....	12	1,328	+0.6	.....	{ -6.2 -3.1 <sup>1</sup>

<sup>1</sup> Making allowance for the normal decrease with age.

From these data, Krieger concludes that it is doubtful whether the human brain loses appreciably in weight during inanition, although comparison with Marchand's norm indicates a small but fairly constant loss of 2.8-5.6 per cent.

Weber ('21) compared the weights of the brain in 1,257 autopsies among civilians at Kiel during the separate years 1914-1918. Body lengths are available, but not body weights. The brain weight averages 1,357 g. in the males, and 1,246 g. in the females, with no apparent difference between the period of good nutrition (1914-1915) and the period of subnutrition (1916-1918).

**Brain Weight in Atrophic Infants.**—Von Buhl ('61) found in 52 cases the average brain weight of the newborn about 352 g. (range 193.5-482). In infants dying in the second or third week after birth, the average brain weight found was 411.5 g. "So ist damit unumstösslich dargethan, dass mit der Abnahme des Körpergewichts das des Gehirnes nicht oder doch am wenigsten abnehme." Parrot ('82) published a table showing the brain weight averaging 286.7 g. in 10 infants 1 - 7 days of age, with average body weight of 1,994 g.; and 359.7 g. in 26 infants 8 - 36 days of age, with body weight of 1,969 g. Manouvrier deduced from these data the independent growth of the brain during inanition in infancy; but he failed to exclude the possibility that in the latter group the brain during an earlier period of normal growth might have attained its greater weight, which was not lost subsequently, in spite of a possible decrease in body weight.

Similarly Ohlmüller ('82) observed that the brain and spinal cord combined weighed 528.8 g. in a well nourished infant of 56 days (body weight 4149.5 g.); while in an atrophic infant of 56 days (body weight 2,381.2 g.), they weighed only 480.9 g. This does not justify the conclusion that there has been a decrease in the weight of the brain and cord in the atrophic infant, because its previous body weight is not stated. Ohlmüller cited data showing that in the newborn the brain weight averages 13 per cent of the body weight, increasing to 15-24 per cent in emaciated infants up to 42 days old. In the absence of exact data concerning the previous body weights, however, it is impossible to draw any conclusions as to what changes in absolute brain weight have occurred during the period of inanition. Ohlmüller found no appreciable difference in the water content. There was an apparent increase in fat content of the brain in the atrophic infants, but no appreciable difference in lecithin in the brain and cord of a starved puppy.

Cantalamassa ('92) at the autopsies of twin infants which had died of starvation in 11 and 23 days after birth, respectively, observed an unusual degree of overlapping at the sutures between the parietal and frontal bones. This he attributed to reduction in the volume of the brain, but it might equally well be ascribed to increased growth in the cranial bones, or to decrease in the cerebrospinal fluid. Overlapping at the cranial sutures was also noted in athreptic infants by Thiercelin ('04), who also concluded that: "Le cerveau s'est atrophié, le liquide céphalorachidien s'est en partie tari, et ce dessèchement du contenu de la boîte crânienne a mené une dépression considérable des fontanelles formant une véritable cavité dont la profondeur peut atteindre 3 ou même 4 millimètres."

This brings us to the work of Variot ('07) who first demonstrated that, in addition to the persistent skeletal growth, there is in infants during inanition an

actual increase in the brain weight, which often appears to correspond to the age, rather than the body weight. He concluded that:

“Les mensurations faites sur le crâne des enfants hypotrophiques vivants, aussi bien que les pesées du cerveau après la mort, semblent concordantes pour nous montrer que les processus hypotrophique ne s'exerce pas sur les centres nerveux comme sur le reste de l'organisme.”

This conclusion was confirmed by Variot and Lassablière ('09), who give data on 12 hypotrophic infants autopsied at 3-21 (average  $13\frac{2}{3}$ ) months of age. Compared with the normal for corresponding age, the brain weight averages nearly normal, ranging from 18 per cent below to 20 per cent above; whereas the corresponding height of the body averaged 10 per cent below nor-

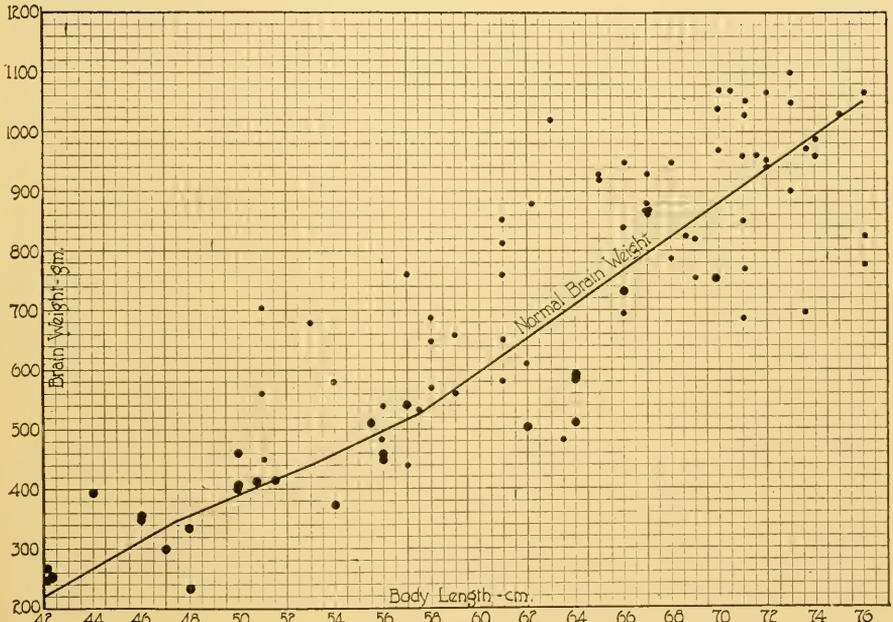


FIG. 60.—A graph showing the individual brain weights in emaciated, atrophic infants. The larger dots represent original Minnesota cases; the others are from various sources. The curve represents the normal brain weight, according to body length, from data compiled by Prof. R. E. Scammon. It is evident that inanition had little or no effect upon the weight of the brain.

mal, and the body weight 37 per cent below normal. Thus during inanition in infants the brain appears capable of continued growth at the expense of the remainder of the body.

Variot's conclusion was also confirmed by the extensive data of Fayolle ('10). In a series of 128 infants, he found the average brain weight in the hypotrophic 0.2 per cent above the normal for corresponding age; the body height being 7.2 per cent below, and the body weight 36.4 per cent below. In a second series of hypotrophics, the head circumference averages 0.01 per cent above normal for age (indicating normal size for the brain); the body height being 5.14 per cent below, and the body weight 24.19 per cent below.

Lesage ('11) agreed that the brain in atrophic infants is the last organ to be affected, but states that if the inanition is prolonged the brain also is finally involved.

From head measurements on 125 children in Czerny's clinic, Sawidowitsch ('14) concluded that "Ernährungsschädigungen, welcher Art sie auch sein mögen, bewirken eine Hemmung in der Gehirnentwicklung." The changes in body length, body weight and brain volume appear to be independent of each other.

Lesage ('14) found a brain weight of 460 g. in an atrophic infant of 4 months, at which age the normal weight is 620 g. Nobécourt ('16) and Marfan ('21), however, support the doctrine that the brain weight in infants is largely independent of the body weight. This is likewise confirmed by the observations of Nicolaëff in famine-stricken children.

Jackson ('22) studied the weights of the body and of various organs (see Tables 2 and 3) in about 50 atrophic infants in comparison with the norms for (1) final body weight; (2) maximum body weight; (3) body length; and (4) age. In this series, the brain averaged about 26 per cent above the norm for final body weight; 1.5 per cent above the norm for the maximum body weight observed during life; 7.7 per cent below the norm for body length; and 12.3 per cent below the norm for age. Thus the brain weight averages slightly higher than that corresponding to the maximum body weight, but lags slightly behind that corresponding to the body length (which has been shown to increase during inanition). That the brain weight in emaciated infants in general averages approximately normal according to body length is apparent from the field graph shown in Fig. 60. Of the individual data represented, 25 (larger dots) are Minnesota cases; the others are from various sources.

**Brain Weight in Adult Animals.**—The resistance of the brain toward inanition was discovered by Collard de Martigny (1828), who noted that the brain appeared unchanged in size in several starved dogs and rabbits. Chossat ('43) first studied the weight of the brain during inanition. In 10 pigeons on total inanition with loss of about 40 per cent in body weight, the brain weight averaged 2.25 g., which exactly equals that in 10 controls of the same initial body weight. Since it is difficult to determine precisely the line of separation between the brain and spinal cord, their combined weight was found to be 3.08 g. in the controls and 3.02 g. in the test pigeons, giving an apparent loss of 1.9 per cent. The (combined) decrease in dry weight appears relatively greater, from 0.64 to 0.58 g., a loss of 9.4 per cent. Findlay ('21) recently likewise found practically no loss in the brain weight of starved pigeons and fowls (Table 13).

In a cat losing about 50 per cent in body weight on total inanition, Bidder and Schmidt ('52) compared the weight of brain and spinal cord with that in a normal control of similar initial body weight. This gave an apparent loss of 37.6 per cent, which was evidently due to a large individual variation. Von Bibra ('54) found no essential change in the brain weights (fresh or dry) in starved rabbits. Valentin ('57) noted weights indicating a loss of about 5 per cent in the brain of marmots with loss of 35.5 per cent in body weight after 166 days of hibernation.

Voit ('66) observed an apparent loss of 3.2 per cent in the brain and spinal cord (combined) of a cat on total inanition with loss of 33 per cent in body weight. Manassein ('68, '69) in 47 adult rabbits with average loss of about 39 per cent in body weight found an apparent *gain* of 3 per cent in the weight of the brain. In 2 cats there was an apparent loss of 10 per cent in brain weight, while in 2 crows the brain weight remained unchanged (with loss of 36 per cent in body weight).

Bourgeois ('70) gave no weights, but stated that the brain often appears entirely normal in starved animals (guinea pigs, rabbits, cats, dogs), contrasting strongly with the loss of weight in other organs.

In the guinea pig, Lazareff ('95) found in guinea pigs (10 in each group) on total inanition with losses in body weight of 10, 20, 30, and 36 per cent corresponding apparent losses in brain weight averaging 1.51, 3.02, 5.54 and 6.05 per cent, respectively. Sedlmair ('99) obtained an apparent gain in the brain weight in 2 starved cats, but the difference in the initial weights in comparison with the control makes conclusions uncertain.

Donaldson ('11) stated that the relative weight of the central nervous system in the leopard frog (*Rana pipiens*) remains nearly constant during hibernation. Ott ('24) found that in this species the weight of the brain remains nearly constant during hibernation and subsequent inanition, although in the male during the later stages of inanition (with body loss of 50-60 per cent) there is an apparent loss of 15-22 per cent in brain weight (Table 6). The percentage of dry substance remains nearly constant.

Jackson ('15) in adult albino rats on water only (acute inanition series), with loss of about 33 per cent in body weight, noted an apparent loss of 5.1 per cent in brain weight. In the chronic inanition series (underfeeding), with loss of about 36 per cent in body weight, there is an apparent loss of 6.6 per cent in the brain weight.

**Brain Weight in Young Animals.**—In 8 rabbits 3 months and 20 days old, with average loss of about 33 per cent in body weight from starvation, Manassein ('69) noted that there was an apparent gain of about 3 per cent in the brain weight, as in adults. In 3 rabbits only 23-25 days old, with loss of 35 per cent in body weight, there was an apparent increase of 7 per cent in brain weight, indicating a persistent growth tendency (unrecognized as such by Manassein, however).

Von Bechterew ('95) found apparently a slight loss, or at least a greatly retarded growth, in the brain weight of newborn kittens and puppies on water only. Schukow ('95) confirmed and extended these results on puppies and chicks, concluding that there is not an actual decrease in the brain weight during inanition, but merely a retardation in growth.

Hatai ('08) stunted 5 litters of albino rats by moderate underfeeding beginning at 30 days of age, so that at 170 days they averaged only 91.5 g. in body weight (controls reaching 146.5 g). In the test rats the brain weight appears normal for corresponding body weight. Donaldson ('11), in a series of 22 litters of albino rats held at nearly constant body weight by more severe underfeeding from 30-51 days of age, found the average brain weight

7.7 per cent less than that in full-fed controls of the same age, but 3.6 per cent greater than the (calculated) initial brain weight. Aron ('11) noted that the brain weight in puppies underfed for long periods is nearly equal to that in the full-fed controls of the same age, but the lack of initial controls makes it impossible to estimate the amount of growth in brain weight during the under-feeding period.

The changes in the brain weight of albino rats of different ages during various degrees of underfeeding were studied by Jackson and coworkers, the results being epitomized in Table 4. Jackson ('15a) observed practically no change in the average brain weight of rats underfed for various periods beginning at the age of 3 weeks or later. Stewart ('18), however, found that if the underfeeding was begun at birth, allowing the body weight to increase slowly from about 5 g. to 15 g. at 10 weeks of age, the brain weight increases to 8 per cent above the normal for corresponding body weight. If the underfeeding is more severe, retarding the body weight to only 10 g. the brain weight increases to 60 per cent above the normal. In still severer inanition, holding the body nearly constant at birth weight for about 16 days, Stewart ('18a) found the brain weight 125 per cent above normal! Sugita ('18), in nursing rats retarded 29-39 per cent in body weight by underfeeding 3-4 days, similarly found the brain 24 per cent above the standard for corresponding body weight. Thus at this early age the brain shows a most remarkably persistent growth tendency during inanition, which enables it (with certain other organs) to grow at the expense of the remainder of the body. This tendency is apparently not so strong in the fetus, however, since Barry ('20, '21) found the brain only 12.5 per cent above normal weight in full term fetuses which had been retarded 40 per cent in body weight by maternal underfeeding during pregnancy.

Stewart ('18a) also studied the weights of the parts of the brain in albino rats held at birth weight (about 5 g.) for 5-18 days. The brain weight in this series averages 114 per cent above normal. In another series, the body weight was allowed to reach 10 g. at 3 weeks, and in these the brain weight appears 33 per cent above normal for corresponding weight. The weights of the various parts (cerebrum, cerebellum and brain stem) in general preserve approximately the same relative weight as in normal individuals having the same brain weight. The olfactory bulbs, however, appear hypertrophied in the younger group.

Data published by Trowbridge, Moulton and Haigh ('18) and by Moulton, Trowbridge and Haigh ('22) indicate that the brain weight in underfed young steers of various ages is both relatively and absolutely somewhat higher than in full-fed controls of the same body weight. This would indicate that in the bovine species, as in man and the rat, the growth of the brain during incomplete inanition appears relatively independent of the body as a whole.

**Recovery of Weight upon Refeeding.**—In young albino rats amply re-fed after underfeeding from 3 to 12 weeks of age, the weight of the brain was observed to be normal by Stewart ('16). In rats underfed from birth for various periods and then re-fed, Jackson and Stewart ('18, '19) found that the

brain does not preserve its relatively high weight, but instead soon lags behind in growth and appears below normal for corresponding body weight. As mentioned in Chapter IV, such rats were found by Jackson and Stewart ('20) to be permanently stunted in body weight. The brain weight in such dwarfed adults was found to be still slightly below the normal for body weight. This would seem to indicate that even though the brain grows persistently in weight during periods of severe subnutrition, it is nevertheless injured in some way so that it may not be able to recuperate fully when subsequently placed under good conditions of nutrition.

2. **Effects on Brain Structure.**—The effects of total inanition, or on water only, upon the structure of the brain in human and infrahuman adult and young will now be considered.

**Human Adult.**—Aside from occasional references to meningeal congestion or brain softening, no data concerning the effects of inanition upon the structure of the human brain are given by the earlier observers. Rokitansky ('54) stated that the nervous system, "so far as relates to its constituent elements, remains exempt," even during extreme general atrophy of the body. Cyr ('69) adopted Parrot's doctrine of an encephalic "steatosis" (to be mentioned later). Bright ('77) found, in a case of human starvation, the brain apparently normal, excepting a small tubercular area.

Popow ('82, '85, '85a) appears to have been the first to report cytological changes in the human brain cells, in a case of starvation from esophageal stricture. Hemorrhagic extravasations, proliferation of the neuroglia and connective tissue, atrophy and cloudy swelling of the ganglion cells were observed. These changes were held to be the possible cause of the mental disturbances observed in this case. As late as 1889, Filipi adhered to Parrot's doctrine of encephalic steatosis, while Cohnheim stated that the tissue of the central nervous system is but very slightly affected by inanition.

Tarassewitsch ('98) described the histological changes in the brain of a religious fanatic, aged 30 years, who died after 35 days of inanition. The Purkinje cells of the cerebellum show slight chromatolysis. The cells of the cerebral cortex present cytoplasmic vacuolation and pigmentation. The nuclei are usually peripheral in position, and stain diffusely, but are rarely changed in shape. Complete breaking down of the cells was not observed. The neuroglia appears loose in texture and the blood vessels congested. Dreyfuss ('06) considered the changes produced by inanition in the nerve cells during insanity as secondary in character. Agostini and Rossi ('07) described vacuolization of the nerve cells and changes in the neurofibrillae during inanition in the insane.

In a man who died of starvation, Meyer ('17) found the brain large (1600 g.) and edematous. The cells of the cerebral cortex appear shrunken, with wide pericellular spaces, and atrophy especially of the cytoplasm. In a victim of the Russian famine, Hassin ('24) found no macroscopic abnormalities in the brain and meninges. Microscopically some degenerative changes appeared, especially an accumulation of lipoids in the ganglion cells, glia, and blood vessels.

**Human Infants.**—The first detailed account of the changes in the brain of infants during inanition was that of Parrot ('68), who described a "steatosis" (fatty degeneration) as characteristic for various organs in athreptic infants. In the brain and spinal cord, the arachnoid presents irregular, yellowish, opalescent spots, due to fatty degeneration of the connective tissue cells. In the substance of the brain and cord, the neuroglia cells appear similarly infiltrated, forming fatty granulations, either microscopic or visible to the naked eye. The corpus callosum is most frequently affected. The cerebral vessels rarely show changes. In his classic treatise, Parrot ('77) described three chief lesions in the brain of athreptic infants—steatosis, hemorrhage and softening, none of which has been found characteristic by most of the later observers. Thiercelin ('04) concluded that the cerebral symptoms (coma, strabismus, convulsions) are due to cerebral congestion and toxemia, rather than to softening or hemorrhage.

Tardieu ('80) mentioned cerebral and meningeal congestion among the signs of death from inanition in the newborn. Talbot ('09) thought the arrested development of the facial region and teeth in malnourished children may be due to interference with the blood supply on account of malnutrition of the brain, "since the brain presides over the development of the tissues." Mönckeberg ('12) described the cell changes in "pedatrophy" as primarily an inanition-atrophy affecting all the organs and tissues in various degrees. Nicolaeff ('23) sometimes observed hyperemia and increase of ventricular and subarachnoid fluid in the brains of famine-stricken children.

**Adult Animals.**—Carville and Bochefontaine ('74, '75) noted that the meninges, brain and spinal cord appear congested in starved dogs. Falck ('75), on the other hand, found the meninges and brain anemic and firm, with a slight amount of fluid at the base of the brain and in the ventricles.

Mankowsky ('82), during inanition in rabbits and dogs, found the meninges and brain pale and edematous, with loss of weight. The cerebral and spinal ganglion cells show atrophic degeneration, with vacuolation, pigmentation, and fatty degeneration; some appearing shrunken and granular. The white substance and neuroglia are unchanged. The changes are sometimes general, sometimes in localized, softened areas. Two dogs were refed to normal weight after a long fast. In one the nervous system appeared anemic; in the other, hyperemic. The ganglion cells showed fatty degeneration, but not the atrophy found in the starved animals.

Rosenbach ('83, '84) described marked changes in the nerve cells of the brain and spinal cord in starved dogs, although the white substance and stroma are but slightly affected. The nerve cells react differently in different regions. The spinal ganglion and anterior horn cells suffer most, with marked atrophy, vacuolation and albuminous degeneration. The posterior horn cells show only cloudy swelling. The cerebellar cells rank next, with shrinkage and vacuolation of the Purkinje cells. The cells of the cerebral cortex show but slight traces of cloudy swelling. The pyramidal cells rarely present coagulation necrosis and vacuolation, but the round cortical cells are more strongly affected. The nuclei in these cells appear less resistant, and show granules, but the nuclear

contour is unchanged. Rosenbach believed that the nerve cells which appear latest in their embryonic development show the greatest resistance to inanition. Further details in the nerve cell changes were described by Rosenbach ('84a, '84c).

Ochotin ('86) studied the changes in the central nervous system in human starvation, also especially in rabbits subjected to various degrees of incomplete total inanition. The changes in the brain were found similar to those in the spinal cord, which will be described in the next chapter.

Coen ('90) studied the changes in 3 rabbits and a kitten after death from total inanition or on water only. The cerebral cortex shows notable atrophy of the nerve cells, with extensive pericellular spaces. The cytoplasm is much reduced, but the nuclei remain unchanged. The layer of small pyramidal cells appears most affected; next come the large pyramidal cells. The nerve fibers show fine, glistening granules, and free droplets of myelin occur, but the neuroglia appears normal. No marked vascular changes occur in the cortex or meninges.

Peri ('93) made a careful study of the nervous system in rabbits, cats and dogs after starvation with loss in body weight up to 45 per cent. He used various fixatives and stains, including those of Weigert, Marchi, Golgi, etc. The changes, both macroscopic and microscopic, in various regions of the brain and cord were found less marked than those described by previous investigators. Venous stasis, diapedesis and slight edema were noted, but no "steatosis." The nerve cells usually appear unchanged, a few showing a slight degree of atrophy but never marked degeneration. The silver methods of Golgi reveal nothing abnormal. The changes found in the spinal cord and sciatic nerve will be mentioned later. Recovery of the brain cells in dogs refed after fasting was described by Lubimoff ('94).

Monti ('95, '95a) obtained more definite changes in the brain cells of fasting rabbits, using the osmic-bichromate and Golgi methods. Some cells remain normal, but others show a "varicose atrophy" with degenerative changes beginning peripherally on the dendrites and extending toward the cell body. This may finally become involved, but the axone and nerve fiber are not injured. The number of cells affected and the extent of the degeneration vary greatly in different regions. In the cerebellum, the Purkinje cells are more resistant than the small cells of the molecular layer.

Bich ('95), in a study of the retinal changes in starved dogs, noted that the meninges appear normal; the brain substance anemic and always edematous.

Ganfani ('97), using the Nissl method, found no appreciable change in the brain cells of fasting rabbits, aside from slight decrease in staining ability. The changes in the spinal cord will be mentioned later.

Lugaro and Chiozzi ('97) used both Nissl and Golgi methods on the brain and cord of fasting dogs and rabbits. In general, changes appear in the nerve cells only in the later stages of inanition, and vary greatly in the site and the intensity of the lesions. The spinal ganglion, Purkinje and cerebral cortical cells are among the first affected, the anterior horn cells being the most resistant. The Nissl substance in the affected cells gradually undergoes chromatolysis, but

the achromatic parts and the nucleus are affected only in later stages. Degeneration of the dendrites was not observed. Since the cytological changes resemble toxic lesions, they concluded that the effects of inanition may be through autointoxication. Soukhanoff ('98, '98a), however, suggested that the toxic agents may interfere with the cellular nutrition, which might explain the similarity of toxic and inanitional lesions.

Daddi ('98, '98a) also found that in fasting dogs the nerve cell changes are in general slight, appearing in but few cells and in late stages of inanition. The chromatic (Nissl) substance undergoes a variable degree of chromatolysis; later the achromatic portion becomes degenerated and vacuolated. In general, the lesions appear more pronounced in the cerebrum, cerebellum and spinal ganglia than in the brain stem and spinal cord; the spinal ganglion and Purkinje cells being affected more than the cerebral. Daddi opposes the autointoxication theory of Lugaro and Chiozzi. Changes similar to those described by Daddi were found by Puglisi-Allegra ('00) in fasting dogs and guinea pigs. Marinesco ('00) and Mühlmann ('10) claimed that chronic nutritional disturbances of the nerve cells in the brain and cord result in pigment formation.

Marchand and Vurpas ('01) in fasting rabbits and guinea pigs found no appreciable changes in the cerebellum. The lesions in the cerebral cortex appear similar to, but slighter than, those in the spinal cord, which will be given in the next chapter. Geeraerd ('01) found the chromatolysis in the cortical cells of the guinea pig slighter in prolonged inanition than in fatigue. Weygandt ('04) briefly describes cortical lesions produced in mice by starvation or insomnia. Panella ('06) found a decrease in the nuclein content of the brain in fasting dogs.

Donaggio ('06, '07), using the silver method, found the neurofibrillae in the nerve cells of adult rabbits very resistant to either inanition or cold alone, but markedly affected by their combination. In general, the fibrolysis is less easily produced than chromatolysis. Coarser bands appear in the fibrillar network, probably by fusion of the fine neurofibrillae. The extent and character of the changes vary in different individuals, and also in different parts of the central nervous system. In the cerebral cortex, the lesions are less intense than in the cerebellum, brain stem and spinal cord. Vacuolation of the cells frequently occurs. Marinesco ('06, '09) described a hypertrophy of the neurofibrillae in nerve cells of kittens subjected to inanition, especially in combination with cold or intoxications.

Riva ('05, '07) found the neurofibrillae of the nerve cells in fasting dogs and rabbits in general very resistant to inanition, but the appearance may be greatly changed by the cytoplasmic vacuoles, which may displace and modify the neurofibrillar network. If the vacuoles are small or absent, the network remains normal. Balli ('07) produced marked lesions in the neurofibrillar network by a combination of inanition and thyro-parathyroidectomy.

In cats subjected to starvation, Beeli ('08) observed that in spite of the failure of the nervous system to lose in weight, degenerative changes occur in the nerve cells. In the cerebellum, the Purkinje cells undergo progressive shrinkage and vacuolation. The changes are less marked in the cerebral cortex. The gray and the white substance contrast sharply in gross appearance.

Following the subcutaneous transplantation of the cerebellum in white mice, Laignel-Lavastine and Jonnesco ('12) described a lipoidal degeneration in the Purkinje cells, which may be in part due to imperfect nutrition. Sundwall ('17) found congestion but slight cytological changes in the cerebral cortex of starved white rats. Asada ('19) made similar observations on fasting rabbits and Findlay ('21) in birds (pigeons and fowls). The papers of Damlevski ('91) and Frankenberger ('17) were inaccessible. The effects of inanition and other abnormal conditions upon nerve cells in general were reviewed by Barbacci ('99), Robertson ('99), Marinesco ('09) and Bardier ('13).

The changes in the nerve cells during **hibernation** have been studied by several investigators. Querton ('98) claimed that there is a partial retraction of the cortical neurones during hibernation, but this has not been confirmed. Chromatolysis with changes resembling those described in the nerve cells during starvation were found by Legge ('99) and by Barconcini and Beretta ('00) in the bat and other hibernating mammals. Cajal ('04) verified the observation of Tello that in reptiles coarse longitudinal neurofibrillae form during hibernation, but split up into finer fibrillae upon the awakening. Rasmussen and Myers ('16) found no significant change in the chromophilous (Nissl) substance in the woodchuck (*Marmota monax*) during hibernation. According to their review of the literature, Legge, Baroncini and Beretta, and Marinesco ('05) found marked changes in the Nissl substance during hibernation, while Levi ('98) and Zalla ('10) observed no chromatolysis. Rasmussen ('19) also found that "Complete inanition for 3 months during winter sleep and for 3 weeks after waking does not modify the morphology, number or distribution of mitochondria in nerve cells" (of cerebellum, spinal cord and spinal ganglia).

**Young Animals.**—A few observations are available concerning the effects of inanition upon the structure of the brain in young animals. Von Bechterew ('95) found the brain softened and hyperemic (especially the gray matter) in starved kittens and puppies. He concluded that:

"Die mikroskopische Untersuchung des Gehirnes der verhungerten Neugeborenen zeigte ausser den Gewebsveränderungen, welche dem Hungertode überhaupt eigenthümlich sind und in ausgeprägte Coagulationsnecrose und dem Myelinzerfall in den Markscheidenhaltigen Fasern bestehen, eine Verspätung in der Entwicklung und Markscheidenbekleidung derjenigen Systeme, welche bis zum Antritt der Hungerperiode noch unentwickelt waren."

The results of von Bechterew were confirmed and extended by Schukow ('95), who found that the retardation of growth in brain weight of fasting newborn puppies is due to failure of myelinization in tracts which had not already begun to myelinize. Since in dogs the brain fibers are the latest to myelinize, these parts are most retarded during inanition. In chicks 15-20 days old, the brain weight is much less retarded. Intensive coagulation necrosis occurs in the brain cells of fasting newborns. On refeeding, the lesions vanish and the brain recovers in weight and development. If the newborn puppies are merely undernourished by restricted nursing, the same pathological changes occur, but they develop much more slowly.

Reinke ('06) found that larvae of *Salamandra maculata* after successive exposures to 4 per cent ether solution may live up to 152 days, but take no food. The medullary tube becomes distended and thin-walled in 10 days; many cells perish, others undergo mitosis (up to 80 days). The final result is a partial regeneration of the central nervous system, which is nourished at the expense of the remainder of the body, especially of the musculature, which becomes strongly atrophied. Reinke further states: "Lässt man Salamanderlarven zunächst hungern und füttert sie dann sehr stark mit lebenden Würmern (Naiden), so treten etwa nach einer Woche eine enorme Menge von Mitosen in fast allen Organen auf, aber ganz regelmässig schubweise."

Sugita ('18), in the underfed young albino rats previously referred to, concluded from a histological study "that by starvation in the early days the brain suffers much in its development in toto, but the cell division is going on quite normally according to age. The growth of the cells in size is retarded and the formation of myelin fibers somewhat diminished by inanition. So the smaller weight and size of the underfed brain is due to an arrest in the growth and development of the constituent neurons and not to a decrease in their number."

*Changes in Chemical Composition.*—Although the chemistry of inanition is outside the scope of the present work, it may be noted incidentally that the brain undergoes relatively slight chemical changes during inanition. Its fat (lecithin) belongs to the phosphorized lipins, which in general are very resistant to starvation. In addition to those found in the papers above cited, data on the chemical changes in the brain during inanition are contained in the works of Aeby ('75), Pfeiffer ('87), Lukianov ('88, '89), Tonninga ('93), Voit ('94), Herter ('98), Durig ('01), Roger ('07), Donaldson ('11), and Donaldson, Hatai and King ('15).

#### (B) EFFECTS OF PARTIAL INANITION

The effects upon the brain by various forms of partial inanition, including dietary deficiencies in protein, fat, salts, vitamins and water, will now be considered.

**Protein Deficiency.**—Paltauf ('17) found the brain weight unaffected in cases of human malnutritional edema and allied conditions.

In a series of young albino rats with loss of about 30 per cent in body weight (initial weight 40-101 g.) on a nearly protein-free diet of starch, suet and water, Hatai ('04) found an apparent average decrease of about 5 per cent in the absolute weight of the brain. No marked alteration occurs in the Nissl substance. In a similar series of rats amply refed after the inanition period, Hatai ('07) obtained prompt recovery in the body weight and brain weight, although certain changes in the chemical composition of the brain (higher water content and lower percentage of ether-alcohol extracts) still persisted.

In albino rats held at nearly constant body weight for prolonged periods on various incomplete protein diets, Osborne and Mendel ('11, '11a) held that the normal proportions in the various parts of the body were maintained, excepting the possibility of a continued growth of the central nervous system, for which some evidence was cited.

Fröhner and Zwick ('15) noted that the brain (like the body in general) appears edematous in cattle on watery, low-protein diets. Koch and Voegtlin ('16) found loss in the weight, and changes in chemical composition, of the body, brain and spinal cord in monkeys and rats on diets of corn-oil cake, corn meal and sweet potatoes, etc. (mixed deficiency). They conclude: "This is, we believe, the first recorded instance in which such an atrophy of the central nervous system has been produced in animals by a change in diet." In monkeys and pigs on these diets, Sundwall ('17) found a variable degree of meningeal congestion, chromatolysis and other cell changes in the cortex, with occasional degeneration of fibers in the internal capsule. In albino rats stunted in growth by an inadequate maize diet (mixed deficiency) after weaning, Holt ('17) noted a slight increase in the brain weight. The relative weight of the olfactory bulbs appears reduced (*cf.* opposite result by Stewart ('18a) on rats underfed from birth), but the number of nerve cells therein is not affected.

**Pellagra.**—The enormous literature on pellagra (assumed to be due primarily to protein deficiency) contains many observations upon the associated changes in the brain, which are of especial interest on account of the frequency with which insanity follows pellagra. Only a few of the papers can be considered here, however. For more complete review of the pathology of pellagra, with extensive bibliographies, the works of Marie ('08, '10), Raubitschek ('15), Sundwall ('17), and Harris ('19) may be consulted.

The pioneer in this field was Lombroso ('69), who emphasized the importance of the brain lesions in pellagra, including thickening and opacity of the meninges, edema and softening of the cerebrum, atrophy of the cerebral cortex, abundant corpora amylacea, and fatty and pigmentary changes in the cortical brain cells. Fraenkel's ('69-'70) extensive data were chiefly from Lombroso's clinic. Fraenkel in 113 autopsies found meningeal thickening in 33, purulent exudate in 4, subarachnoid hemorrhages in 5, marked brain edema in 24, atrophy of cerebral cortex in 11. The brain weight was variable; in 28 cases, 7 appeared increased and 8 decreased.

Tuczek ('93), however, in a careful study of 8 cases of pellagra, found nothing abnormal in the cerebral cortex, cerebellum, pons and medulla, although the nerve cells of the cranial nerve nuclei appear richly pigmented. Rossi ('98) noted cytoplasmic vacuolation, pigmentation and disintegration of the Nissl bodies, sometimes also nuclear displacement and degeneration, in the cerebral cortical cells of pellagrins. These findings in the brain cells were confirmed and extended by Babes and Sion ('00), and several other investigators cited by Harris ('19). Parhon and Papinian ('05) and others demonstrated lesions in the neurofibrillae of the pyramidal cells in the cerebral cortex, especially in the large Betz cells. Marinesco ('09) found that the brain cells undergoing chromatolysis also show pigmentary degeneration. The neuroglia proliferates. He found, as an exception, that the cells of Purkinje remain normal; but Harris ('10) noted marked degenerative changes in the Purkinje cells in one case. Hamill ('12) observed a variable chromatolysis in the large pyramidal cells of the cortex.

The changes in the brains of insane pellagrins were thoroughly studied by Kozowsky ('12), who found the meninges variably hyperemic and thickened.

The brain is always markedly sclerosed in all parts, sometimes edemic. There is proliferation of the neuroglia, and the corpora amylacea probably represent altered glia cells. The nerve cells of the brain all show a variable degree of change. Pigmentation is the commonest (also found in the sympathetic ganglia). The tigroid (Nissl) substance undergoes granular disintegration, first in the circumnuclear zone; later the whole cell becomes homogeneous, sometimes greatly vacuolated; the nucleus may be displaced and finally disappears; ultimately the whole cell may disintegrate into several small masses. The degree of cell change is proportional to the length of the period of insanity.

Mott ('13) also found degenerative changes with a variable degree of chroma-lysis and lesions of the neurofibrillae in the Betz and Purkinje cells in a case of pellagra. The changes are less intensive than those found in the spinal cord (to be mentioned later).

**Fat Deficiency.**—In several rats which had been fed by McCollum on lipid-free rations, with retarded growth of the body, Hatai ('15) found the brain and spinal cord each apparently reduced about 2 per cent in weight, the gray substance being affected more than the white. In 45 human autopsies in cases of edema apparently due to insufficient food, especially poor in fat and protein, Prince ('21) observed no macroscopic lesions in the nervous system.

**Salt Deficiency. Rachitis.**—In human rickets, the occurrence of hydrocephalus was noted by Whistler (1645) and Glisson (1650). Seibold (1827) noted an increase in the fluid of the brain ventricles (also subdural), and an enlargement of the Pacchionian bodies. Comby ('01) found a variable tendency to hydrocephalus in rachitic infants, and Stoeltzner ('03) mentioned mild hydrocephalus as a possibly significant condition. Cheadle and Poynton ('07) likewise believed that the brain may be involved in rickets. Pfaundler ('22) states that in human rickets the brain is enlarged, as though swollen; vascular congestion causes ventricular dropsy, and the softened cranium permits hydrocephalic enlargement. Karger ('20) claims that the enlargement of the rachitic brain is not due to hydrocephalus. "In den bekannten grossen rachitischen Schädeln findet sich in der Regel kein Hydrozephalus, sondern ein abnorm grosses Gehirn; in diesem sind bisher mikroskopisch keine wesentlichen Abweichungen von normalen nachgewiesen worden und die Versuche, diese Frage auf chemischen zu beantworten, haben bis jetzt zu eindeutigen Ergebnissen nicht geführt."

Neurath ('24) reviews the neurologic changes in rickets, especially the cerebral changes, which are associated with mental retardation in infants.

In dogs and pigeons on low salt diets, Forster ('73) observed weakness, trembling and paralysis, but no macroscopic lesions of the central nervous system at autopsy. In puppies on calcium-poor meat and lard diet, producing a rachitic (or pseudorachitic) condition, Voit ('80) found the brain weight nearly normal or possibly (as he thought) above normal. Quest ('06) demonstrated that the brain in such rachitic puppies shows an increased water content, but normal calcium content. Jackson and Carleton ('23) found the brain weight nearly normal in a large series of albino rats in various stages of experimental rickets.

**Vitamin Deficiencies.**—Aside from rickets, which (as stated in Chapter V) probably involves a vitamin factor in addition to the mineral deficiency, the brain has been studied in beriberi (vitamin B deficiency) and scurvy (vitamin C deficiency). Meyerstein ('22) made a few observations on the brain in young white rats on diets deficient in vitamins A and B. Lopez-Lomba ('23) found the brain unchanged in weight in pigeons on a vitamin-free diet.

**Beriberi.**—The conspicuous neural symptoms in beriberi clearly indicate lesions of the nervous system. These have been found chiefly in the spinal cord and peripheral nervous system, but Rumpf and Luce ('00) cited observations by themselves and previous investigators indicating hyperemia and edema of the brain, and occasionally slight hydrocephalus internus, in human beriberi. In experimental beriberi of pigeons, chicks, cats, dogs and white mice, no definite change was found in the nervous system.

Walshe ('18, '20) has recently reviewed the literature and finds that "Since the original investigations of Baelz, Scheube, Pekelharing and Winkler (1882-1887) there has been a striking unanimity among pathologists that the nervous lesion of beriberi is not specific for the disease, and is not to be distinguished from that of a toxic polyneuritis." Walshe agrees with Eijkman that even though beriberi be due to a vitamin deficiency ("Teilhungertheorie"), the ultimate cause may yet prove to be a nervous poison produced by a disordered metabolism arising from vitamin deprivation.

McCarrison ('19, '19a, '21) believes that absence of the so-called "anti-neuritic" factor, vitamin B, leads to functional and degenerative changes, not only in the central nervous system, but also in every organ and tissue in the body. In pigeons on a diet of autoclaved rice with butter and onions (deficient in protein as well as in vitamin B), the brain shows an increase of 14 per cent in weight, although this increase does not appear in polyneuritic pigeons on rice diet alone. According to Findlay ('21) the brain in avian beriberi, though nearly constant in weight (Table 13), shows a loss of Nissl granules and a decrease in nucleic acid content, both of which are restored upon administration of vitamin B. Hofmeister ('22) found in severe beriberi of rats marked lesions with hemorrhages in the cerebellum and brain stem, which are proportional to the nervous symptoms, and lead to degeneration of the brain cells. As no evidence of a degeneration in the peripheral nerves was found, the condition in rats is considered not a polyneuritis but rather a *cerebral purpura* similar to the hemorrhagic encephalitis which occurs in chronic poisoning with alcohol, lead or arsenical compounds.

**Scorbutus.**—In scurvy, there are in general no specific changes in the nervous system, aside from occasional hemorrhages, which Sato and Nambu found in the brain once in 6 cases. There are no definite changes in the nerve cells or fibers, according to the literature reviewed by Hess ('20). Bessesen ('23), however, found an apparent average increase of 10-12 per cent in the weight of the brain in scorbutic guinea pigs (Table 12). This is due to the fact that the loss in brain weight is relatively less than the loss in body weight.

**Aqueous Inanition.**—Schuchardt ('47) noted an apparent loss of 6 per cent in the weight of the brain and cord in pigeons with loss of 44 per cent in body

weight on a dry barley diet. In a dog with loss of 20 per cent in body weight after 4 weeks on dry food, Falck and Scheffer ('54) found an apparent gain of 7.2 per cent in the weight of the brain, in comparison with a control; but the water content remained normal. Bowin ('80), in rabbits and dogs on a dry diet with marked loss in body weight, apparently obtained an increase in the relative weight and the water content of the brain, but the exact data are lacking in the abstract by Mühlmann.

Pernice and Scagliosi ('95, '95a) studied the effects of a dry diet upon a dog and 3 half-grown chicks, which died with loss of 24-41 per cent in body weight. In the dog, the meninges and brain were strongly congested. The various layers of nerve cells and fibers in the cerebral cortex in general appear cloudy, poorly staining with carmine, and often distinctly atrophic. The fibers stain poorly by the Pal-Weigert method. The cerebellum also appears markedly hyperemic, with degenerative changes especially in the superficial molecular and the Purkinje cell layers. In the chicks, somewhat similar changes were found. Atrophy and cloudy degeneration are especially evident in the large pyramidal cells. Similar atrophic and degenerative changes appear in the cells of the cerebellar cortex and in the gray substance of the medulla oblongata.

The effects of a dry diet upon the brain weight in albino rats were noted by Kudo ('21, '21a), as shown in Tables 9 and 10. The brain was often found markedly congested, especially in the adult. In the adult acute thirst series, with average loss of 33 per cent in body weight, the brain weight remains unchanged; while in the chronic thirst series, with loss of 52 per cent in body weight, the average loss in brain weight is 4.2 per cent. In young albino rats held at nearly constant weight on relatively dry diets from one month of age for various periods (up to 13 weeks), the brain weight shows no significant change.

## CHAPTER XI

### EFFECTS ON THE SPINAL CORD

The spinal cord, like the brain, appears relatively resistant to the effects of inanition, although the nerve cells show marked degenerative changes in certain types of partial inanition (pellagra, etc.). After a brief summary, the effects of inanition upon the spinal cord will be considered under (*A*) total inanition, and (*B*) partial inanition.

#### SUMMARY OF EFFECTS ON THE SPINAL CORD

In general, as might be expected, the changes in the spinal cord during inanition resemble those in the brain, although differing in some details. In **weight** the adult spinal cord suffers little or no loss, the decrease usually being less than 10 per cent, even at death from either total or partial inanition. In young animals during inanition the spinal cord, like the brain, exhibits a persistent growth with retarded or even declining body weight. This may occur during partial inanition (scurvy, aqueous inanition). Upon ample refeeding after a period of inanition, the spinal cord usually recovers its normal proportionate weight, although after severe or prolonged inanition in young animals the later growth of the spinal cord upon refeeding may be subnormal.

The **structural changes** in the spinal cord are also in general comparatively slight, especially in the white substance, although congestion is frequent and variable changes in the gray substance appear, especially in the later stages of inanition. These changes resemble those found in the brain, sometimes being less intensive but often more so. During **total inanition** (complete or incomplete) the nerve cells, especially in the anterior horn, may undergo atrophic degeneration with a variable degree of cytoplasmic vacuolation, chromatolysis, neurofibrillar derangement, and nuclear enlargement or pycnosis, rarely karyolysis or karyorrhexis. In extreme cases, some cells may degenerate and disappear entirely; while others show comparatively slight changes. The medullated fibers may show diffuse degenerative changes, probably secondary to the disturbances in the nerve cells. Proliferation of the neuroglia may occur. The changes during hibernation are comparatively slight.

In the various forms of **partial inanition**, the structural changes in the spinal cord in general resemble those during total inanition, with certain special features in addition. In protein deficiency (including pellagra) the congestion is greater and degenerative changes in the nerve cells are usually more intensive, involving pigmentary degeneration and frequently total necrosis and disintegration, especially in some regions. There are also more extensive degenerative changes in the white substance, especially in the posterior and

lateral columns, with associated sclerosis, due to proliferation of the neuroglia. Ependymal proliferation often obliterates the central canal. In beriberi and scurvy, the changes in the cord are slight, but in aqueous inanition (thirst) the degenerative changes, like those in pellagra, are markedly intensive. The structural changes found during the various types of inanition are not specific, but resemble those produced by various toxic agents and other abnormal conditions.

#### (A) EFFECTS OF TOTAL INANITION, OR ON WATER ONLY

These effects will be considered under (1) changes in weight and (2) changes in structure.

1. **Changes in Weight.**—For the changes in weight of the **human** spinal cord during inanition, no data have been found in the literature. In 4 cases observed by me, in which the spinal cord was weighed in atrophic infants (see Table 3), there appears to have been little if any loss in weight in this organ; but conclusions are uncertain on account of the small number of cases and the lack of an adequate norm for comparison.

**In Adult Animals.**—Chossat ('43) found in starved pigeons an apparent decrease in average weight of the spinal cord from 0.83 g. to 0.77 g. or a loss of 7.2 per cent (body loss about 40 per cent). In 3 marmots hibernating about 166 days, with average loss of 35.5 per cent in body weight, Valentin ('57) noted an apparent decrease of only about 3 per cent in the weight of the spinal cord. Voit ('66) observed an apparent loss of about 3 per cent in the combined weight of brain and cord in a cat starved with loss of 33 per cent in body weight. Manassein ('68, '69) found the average weight of the spinal cord practically unchanged in 11 adult rabbits starved with loss of about 39 per cent in body weight. In a normal control dog of 15.4 kilograms body weight, studied by Voit ('94), the spinal cord weighed 22.6 g. while in a test dog reduced by starvation from 17.4 to 11.78 kilos the spinal cord weighed 23.5 g.

In 4 groups of guinea pigs (10 in each group) on total inanition with average losses of 10, 20, 30 and 35.5 per cent in body weight, Lazareff ('95) found an apparent increase of 1.05 per cent in the average weight of the spinal cord in the first group, and losses of 6.82 per cent in each of the other 3 groups (Table 5). Sedlmair ('99) apparently obtained a slight increase in the weight of the spinal cord in 2 starved cats, but the difference of initial body weights in comparison with the control makes conclusions uncertain. Jackson ('15) found the average weight of the spinal cord practically unchanged in adult albino rats in the acute inanition series (on water only), with loss of 33 per cent in body weight; while in the chronic (incomplete total) inanition series, with loss of 36 per cent in body weight, there is an apparent average loss of 4 per cent in the weight of the spinal cord. Ott ('24) observed in frogs but slight loss in the weight of the spinal cord during hibernation and with losses in body weight up to 40 per cent. With losses of 50 and 60 per cent, however, there was an apparent loss of 14 and 25 per cent, respectively, in the male frogs (Table 6). In general, therefore, as in the brain, there is little or no loss in the weight of the spinal cord during starvation, excepting extreme stages.

In young animals, the spinal cord was observed by Bechterew ('95) to increase in weight in fasting newborn kittens and puppies, even with decrease in body weight. Hatai ('08) found the spinal cord weight apparently normal for the body weight in albino rats underfed from 30 days of age to 170 days, the body weight being retarded to 91.5 g. (controls of same age reaching 146.5 g.). Donaldson ('11a), however, noted an apparent increase in the spinal cord of albino rats held at about 34 g. in body weight from age of 30 days to 51 days.

The changes in the weights of the spinal cord in young albino rats underfed at various ages by Jackson and his associates are shown in Table 4. In rats held at constant body weight by underfeeding from 3 to 10 weeks of age (or later), Jackson ('15a) found an increase of about 36 per cent in the weight of the spinal cord. In rats underfed from birth, Stewart ('18, '19) obtained still more intensive growth of the spinal cord, which averaged 70 to 83 per cent above the normal for corresponding body weight. In the newborn offspring retarded by maternal underfeeding during pregnancy, however, Barry ('20, '21) did not find this intensive growth, the spinal cord being nearly normal in weight.

The weight of the spinal cord was found above the normal for corresponding body weight in young steers with growth retarded for long periods on subnormal rations by Trowbridge, Moulton and Haigh ('18), and Moulton, Trowbridge and Haigh ('22, '22a, '22b). This would indicate that in the bovine species, the spinal cord, like the brain and skeleton, shows a persistent growth on a low plane of nutrition.

**Effects of Refeeding.**—In young rats amply refed after underfeeding from 3 to 12 weeks of age, Stewart ('16) found that the spinal cord had returned to its normal weight in proportion to the body within two weeks. In rats underfed from birth for various periods (resulting in relative hypertrophy of the spinal cord), and then amply refed to body weights of 25 to 75 g., Jackson and Stewart ('19) found the spinal cord 7.5 to 11.2 per cent below normal weight after the longer underfeeding periods, indicating an inhibitory after effect of inanition, similar to that previously mentioned for the brain. Likewise in young rats permanently stunted by early or long periods of underfeeding, Jackson and Stewart ('19a, '20) found that the spinal cord failed to reach a weight proportional to that normally found at corresponding body weight.

2. **Changes in Structure. Human Adults.**—Ochotin ('86) described the nerve cells in the spinal cord of a very emaciated young man (with mandibular necrosis, anemia, chancroids, etc.). The cells appeared normal in form and size, but mostly cloudy or granular; nuclei variable, sometimes normal or even enlarged, rarely appearing filled with lymphoid corpuscles (nuclear fragmentation?).

In a woman in whom death from chronic starvation was suspected, Placzek ('98, '99) found the spinal cord macroscopically normal, but microscopically showing variable atrophic degenerative changes in the anterior horn cells. In the earlier stages of degeneration the Nissl bodies appear slightly irregular and the nucleus peripherally placed; in advanced stages the Nissl bodies are destroyed, the cytoplasm atrophic, and the nucleus shows pycnosis or karyorrhexis. In the cervical and thoracic regions of the cord, many of the anterior

horn cells are reduced to small structureless remnants or have totally disappeared. The Marchi method also shows diffuse degeneration in the nerve fibers of the white substance.

In a man who died from starvation, atrophic changes were likewise found by Meyer ('17) in the anterior horn cells. "The nuclei are small and fragmentation of some nuclei apparently has taken place in these cells, and considerable loss of material has occurred. Some of the cells are mere remnants and all are surrounded by very wide clear zones. Clear areas are also scattered throughout the gray substance." The fiber tracts of the cervical cord and a dorsal nerve root "contain many more neuroglial cells than are normally present. Considerable shrinkage and vacuolation of the myelin are present, and the cross sections of the fibers are irregular in outline."

In the **human infant**, Parrot ('68, '77) described as characteristic for athrepsia a steatosis (fatty degeneration) in the meninges and neuroglia of the spinal cord, as previously mentioned for the brain. Thiemich ('00) found in the spinal cord of atrophic infants by the Marchi method variably degenerative changes in certain tracts, but no correlation of these lesions with clinical nervous symptoms was evident.

In **adult animals**, certain effects of inanition upon the structure of the spinal cord were mentioned in the preceding chapter in connection with similar changes in the brain, as observed by Mankowsky ('82), Rosenbach ('83, '84), Lugaro and Chiozzi ('97), and Daddi ('98, '98a). Rosenbach found the degenerative changes more apparent in the nerve cells of the spinal cord than in the brain cells; while Lugaro and Chiozzi and Daddi found the anterior horn cells more resistant, especially with reference to the Nissl granules.

Carville and Bochefontaine ('74, '75) noted congestion of the meninges, brain and spinal cord in a starved dog. The fat around the spinal cord, like the orbital, appears transformed into a gelatinous, amorphous mass. Schulz ('84) maintained that the vacuoles described by Rosenbach in the nerve cells during starvation are artefacts.

Popov ('85) described marked changes in the spinal cord of starved rabbits (total inanition), including proliferation of the neuroglia, congestion and sometimes hemorrhage. The nerve cells show variable degenerative characters; some atrophic, with scanty granular or homogeneous cytoplasm (the granular sometimes more peripheral and the homogeneous circumnuclear), or even naked nuclei. In other cases the nucleus appeared more active, with "Kernfiguren," occasionally double or multiple (fragmented?) nuclei.

Ochotin ('85, '86) studied rabbits subjected to various degrees of complete or incomplete total inanition. In both types the changes appear greatest in the lower and upper parts of the spinal cord. Congestion and hemorrhage are conspicuous in the incomplete (chronic) inanition, but not in the complete. In animals killed after loss of 10 to 13 per cent in body weight during complete inanition, or 14-30 per cent during incomplete inanition, the nerve cells show beginning degeneration with whitish appearance. In more advanced stages, the cells show variable degenerative changes. Some are greatly enlarged, with disintegrated or obliterated nuclei (sometimes multiple) and vacuolated,

poorly-staining cytoplasm. Others show cloudy or granular cytoplasm, the nuclei staining well with carmine. The coagulation necrosis and plasmatic exudate described by Rosenbach were not found.

Downarowitsch ('92) was apparently the first to make systematic nuclear measurements of the nerve cells, in 3 rabbits killed after 8 days of total inanition with loss of about 40 per cent in body weight. In these and 3 normal controls, the cervical and lumbar enlargements of the cord were fixed in mercuric chloride and the long and short axes of the nuclei of 600 anterior horn cells measured in stained sections. From the average measurements, the corresponding volume of the nucleus (assumed to be an ellipsoid) was calculated to be 1115.97 cubic micra in the normal, and 832.47 cubic micra after inanition, indicating a decrease in volume of 25.4 per cent. The nucleolus was also measured, and its average volume (considered spherical) apparently loses 42.5 per cent during inanition.

Peri ('92, '93), carefully studied various regions of the central and peripheral nervous system by various methods (Weigert, Marchi, Golgi, Cajal, etc.). Grossly only venous stasis and mild edema were found, never the "steatosis" described by Parrot ('68), Filipi ('89) and others. Histologically, but very slight changes appear in the rabbits, probably on account of the short duration of inanition (3-5 days, with water); in the cats (fasting 15 days, with loss of 43-45 per cent in body weight) the changes were somewhat greater; and in the dogs (fasting 27-34 days, with loss of 43-44 per cent) the changes were greatest. But even in the dogs most of the nerve cells in the brain and spinal cord appear normal, relatively few showing degenerative changes. In the anterior horn cells, hyalin degeneration occurs rarely, with nuclear disappearance; but the Marchi and silver methods show nothing abnormal. The neuroglia appears normal, but diapedesis is somewhat frequent. Peri ascribed the degenerative appearances described by Mankowski, Rosenbach, Popow and Coen to the inadequacy of the older technique employed.

Barrows ('98), using Hodge's method measured the nerve cells of the spinal cord, spinal ganglia and occipital cortex in 3 starved rats with normal controls, and found:

"(1) A decided shrinkage in size of the cells and nuclei in the famished animals, averaging about 20 per cent, and a still greater shrinkage in the nucleoli.

"(2) An evident exhaustion of the substance of the famished cells, as shown by their faint staining with osmic acid and the notable absence of nuclei and nucleoli. The protoplasm of these cells shows a very fine vacuolation, not so marked as that described by Rosenbach for starving animals and by Hodge for extreme fatigue. In the brains of famished rats the pericellular lymph spaces are considerably enlarged."

About this time, the Nissl method was introduced and was applied by several investigators to the nerve cells of animals subjected to inanition. Tauszk ('94), a pioneer in this field, found by this method that chromatolytic changes appear more distinct in chronic than in acute inanition, and were most apparent in the cervical region of the spinal cord in rabbits. Ganfini ('97), in rabbits killed after 5-7 days of inanition, found the most marked changes in the anterior

group of the anterior horn cells (Fig. 61). In these cells the Nissl granules undergo chromatolysis, and the nucleus appears swollen. Schaffer ('97) noted that the chromatolytic changes in the anterior horn cells of fasting rabbits are more intensive, and accompanied by greater vacuolation of the cytoplasm, in total inanition, than with water only. The nucleus also becomes deeply stained throughout. Jacobsohn ('97) failed to confirm Schaffer, however, and Placzek ('99) found no nuclear changes, but merely chromatolysis (also some degeneration in the posterior column by the Marchi method). The work on nerve cell changes during inanition up to 1898 was reviewed by Barbacci ('99), Robertson ('99), and more recently by Marinesco ('09).

Further studies on the anterior horn cells of fasting rabbits and guinea pigs were made by Marchand and Vurpas ('01), using various stains (picrocarmine, haematoxylin, Nissl's, Pal-Weigert, Marchi and Golgi methods). The changes

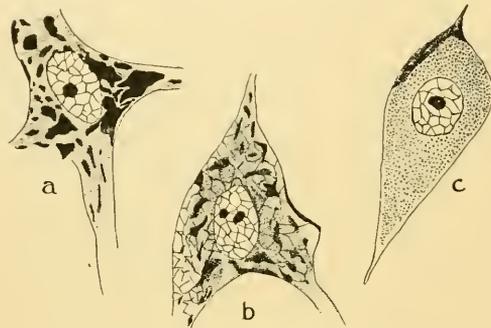


FIG. 61.—Nerve cells from the ventral horn of the spinal cord in the rabbit, stained by Nissl's method. *a*, cell from normal control; *b*, *c*, cells showing the progressive disintegration of the Nissl bodies after 5 to 7 days of total inanition. (Ganfini '97.)

are described in 3 stages, with intermediate forms: (1) cell size unchanged; cytoplasm becomes decolorized, with pale Nissl granules; nucleus central and unstained, with distinct nucleolus; (2) cell somewhat shrunken, with fewer and thicker processes; Nissl bodies finely granular; nucleus eccentric and irregular in form, deeply staining with nucleolus still distinct; (3) preceding changes more extreme, with irregular cell outline, shorter and less numerous cell processes; deeply-staining, non-granular, vacuolated cytoplasm; nucleus atrophied and deeply staining or disappeared; no cell pigment. The lesions appear by various stains, best by Nissl's method. The neuroglia and medullated nerve fibers appear normal.

Holmes ('03) described chromatolysis, vacuolation and nuclear swelling in the nerve cells of the spinal cord in frogs subjected to exhaustion and inanition; and Mourre ('04) similarly found chromatolysis in the nerve cells of guinea pigs. Gurewitsch ('08) found chromatolysis to a slight degree in starved rabbits; but more pronounced in dogs, surviving for a longer period. The changes found by various investigators in the nerve cells during hibernation will be mentioned later

We come now to the era of investigation of the intracellular neurofibrillae. By means of a modified silver method, Cajal ('04a) and Dustin ('06) demonstrated marked changes in the nerve cells of leeches starved 2 months or more. There is partial degeneration and resorption of the neurofibrillar network; the fibrillae thicken, the meshes become narrower, and finally the nucleus breaks up into irregularly scattered, deeply-staining granules. A similar thickening of the neurofibrillae probably occurs in the nerve cells of adult mammals (dog and rabbit) subjected to cold, especially in combination with inanition.

Donaggio ('06, '07) likewise obtained modifications of the endocellular network of neurofibrillae in the nerve cells of rabbits under the combined influence of cold and inanition, neither factor alone appearing effective. In the anterior horn cells, the fine fibrillar network presents coarser bands, possibly formed by fusion of the neurofibrillae. Riva ('05, '06, '07) also found that inanition alone usually produces relatively slight changes in the neurofibrillae of the brain, spinal cord and spinal ganglia in fasting dogs and rabbits (Fig. 62). The endocellular network may be considerably modified, however, in cases where large vacuoles cause mechanical displacement of the neurofibrillae. The results of Donaggio and Riva were confirmed and extended by Gurewitsch ('08a) in the spinal cord of fasting rabbits and dogs, and by Mattioli ('10) in rabbits. The

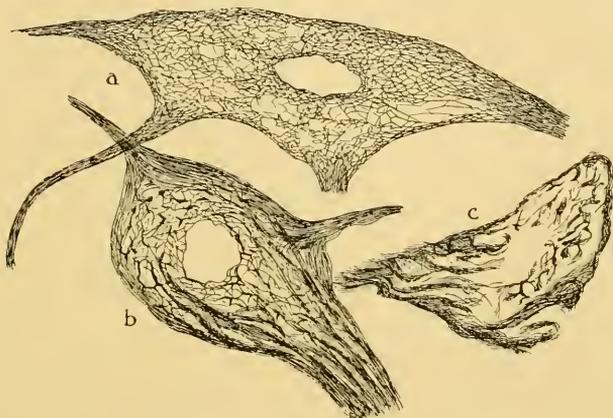


FIG. 62.—Nerve cells from the ventral horn of the spinal cord in the dog, showing the variable changes in the neurofibrillae by Donaggio's silver method after a loss of about 50 per cent in body weight from total inanition. *a*, a cell in which the neurofibrillae have retained nearly normal structure; *b*, cell showing some vacuolation in the perinuclear region; *c*, cell with disorganized neurofibrillae crowded into bundles between the numerous large cytoplasmic vacuoles. (Riva '06.)

literature on these effects of inanition upon the nerve cells in general is fully reviewed by Marinesco ('09).

In *Necturus maculatus* starved 4 months the spinal cord was found nearly normal by Smallwood and Rogers ('11). After 16 months, however, the spinal cord appears greatly reduced in size, with atrophy especially of the gray substance. Changes found in the spinal ganglia will be mentioned in the next chapter. In the nerve cells of the spinal cord in *Triton cristatus* fasting 1-6 months, Frankenberger ('17) described nuclear changes resembling pycnosis.

In starved albino rats (on water only), Sundwall ('17) noted marked congestion and edema of the spinal cord; anterior horn cells swollen, vacuolated and chromatolytic, with vesicular or pycnotic nuclei. There is diffuse degeneration of the various nerve fiber tracts, especially in the posterior columns.

**Changes during Hibernation.**—Since hibernation represents a special type of inanition, the corresponding changes in the nerve cells of the spinal cord may be separately considered. (The observations on the brain cells during hibernation by Querton '98, Legge '99, Baroncini and Beretta '00 and Marinesco '05 were mentioned in Chapter X.) First as to the Nissl substance, no appreciable change

in the anterior horn cells was found in the hibernating hedgehog (*Erinaceus*) by Jacobsohn ('97) and Levi ('98). The results of Zalla ('10) were negative for the dormouse (*Myoxus glis*), and inconstant for amphibia (*Rana*, *Bufo*, *Bombinator*). Rasmussen and Myers ('16), who reviewed the literature in detail, could find no change in the hibernating woodchuck (*Marmota monax*). On the other hand, definite seasonal changes in the Nissl substance were found by Bühler ('98) in the frog; likewise by Levi ('98) in *Rana*, *Bufo* and *Zamenis viridis* (adder). Chromatolytic and other nerve cell changes during hibernation were observed by Legge ('99) in hibernating bats (*Vespertilio murinus*, *Rinolophus ferrum equinum*, etc.); by Baroncini and Beretta ('00) in *Myoxus*, *Vespertilio* and *Vesperugo*; by Marinesco ('05) in *Erinaceus*; by Cutori ('07, '08) in *Testudo graeca*; and by Zalla ('10) in reptiles (*Lacerta*, *Zamenis*, *Tropidonotus*).

The changes in the neurofibrillae during hibernation may be due to the combined effect of cold and inanition. Tello ('03) found in dormant lizards the appearance of unusually coarse neurofibrillae in the motor cells of the anterior horn, but not in the brain cells. Cajal ('04 '04a) and Dustin ('06) obtained similar results in leeches and in mammals exposed to cold, especially during fasting. The coarse fibrillae apparently split up again upon the awakening and resumption of activity. Marinesco ('05) noted similar results in young cats and dogs, but no change in the hibernating hedgehog (*Erinaceus*). Cutore ('07, '08), however, found somewhat different changes in the anterior horn cells of *Testudo graeca* during hibernation, the peripheral zone of cytoplasm becoming vacuolated and the neurofibrillae more attenuated. Rossi ('10, '10a) noted the thickening of the neurofibrillae in the hibernating adder (*Zamenis*) and dormouse (*Myoxus*). Zalla ('10) also obtained the characteristic changes of the neurofibrillae in reptiles, and also (less markedly) in mammals (*Myoxus*). These changes in the neurofibrillae apparently have no definite relation to the changes in the chromophile (Nissl) substance, however, and represent a non-specific reaction to various pathological conditions. The conflicting results obtained by various investigators doubtless depend chiefly upon differences in species, in the technique employed, and in the stage of hibernation studied.

As mentioned in Chapter X, Rasmussen ('19) found no change in the morphology, number or distribution of the mitochondria in the nerve cells of the cerebellum, spinal cord or spinal ganglia in the woodchuck (*Marmota monax*) after 3 months of hibernation and even after 3 weeks of further inanition upon awakening.

The experiments of Reinke ('06) on the **regeneration** of the central nervous system of etherized (fasting) Salamander larvae were mentioned in Chapter X. Rossi ('10, '10a) studied the phenomena of regeneration in the spinal cord of the adder (*Zamenis viriflavus*) and the dormouse (*Myoxus glis*) during hibernation. The regenerative process appears to be somewhat retarded, especially in the cold-blooded animals, as shown by the Cajal method.

#### (B) EFFECTS OF PARTIAL INANITION

The effects of partial inanition upon the spinal cord have been observed chiefly in protein deficiency (pellagra), vitamin deficiency (beriberi and scurvy),

and water deficiency. A slight relative atrophy of the brain and spinal cord of albino rats on a lipid-free ration was observed by Hatai ('15), as mentioned in Chapter X.

**Protein Deficiency.**—Hatai ('07) found that in albino rats 1 month old, subjected to a starch-fat diet for 3 weeks (with marked loss in body weight) and then amply refed on mixed diet, the spinal cord and brain, as well as the body, recovered normal weight, though certain differences in chemical composition appear. Koch and Voegtlin ('16) observed marked loss in weight of the spinal cord and brain, as well as of the body, in monkeys and rats on protein-poor diets of corn-oil cake, corn meal, sweet potatoes, etc. (mixed deficiency). In these monkeys, Sundwall ('17) found meningeal congestion, degeneration of Burdach's column in the cervical region and of Goll's column in the dorsal region, with swelling and chromatolysis of the cells in the anterior horn and spinal ganglia.

**Pellagra.**—Although degenerative lesions of the spinal cord in pellagrins were noted by Lombroso ('69), the first detailed account was given by Tonnini ('83, '84). In 51 cases, he found the meninges anemic in 8; opaque and thickened in about half; calcareous infiltration of the arachnoid in 27. These changes appear rare in the cervical region. The cord is usually asymmetrical and anemic; hyperemia and softening were found in 20 cases. In 13 cases studied microscopically, great pigmentation of the anterior and the posterior horn cells appears in 8; and granulo-pigmentary degeneration is frequent. Cell atrophy was noted once in the cervico-dorsal, and twice in the lumbar region. Degeneration was found twice in the lateral column and once in the posterior. Belmondo ('89) examined 8 cases and likewise found in severe pellagra a sclerosis of the posterior and lateral columns, involving the crossed pyramidal tracts, together with changes in the pia and gray substance (chiefly pigmentary atrophy). Corpora amylacea occur and the central canal may be closed by ependymal proliferation. Similar changes were found in 8 cases by Tuzcek ('93) in the posterior and crossed pyramidal tracts, with variable atrophy of the nerve fibers and glial fibrosis. The intensity of the lesions, which are symmetrical, decreases from below upward. The central canal is obliterated, but the meninges, nerve roots and gray substance appear normal.

Marie ('94) concluded that the lesions in the spinal cord are due to a poliomyelitis posterior, with associated degeneration of the endogenous fibers of the posterior and lateral columns.

Using the Nissl method, Rossi ('98) found a variable degree of chromatolysis in the spinal cord of pellagrins, affecting either the periphery or the entire nerve cell. The cells show variable deformity, sometimes pigmented, sometimes homogeneous or vitreous in appearance. The nuclei may be peripheral or disappear. The dendrites may be greatly altered or absent; and the entire cell may disintegrate. Rossi's results were confirmed and extended by Babes and Sion ('00), who concluded that the changes in the white substance are chiefly or entirely exogenous in origin, opposing the endogenous theory of Tuzcek and Marie. The degenerative changes were traced from the dorsal roots into the cord, with resultant changes resembling tabes. Changes also occur in the cells of the gray substance, especially in Clarke's column and the anterior horn, with a peculiar

proliferation of neuroglia around the degenerating nerve cells. Further investigations on the results by Nissl's method are cited by Marie ('08, '10). Roberts ('12) described the degenerative changes in the nerve cells as shown by Nissl's technique and by other methods.

Parhon and Papinian ('05) applied the modified silver technique and found neurofibrillar lesions in the nerve cells of the spinal cord, most pronounced in the cervical region. In the lumbar and sacral regions the central neurofibrillae are most affected, those in the cell periphery and processes being more resistant. These results were confirmed by Valtorta ('12), Bravetta ('11), Rezza ('12) and others (cited by Harris '19).

Harris ('10) found sclerosis of the posterior and lateral columns in 4 out of 5 cases of pellagra, with constant degenerative changes in the nerve cells, similar to those described by earlier investigators. Anderson and Spiller ('11) concluded that in pellagra "The degeneration is caused by some toxic or infectious substance affecting all parts of the cerebrospinal axis, producing cellular degeneration and diffuse degeneration of nerve fibers in the posterior and anterolateral columns."

In the spinal cord of 16 insane pellagrins, Kozowsky ('12) found the typical changes in the nerve cells, especially of the anterior horn and Clarke's column, and mostly in the middle and lower segments of the cord. The lateral pyramidal tracts are most frequently involved; the posterior columns next. There is increased fibrosis along the blood vessels, which may be obliterated; sometimes passive congestion and small hemorrhages occur. Similar lesions were described by Hamill ('12), Mott ('13), and other investigators cited by Raubitschek ('15) and Harris ('19).

**Vitamin Deficiencies.**—The vitamin deficiencies in which the spinal cord has been studied concern chiefly vitamin B (in beriberi) and vitamin C (in scurvy).

**Beriberi.**—Rumpf and Luce ('00) reviewed the literature indicating that previous investigators of **human** beriberi found no significant changes in the spinal cord, aside from occasional atrophy of the anterior horn cells. Rumpf and Luce found: "einen spärlichen Ausfall sowie eine unbedeutende Degeneration der Vorderhornganglienzellen in allen Rückenmarkssegmenten." Duerck ('08) also made an extensive review of the subject (bibliography of 245 titles) and described 11 original cases of human beriberi. The changes in the nervous system, including the spinal cord, are variable in degree and not specific in character, resembling the degenerations due to toxic causes.

**Experimental Beriberi.**—In avian polyneuritis, Vedder and Clark ('12) by Nissl's method found absence of the tigroid bodies in the cells of both ventral and dorsal horns of the spinal cord (Figs. 63, 64). The stainable substance is massed at one side of the cell and the nucleus sometimes stains poorly. The mitochondria appear normal in these cells, however, even when the tigroid bodies are markedly altered. Schnyder ('14), however, could find no appreciable change in the structure of the spinal cord in various animals (white mouse, pigeon, chick, cat, dog) dying from beriberi. He used various histological methods, including the Pal-Weigert. Findlay ('21) noted nearly complete disappearance of the Nissl granules in avian beriberi (pigeons and fowls).

In pigs placed on a ration of wheat, etc., Hart, Miller and McCollum ('16) obtained nervous symptoms and lesions resembling those of beriberi. The

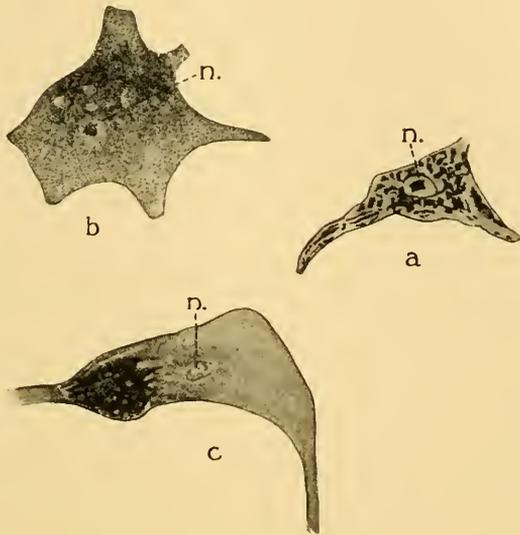


FIG. 63.—Nerve cells from the ventral horn of the spinal cord in fowls (Giemsa blood stain). The nucleus, *n*, is indicated in each. *a*, cell from normal animal, showing Nissl bodies; *b*, *c*, cells from fowl with polyneuritis (beriberi) after 24 days on polished rice diet. The nucleus has degenerated; the Nissl bodies have disintegrated, and the stainable substance is collected in irregular masses at one side of the cell. (Vedder and Clark '12.)

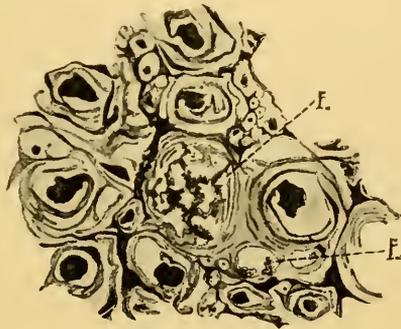


FIG. 64.—A portion of a cross section of the ventromarginal column of the spinal cord in a fowl with polyneuritis (beriberi) on a polished rice diet. Stained with hematoxylin and acid fuchsin. *f*, *f*, nerve fibers in advanced stages of degeneration. (Vedder and Clark '12.)



FIG. 65.—Sciatic nerve fiber (teased preparation) from fowl with polyneuritis (beriberi) on polished rice diet. Shows advanced degeneration, with disintegration of the axone, *a*. Hematoxylin and acid fuchsin stain. (Vedder and Clark '12.)

anterior horn cells and nuclei appear shrunken and degenerated; the Nissl granules indistinct and the cytoplasm homogeneous. They considered the condi-

tion probably due to some toxic substance in the wheat rather than to the absence of any dietary factor, however.

**Scorbutus.**—In human scurvy, lesions of the spinal cord appear rare. Sato and Nambu ('08) found nothing abnormal by Marchi's method. Feigenbaum ('17) observed hemorrhages in the spinal cord, however, and Hess ('18a) described focal degeneration in the lumbar cord, involving mainly the anterior horn cells, in a case of infantile scurvy. For experimental scurvy, no data have been found in the literature, excepting those of Bessesen ('23) who found a marked apparent increase in the weight of the spinal cord in scorbutic young guinea pigs (Table 12). This is explained in part by the corresponding loss in body weight.

**Aqueous Inanition.**—As to the effects of thirst (dry diet) on the weight of the spinal cord, Falck and Scheffer ('54) found that in a dog with loss of about 21 per cent in body weight, the spinal cord apparently lost 7.1 per cent. Kudo ('21, '21a) studied the effects of a dry diet in albino rats (Tables 9 and 10). In adults, the spinal cord in the acute thirst series shows an apparent average loss of 1.8 per cent (body weight loss 36 per cent); while in the chronic thirst series it lost 6.7 per cent (body weight loss 52 per cent). In young albino rats (1 month old) in which the body weight was retarded for various periods by a dry diet the spinal cord shows a marked and progressive increase in weight, ranging from 20.8 to 53.1 per cent. This resembles the increase found in young rats during general underfeeding (incomplete total inanition) as previously mentioned.

The structural changes in the spinal cord produced by dietary deficiency of water were studied by Pernice and Scagliosi ('93, '95, '95a). In a dog, the cord presents capillary congestion. The nerve fibers appear variably atrophic, especially near the gray substance. There is a distinct decrease in the size and number of the nerve cells, especially in the anterior horns. Many cells have entirely disappeared; others have degenerated into an amorphous mass of fatty granules. The stroma is increased in amount and the central canal widened. In 3 chicks, the pia mater appears thickened, rich in nuclei, with a few sub-pial hemorrhages. There is congestion, glial proliferation and atrophy of the nerve fibers and cells (Fig. 66), as in the dog. In general, the cells are small, poorly stained, and often without processes. Irregular, vacuolated or granular masses, or empty cavities, are found replacing degenerated cells, especially in the anterior horn of the lumbar region. The gray substance shows whitish-yellow, granular areas of softening, especially near the central canal, which in the lumbar cord appears enlarged and contains blood, etc.

In rabbits dehydrated by various methods, Brasch ('98) found variable changes by the Nissl method, especially in the nucleus of the nerve cells of the spinal cord and spinal ganglia. The nuclear changes present two types: (a) nucleus rather small and pycnotic (sometimes karyorrhexis); (b) nucleus large, with stellate masses of variable stainability around the nucleolus. Transitional forms also occur. Brasch concludes that the retraction of the nuclear contents from the nuclear membrane is not a necrobiotic, but a purely physical phenomenon, caused by the dehydration and capable of recovery when the normal water supply is restored.

## CHAPTER XII

### EFFECTS ON THE PERIPHERAL NERVOUS SYSTEM

As might be expected, the peripheral nervous system resembles the central nervous system in its notable resistance to inanition, likewise in showing a marked susceptibility to certain types of partial inanition (pellagra, beriberi, thirst). The effects of inanition upon the peripheral nervous system will first be summarized briefly, and then considered in detail under (*A*) total inanition, and (*B*) partial inanition.

#### SUMMARY OF EFFECTS ON THE PERIPHERAL NERVOUS SYSTEM

In general, the peripheral nervous system, like the central, appears relatively resistant to inanition. The **nerve cells**, however, in both spinal and sympathetic ganglia, may show progressive degenerative changes, including cytoplasmic atrophy, vacuolation and chromatolysis as well as nuclear changes, similar to those found in the central nervous system. The spinal ganglion cells and stroma in amphibia contain small fat droplets, which are chiefly resorbed during inanition. The nerve cell changes in general appear variable in the different types of *partial inanition*, being most pronounced in pellagra, in which pigmentary atrophy is frequent.

Although the medullated **nerve fibers** are also resistant, the myelin sheath may show a slight degree of atrophy, especially in extreme stages of inanition. Wallerian degeneration may also occur, probably secondary to the above mentioned degenerative changes in the nerve cells. The nerve endings in muscle appear but slightly affected. Atrophy and degeneration of the peripheral nerves, including cranial, spinal and sympathetic, are also found variably developed in the different types of *partial inanition*. They occur in pellagra, and are especially characteristic of beriberi (excepting in mice and rats), although they may be slight or absent unless the disorder is somewhat prolonged. In aqueous inanition, a notable decrease in the weight of the sciatic nerve trunk has been demonstrated in adult rats, which may be due partly to the loss in the included adipose tissue. In the young rat, there is during thirst a persistent growth in weight of the sciatic trunk, similar to that occurring in the spinal cord during inanition.

During inanition the perineurium and endoneurium may undergo proliferation, and the resulting fibrosis tends to replace the loss in substance due to atrophy) of the neurones. In certain types of partial inanition (pellagra, beriberi and thirst), the changes may resemble those of a chronic neuritis, with round cell infiltration.

In this connection it may be recalled (as shown in Chapter III) that a relatively marked resistance of the nervous system to inanition was likewise

observed among invertebrates; in *Planaria* by Schultz ('04), Stoppenbrink ('05), Berninger ('11) and Lang ('12); in *Lineus* by Nusbaum and Oxner ('12); in leeches by Cajal ('04a); and in *Limax* by Smallwood and Rogers ('08, '09, '10). So far as known at present, we may therefore conclude that in general throughout the animal kingdom the nervous tissue appears relatively resistant to inanition although subject to degenerative changes, especially in the extreme stages.

#### (A) EFFECTS OF TOTAL INANITION, OR ON WATER ONLY

In **man**, but relatively few observations upon the peripheral nervous system during inanition are available. Rokitsky ('54) held that the elements of the nervous system are exempt from general atrophy, but Luciani ('89, '90) believed the rapid decline toward the end of starvation to be due to disorganization of the nervous system. The neurasthenia so frequently found during undernourishment, as noted by Blanton ('19) in German school-children and by Rubner ('19) in adults, is probably due primarily to central rather than peripheral nervous lesions. Blaschko ('83) did not find a primary degeneration in the plexuses of Auerbach and Meissner during infantile intestinal atrophy, although such degeneration is mentioned by Baginsky ('84). Meyer ('17) found increased neuroglia with considerable shrinkage and vacuolation of the myelin in the nerve fibers of a cervical nerve root in a man who died of starvation.

The observations upon the **lower animals** are more numerous. Carville and Bochefontaine ('75) found the sciatic nerve fibers apparently normal in 2 dogs starved 27 days (on water only). Degenerative changes in the spinal ganglion cells, more or less resembling those in the nerve cells of the brain and cord, were found by Mankowski ('82), Rosenbach ('83, '84), Lugaro and Chiozzi ('97), and Daddi ('98, '98a), as mentioned in Chapter X on the brain. Changes observed by Barrows ('98) in spinal ganglion cells, and by Cajal ('04a) and Dustin ('06) in the neurofibrillae of nerve cells in the leech were mentioned in Chapter XI on the spinal cord. The observations by Riva ('05, '06, '07) on the neurofibrillae and by Rasmussen ('19) on the mitochondria of spinal ganglion cells during inanition were also mentioned in Chapter XI.

Microphotographs showing in general but slight changes in the spinal ganglion cells of starved rabbits were published by Martinotti and Tirelli ('01). A few cells show marked cytoplasmic and nuclear degeneration.

Morat ('01) and Bonne ('01) discovered that the spinal ganglia of the frog (species not stated) appear yellow in winter during hibernation, due to an abundance of fat droplets of variable size in and around the ganglion cells. The fat droplets appear to be derived from the capsule cells; they diminish when the frog revives from torpor in the spring, and disappear completely in the summer.

Smallwood and Rogers ('11), as previously mentioned, found but little change in the spinal cord of *Necturus maculatus* after 4 months of fasting, but marked changes after 16 months. The reddish masses of fat associated with the dorsal root ganglia disappear. The ganglion cells each contain an apparently

normal nucleus, with finely granular cytoplasm enclosing a yellow oil droplet. The greater part of the cell body is occupied by a large vacuole, containing a lymph-like fluid.

Changes found by Lodato ('98) in the retinal ganglion cells of fasting dogs will be mentioned in Chapter XIII, in connection with the eyeball.

In starved rabbits, cats and dogs, Peri ('93) made a careful study of the sciatic nerve and concluded:

“Dans le système nerveux périphérique, les alterations sont généralement atrophiques. La myéline est diminuée, spécialement chez les animaux qui restent longtemps à jeun. Aucune altération dans la constitution de cette substance. Le cylindreaxe ne diffère en rien du cylindreaxe normal. Toutes les préparations, faites avec les différentes méthodes, sur les nerfs périphériques, servent uniquement à confirmer les diminutions de la myéline.”

Findlay ('21) found the sciatic nerve degeneration much less marked in starvation than in avian beriberi.

Merzbacher ('03) found that section of the peripheral nerves in hibernating bats causes little or no degeneration, but the degenerative process is more rapid in the animals artificially warmed and awakened. Similar phenomena were observed in hibernating frogs. Hibernating mammals temporarily resemble the cold-blooded animals in their reactions.

Sokoloff ('76) discovered that in fasting summer frogs the nerve endings in muscle (studied chiefly by the gold method) are apparently not much affected and show up clearly among the degenerated muscle fibers. The “muscle corpuscles” and “nerve end buds” appear hypertrophic and hyperplastic.

In the **sympathetic system**, Isaëw ('87) studied the intestinal ganglia (plexuses of Auerbach and Meissner) in starved dogs. The ganglion cells were rarely found cloudy and swollen; oftener granular and vacuolated. The nuclei are sometimes well preserved, sometimes degenerated. The nerve fibers also appear cloudy, and the interstitial tissue infiltrated with round cells. Statkewitsch ('94) found a marked cytoplasmic vacuolation, less frequently a fatty degeneration, in the cardiac ganglia of a starved cat.

Uspenski ('96) described the changes in various peripheral ganglia (nodosum, superior cervical sympathetic, celiac and cardiac) of rabbits fasting with loss in body weight of 15.3 to 45 per cent. After osmic fixation, two cell types are found, dark and light. The dark cells are smaller and most affected. The celiac ganglia show the greatest changes; the cardiac ganglia present the least. The cytoplasm undergoes a variable degree of vacuolation and hyalin degeneration. The nucleus may also degenerate, becoming hypochromatic or pycnotic. The nucleolus is often extruded. Some cells may be entirely destroyed; others nearly normal. The cytoplasm may be markedly degenerated, with nearly normal nucleus, or *vice versa*. The degenerative changes appear even in the earlier stages of inanition. If the rabbits are refed after inanition, the nuclei soon become normal but complete regeneration of the cytoplasm requires a long time. Eve ('96), however, found no apparent decrease in the Nissl substance in the sympathetic nerve cells of the starved frog and rat. The article by Zuboff ('03) was inaccessible.

## (B) EFFECTS OF PARTIAL INANITION

The effects of partial inanition upon the peripheral nervous system have been studied chiefly in connection with protein deficiency (pellagra), vitamin deficiency (beriberi and scurvy) and water deficiency (thirst).

**Pellagra.**—Fraenkel ('69-'70) mentioned pigment formation in the sympathetic ganglion cells as frequent in pellagra; but Tuczec ('93) found the peripheral sympathetic nerves in general unchanged; likewise the spinal nerve roots.

Rossi ('99) by Nissl's method found in the spinal ganglia of pellagrins progressive chromatolysis, nuclear displacement and degeneration, with proliferation of the neuroglia. These findings were confirmed by Amabilino ('03, cited by Harris '19). Babes and Sion ('00), aside from occasional fibrosis, noted but little change in the spinal ganglion cells. They found, however, degenerative changes in the spinal nerve roots and larger peripheral nerve trunks, indicating peripheral neuritis, and supported the theory of an exogenous origin of the degeneration in the white substance of the cord (opposing the endogenous theory of Tuczec and Marie, also advocated by Marinesco '09). Marie ('08, '10) mentioned the occurrence of degeneration in the anterior root fibers and of pigmentation in the peripheral spinal and sympathetic ganglia. Kozowski ('12) noted degenerative changes in the peripheral nerves and nerve endings, also pigmentation of the sympathetic ganglion cells. Raubitschek ('15) made an extensive review of the changes during pellagra in the peripheral nervous system, including sclerosis in the spinal ganglia and posterior roots, degeneration in the peripheral nerve fibers, and fibrosis with simple or pigmentary atrophy in the sympathetic ganglion cells.

**Beriberi.**—In human beriberi, Baelz ('82) described degenerative changes in most of the spinal nerves, and especially in the various sympathetic plexuses (cardiac, pulmonary, splanchnic, celiac and renal). Rumpf and Luce ('00) summarized the changes in the peripheral nerves as: "eine Neuritis chronica interstitialis mit ziemlich beträchtlichem Markfaserausfall und parenchymatöser Markfaserdegeneration." They cite earlier observations (by Baelz, Scheube, Pekelharing and Winkler) showing a chronic interstitial neuritis with atrophy and degenerative changes in the peripheral nerves (vagus, recurrent, phrenic and especially the spinal nerves).

In 125 necropsies in cases of beriberi, Ellis ('98) similarly found marked degenerative changes constantly in the phrenic, and vagus nerves and cardiac plexuses (probably causing death); also in the splanchnic nerves, and the pulmonary, celiac, and renal plexuses and their branches. He concluded that the symptoms of beriberi are obviously caused by degeneration of the peripheral spinal nerves in the paralytic cases, and of the phrenic and vasomotor nerves in the "moist" cases. Duerck ('08) and Vedder ('13) gave excellent illustrations showing the degenerative changes in the peripheral nerves. Strong and Crowell ('12) found that all nerves (vagus, phrenic, femoral, popliteal, sciatic) show marked degeneration of the medullary sheaths by the Marchi method. There is no proliferation of neurilemma nuclei or leukocytic infiltration.

In 18 necropsies in cases of infantile beriberi, Andrews ('12) sectioned and stained various nerves (vagus, phrenic, intercostal, anterior tibial) by the Marchi method. There is degeneration of some fibers, but not so extensively as in the adult. Nagayo ('23) states that the peripheral nerve lesions are similar in human beriberi and in experimental polyneuritis.

In **lower animals**, the condition of polyneuritis was found by Eijkman ('97) in his classic work on experimental beriberi by a polished rice diet in chicks. He observed atrophic and degenerative changes in the peripheral nerves as well as in the spinal cord (especially in the anterior horn cells). Eijkman ('13) thought the lesions caused directly by a toxin, arising probably from a metabolic disturbance involved in the dietary deficiency. Vedder and Clark ('12) studied polyneuritis gallinarum in 56 fowls on polished rice diet. In marked cases, the vagus fibers usually all show degenerative changes, but none appear in the cervical sympathetic ganglia or in their preganglionic or postganglionic fibers. All of the fowls on the diet 35 days or more showed degeneration in the sciatic nerve fibers, whether neuritic symptoms were present or not (Fig. 65). In advanced degeneration, the myelin sheath breaks up into globules and the axis cylinder disintegrates. Similar degenerative changes appear also in the nerve fibers of both dorsal and ventral spinal nerve roots, with chromatolysis and other changes in the large nerve cells of both ventral and dorsal horns.

Schnyder ('14), however, found no changes in the sciatic nerve of white mice dying from experimental beriberi, and but slight degeneration in birds, cats, and all but one of 4 dogs (one showing marked degeneration in the sciatic). He suggests that the lesions in the peripheral nerves may appear only when the disorder is prolonged. Tasawa ('15) observed various degenerative changes in experimental polyneuritis (200 chicks and 150 pigeons), and also the regenerative processes.

Voegtlin and Lake ('19) described degeneration of the myelin sheaths in the spinal cord and peripheral nerves of cats, dogs and rats with polyneuritis produced by dietary deficiency. Kimura ('19) claimed that in beriberi of birds the degeneration of the medullated nerve fibers begins in the axone, rather than in the medullary sheath. He also describes degenerative changes in the nerve fibers and cells of the spinal cord. According to Funk ('22), similar studies were made by Weill and Mouriquand ('17), Kato and Shizume ('19) and Paguchi ('19). Findlay ('21) noted nearly constant myelin sheath degeneration in the sciatic, and also degenerative changes in the sympathetic ganglia of the intestine and suprarenal, in avian beriberi.

Karr ('20) showed that in the dog on diets deficient in vitamin B, the nerve lesions appear only in those which continue to eat nearly up to the time of appearance of the nervous symptoms; otherwise they die of starvation without the nerve lesions. Hofmeister ('22), in conformity with the above mentioned observations of Schnyder ('14) on white mice, finds that in beriberi of rats there is no evidence of a degeneration of the peripheral nerves, although in severe cases lesions occur in the brain (as mentioned in Chapter X).

McCarrison ('21) points out that typical Wallerian degeneration may occur in the sciatic and vagus nerves of apparently healthy pigeons, though less

frequently than in those with polyneuritis columbarum. Degenerative changes were also found in the nerve cells of the intestinal and suprarenal sympathetic ganglia. Wallerian degeneration was likewise noted in the femoral nerve of monkeys on diets deficient in vitamin B, but not in controls.

**Scorbutus.**—In human scurvy, no lesions in the peripheral nerves were found by Schödel and Nauwerk ('00), Sato and Nambu ('08) or Aschoff and Koch ('19), the last named having examined the vagus in 22 cases. In experimental scurvy in the guinea pig, Holst and Frölich ('12) observed frequent indications of Wallerian degeneration in the nerves, often typical in isolated fiber-bundles, but attached no great significance to the findings. Ingier ('13) also found a variable degree of degeneration in the peripheral nerves (including sciatic, peroneal, vagus and phrenic) of scorbutic guinea pigs. Hess ('20) states



FIG. 66.—A portion of a cross section of the thoracic spinal cord in a young fowl subjected to aqueous inanition (dry diet). Stained by the Pal method, showing some nerve fibers of the white matter (above) and a portion of the adjacent grey matter (below). Several atrophic and shrunken ventral horn cells appear; also some vacuoles where cells have disappeared. The neuroglia shows proliferation of nuclei.  $\times 266$ . (Pernice and Scagliosi '95a.)

that the sheaths of the large nerves as well as those of the vessels are very often invaded by hemorrhage in scurvy. The extravasated blood is found to lie around but rarely among the nerve fibers, which show no pathological changes.

**Aqueous Inanition.**—In a dog which died after 11 days on dry bread, Pernice and Scagliosi ('95, '95a) found that the sciatic nerve fibers appear below normal in size and stain less intensely (by alum-carmine and Weigert's method). But few structural changes were observed, including a thickening of the perineurium and (partly) of the endoneurium, accompanied by a slight round cell infiltration. In 3 chicks which died after 8–10 days on a dry maize diet, the sciatic, vagus and glossopharyngeus nerves were studied in cross section (Schultze-Ranvier method), showing atrophy of the medullated fibers, and granular degeneration of the myelin sheath. Irregular and poor staining of the medullated fibers was also found in teased preparations (Fig. 67). The axone is often atrophic, and may show irregular swellings and deformities (especially when

fixed in Müller's fluid and stained by Weigert-Pal method). There is also hyperemia and proliferation of the connective stroma, and the markedly atrophic nerve fibers may be separated by a granular substance apparently derived from the degenerated fibers.

The effect of various methods of dehydration upon the nerve cells in the spinal ganglia and cord of rabbits was studied by Brasch ('98) who found finely granular degeneration of the Nissl substance in extreme cases only. The nuclear changes are more prominent and present two types: (*a*) nucleus rather small and pycnotic (sometimes karyorrhexis); (*b*) nucleus large, with stellate masses of variable stainability around the nucleolus. The former type apparently develops more slowly, the latter more rapidly; and transitional forms occur. The changes are apparently physical rather than necrobiotic, and are capable of recovery upon restoration of water.

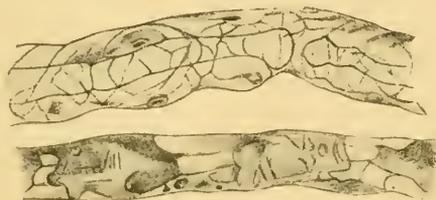


FIG. 67.—Two degenerated nerve fibers (Pal stain; teased preparation) from the sciatic nerve of a young fowl subjected to aqueous inanition (dry diet). The axone is visible in the upper fiber.  $\times 600$ . (Pernice and Scagliosi '95a.)

In young albino rats (1 month old) held at nearly constant body weight by a relatively dry diet for various periods (see Table 10), Kudo ('21a) found a continued growth in the weight of the sciatic nerves, similar in most cases to that in the spinal cord. With adult rats in the acute thirst series (body loss 36 per cent), he found an apparent average loss of 21.3 per cent in the weight of the sciatic nerves; and in the chronic thirst series (body loss 52 per cent) a loss of 22.1 per cent. This would indicate that in adults the loss during thirst (aqueous inanition) is relatively greater in the peripheral than in the central nervous system, according to the data cited in Chapters X and XI. This may be due partly to the atrophy of adipose tissue which occurs normally intermingled in the trunk of the sciatic nerve; but it nevertheless is in harmony with the findings of Pernice and Scagliosi (above cited), who described an atrophy of the sciatic nerve fibers.

## CHAPTER XIII

### EFFECTS ON THE VISUAL APPARATUS

The visual apparatus includes the eyeballs, together with the accessory organs, lacrimal glands, conjunctiva, etc. General impairment of the visual apparatus has frequently been observed in cases of famine or malnutrition. Recently a specific disorder (xerophthalmia) has been shown to result from deficiency of vitamin A. Apparently the deficiency lowers the resistance to bacterial infection, which is the direct cause of the ophthalmia. Thus dietetics becomes a factor of importance in ophthalmology, and particularly among malnourished children. Following a brief summary, the effects of inanition upon this apparatus will be considered under (*A*) total inanition, and (*B*) partial inanition.

#### SUMMARY OF EFFECTS ON THE VISUAL APPARATUS

During **total inanition**, or on water only, there is but little or no loss (sometimes even an increase) in the weight of the eyeballs, although the remaining orbital contents (muscles, fat, etc.) undergo the usual atrophy. In the young, both human and infrahuman, there occurs during chronic inanition a persistent growth in weight of the eyeballs, similar to that found in the nervous system. The eyeballs usually resume their normal proportions after appropriate refeeding.

During total inanition (complete or incomplete) the eyes may remain normal in appearance; or conjunctivitis, corneal ulceration, etc. may occur (probably due chiefly to vitamin deficiency). Histologically, progressive atrophic and degenerative changes occur in the tissues of the eyeball. These changes are usually comparatively slight, affecting the iris, ciliary processes and muscle, choroid and especially the cornea and retina. The retina may present anemia, edema and cellular degeneration, notably in the ganglionic layer. In salamander larvae, mitosis is almost completely suppressed in the cornea during total inanition.

In the various types of **partial inanition**, as in total inanition, there is a marked tendency to progressive increase in the weight of the eyeballs in the young, and little or no loss in adults. Dimness of vision in the form of nyctalopia (night blindness) or hemeralopia (day blindness) has been observed during famine edema and scurvy, with retinal and conjunctival hemorrhages in the latter. Conjunctivitis may occur in these conditions, as well as in pellagra and especially during aqueous inanition (thirst).

The visual apparatus in the young is remarkably sensitive to a deficit in vitamin A, which produces a typical **ophthalmia** in both human and lower species (mammals and birds). In the earlier stages, there is a mild conjunctivitis with

xerophthalmia, involving cornification and degeneration of the corneal epithelium, edema of the substantia propria and progressive leukocytic infiltration. Later the conjunctivitis becomes more severe, with purulent panophthalmia and keratomalacia, leading in extreme stages to corneal perforation and consequent destruction of the eyeball. There are also characteristic lesions in the lacrimal glands, with a disturbance of secretion which may contribute in producing the changes in the eyeball. The conjunctivitis and keratomalacia are associated with bacterial infection. This appears to be secondary to the primary effect of the vitamin deficiency, which produces a specific lowered resistance in the tissues of the visual apparatus. Upon adding vitamin A to the diet, recovery is prompt, excepting in extreme stages with corneal destruction.

#### (A) EFFECTS OF TOTAL INANITION, OR ON WATER ONLY

In the **human adult**, the earlier observation upon the visual apparatus during malnutrition included conjunctivitis and corneal lesions, evidently corresponding to the disorder now known as xerophthalmia and considered as due to a deficiency of vitamin A. The earlier literature, as reviewed by Cyr, ('69) and Blegvad ('24), will therefore be presented later, in connection with this topic. Bourgeois ('70) noted that the human eyeball retains its volume during starvation.

Luciani ('89, '90) observed the retina during the 30 day fast of Succi. He found nothing abnormal until the 28th day, when there was a slight narrowing of the visual field and also a slight constriction of the retinal vessels, of doubtful significance.

In a man who died of starvation, Meyer ('17) noted that the eyes were deeply sunken, the periorbital fat "absolutely depleted" and the eyeballs very soft.

Numerous observations indicate an increase in certain visual disorders attributed to malnutrition during the recent war period. Thus Seefelder ('19) noted an increase in acute glaucoma, conjunctivitis and keratomalacia (the latter, at least, probably due to partial inanition). Feilchenfeld ('20) concluded that the eye is very sensitive to malnutrition, which during war famine resulted in an increased number of lesions of the eyelids (extensions from facial eczema); retinal hemorrhages and thrombosis of the central vein; apoplexy and glaucoma. The general weakness also causes a marked decrease in the power of accommodation. Pick ('20) likewise noted a marked increase in certain ocular disorders as a result of malnutrition during and since the war.

Most of these ocular symptoms during famine are probably due chiefly to lack of vitamin A (xerophthalmia) and vitamin C (scurvy), to be considered later, as well as to the lowered resistance with increased susceptibility to infections in general.

In malnourished and emaciated **infants**, the corneal ulcerations (keratomalacia) described by Mackensie ('57), Blessig ('66), von Graefe ('66), Gama Lobo ('66), Teuscher ('67), Tardieu ('80), de Gouva ('83), Thalberg ('83), Kubli ('87), Schiele ('07) and Stolte ('22) doubtless likewise belong chiefly in the category of xerophthalmia, to be considered later. Ohlmüller ('82) recorded for the eyeballs a weight of 5.41 g. in an atrophic infant of 56 days (body weight

2,381 g.) and of 7.90 g. in a well-nourished infant of the same age; but no conclusion can be drawn, since the previous body weight of the emaciated infant is unknown. The weights of the eyeballs observed by me in atrophic infants (Table 3) are always above the normal weight at birth (3.2 g.), even in those infants which have never reached a body weight of 3,200 g. This would indicate a persistent growth of the eyeballs in atrophic infants, corresponding to that which will be shown later for underfed young animals.

The regenerative process in corneal lesions of an atrophic infant was studied by Sachsaler ('03). He noted that the non-vascularity of the cornea is unfavorable to vitality, so that keratomalacia and xerosis conjunctivae often precede loss of body weight as signs of general infantile malnutrition.

Schindler ('19), by a comparison of 288 healthy infants of the first year with 172 malnourished infants, demonstrated a marked increase in the pigmentation of the iris in the latter group. Schindler thinks this increased pigment may be hematogenous in origin due to increased destruction of blood in the atrophic infants.

The changes in the visual apparatus during total inanition in the **lower animals** include (1) weight changes, in young and adult; and (2) structural changes. As to **changes in weight in young animals**, Manassein ('69) observed an apparent average increase of 12 per cent in the weight of the eyeballs during inanition in 3 young rabbits (23-25 days) and of 24 per cent in 8 somewhat older (3 months, 20 days). The corresponding decrease in body weight was about 30-35 per cent. Jackson ('15a) found that in albino rats held at constant body weight by underfeeding from 3 to 10 weeks of age, the eyeballs increase about 50 per cent in weight, showing under these conditions an intensity of growth greater than that in any other organ of the body (Table 4). A similar tendency was found also in somewhat older rats, and in those underfed for longer periods. Stewart ('18, '19) noted that if the underfeeding was begun at still earlier periods, the relative intensity of growth in the eyeballs appears even greater; a maximum increase of 143 per cent occurring in rats held at birth weight by underfeeding for an average of 16 days. In the newborn offspring retarded in growth by maternal underfeeding, however, Barry ('20, '21) found an increase of only 31 per cent above normal in weight of the eyeballs.

In young albino rats amply refed after underfeeding from 3 to 12 weeks of age, Stewart ('16) found that the relatively heavy eyeballs apparently return to normal proportions within four weeks of refeeding. In rats underfed from birth to 3, 6 or 10 weeks and then amply refed to a body weight of 25-75 g., Jackson and Stewart ('19) observed that the eyeballs still tend to be slightly above normal in weight (Table 7). In rats permanently stunted in body weight by underfeeding from 3 to 20 weeks of age, and then refed to maximum size attainable, Jackson and Stewart ('20) found the eyeballs averaging 10.7 per cent subnormal in weight; while in those which had previously been underfed for nearly a year before refeeding, the eyeballs average 18 per cent overweight (Table 8). Apparently there is much irregularity in the recovery of normal proportionate size in the eyeballs after periods of underfeeding in young albino rats.

In **adult animals**, Collard de Martigny ('28) noted a depression of the cornea, which might indicate an atrophic collapse of the eyeball during starvation, but there is no evidence by weights to support this idea. Chossat ('43) observed even an apparent *increase* of about 5 per cent in the average weight of the eyeballs in starved pigeons. Schucharadt's ('47) data indicate a slight loss in the eyeballs of starved pigeons. Bidder and Schmidt ('52) found an apparent loss of 68 per cent in the orbital contents of a starved cat, but this included the orbital fat, muscles, etc., as well as the eyeball. Valentin ('57) published data indicating an apparent loss of 8.6 per cent in the average weight of the eyeballs in 3 hibernating marmots, with loss of 35.5 per cent in body weight. In 47 adult rabbits, with average loss of about 39 per cent in body weight, Manassein ('68, '69) found the weight of the eyeballs practically unchanged (increase of 1 per cent). Bourgeois ('70) likewise found practically no loss in the weight of the eyeballs during starvation in rabbits, guinea pigs, cats and dogs, which was confirmed by Voit ('94) for the dog, by Sedlmair ('99) for the cat, and by Cattaneo ('00) for the rabbit. Bich ('95) found the weight of the eyeballs usually increased (ascribed to edema) in dogs either on total inanition or on water alone.

Jackson ('15) noted an average apparent loss of only 4 per cent in the weight of the eyeballs in adult albino rats during acute inanition (on water only), and a loss of 6 per cent during chronic (incomplete total) inanition (Table 4).

Ott ('24) found that in frogs during hibernation and subsequent inanition with loss up to 60 per cent in body weight, the eyeballs remain nearly constant in weight up to the later stages. Then they present an *increase* in weight, reaching 12 per cent in the males and 22 per cent in the females (Table 6). This increase is not due merely to absorption of water.

Manassein ('69) recorded the weight of the **Harderian glands** in fasting rabbits. In 47 adult rabbits with average loss of about 39 per cent in body weight, there was an apparent loss of 28 per cent in the glands. In 8 younger fasting rabbits ( $3\frac{2}{3}$  months old) with body loss of about 33 per cent, the glands apparently lost only 2 per cent; and in 3 rabbits 23-25 days old, with loss of 35 per cent in body weight, the glands apparently *increased* 22 per cent in weight. These glands were also found 22 per cent above normal weight in 5 (adult) rabbits which had been fully refed after a period of inanition. The large weights (usually nearly 1 g., often more, for the normal) recorded by Manassein for these glands, however, raises the suspicion that they may not have been the Harderian glands. Krause (*Anatomie des Kaninchens*, Lpz., 1868) gave the weight of the Harderian gland of the rabbit as 0.06 g.; of the (closely associated) infraorbital salivary gland as 0.15 g.; of the parotid as 1.1 g.

As to **structural changes** in the eyeballs of animals during inanition, Bourgeois ('70) observed that in starved mammals (guinea pigs, rabbits, cats and dogs) the cornea is flaccid and opaque, but does not present ulceration and perforation, such as has often been observed in human starvation. Healing of corneal wounds during inanition is imperfect. Carville and Bochefontaine ('74, '75) stated that in a starved dog the orbital fat is replaced by a gelatinous

mass, which under the microscope shows an amorphous structure with blood capillaries (usually empty). In fasting dogs, Falck ('75) found the conjunctiva inflamed; the cornea cloudy and opaque; the eyeball white, moist and soft; the eye-muscles greatly atrophied; and the orbital fat reduced or absent.

Von Bechterew ('95) observed that the opening of the eyelids is delayed in newborn puppies and kittens subjected to inanition. Similarly Stewart ('18), in albino rats underfed from birth, noted that the opening of the eyelids is somewhat delayed in time, but nevertheless appears at a lower body weight than in the normal controls.

Bich ('95) made an extensive study of the visual apparatus, especially of the retina, in 24 dogs during inanition, with or without water (no difference noted). He described the conjunctiva as pale and frequently dry; the cornea transparent and shiny; the pupil usually dilated, sometimes contracted; the orbital fat almost disappeared. He figured and described a series of progressive retinal changes, beginning when the dogs have lost about 20 per cent in body weight. Histologically the ganglion cells show at first cloudy swelling and well-defined pericellular spaces; later a cytoplasmic vacuolation. The normal structure may be recovered upon refeeding, except in extreme stages, when recovery may be delayed, even when the body weight is restored to normal. Aside from the ganglion cells, all other elements of the retina during inanition appear abnormally separated by a condition of edema.

Lodato ('98, '98a) likewise made a careful study of the ocular changes in 8 dogs subjected to inanition, with or without water, for 11-30 days, with various methods of fixation and staining. No histological differences were found between those with and those without water; but the latter lived longer and, although vision is conserved, showed more clearly certain ophthalmoscopic changes, including retardation of pupillary reflex, constriction of retinal arteries, and dilation of veins.

Histologically the sclera and cornea in these dogs show no change, excepting a partial loss of the epithelium behind Descemet's membrane. The iris appears thin and anemic, with constricted vessels; the anterior layer of epithelium very deficient; muscle cells and nuclei, also the ciliary muscle, stain faintly. The cells covering the ciliary processes also present cloudy swelling with poorly staining nuclei; numerous free pigment granules appear to have migrated from the pigment cells of the ciliary processes. The choroid and vessels appear atrophic, especially peripherally; less so toward the optic papilla. The optic nerve shows changes of doubtful significance, but the ciliary nerve presents marked atrophic degeneration by the Weigert-Pal method.

The retinal vessels are constricted, with dilated perivascular spaces, especially in the vessels of the papilla. The pigmented epithelial cells of the retina are swollen, with granular cytoplasm containing few pigment granules. No apparent change occurs in the rods and cones. By Nissl's method, the amacrine cells show chromatolysis. The ganglionic and nerve fiber layers appear moderately edemic. The ganglion cells appear swollen, with poorly staining nuclei and widened pericellular spaces. Nissl's stain shows the cytoplasm affected with a variable degree of chromatolysis, vacuolation and degeneration. The

nucleus in many cells is irregularly shrunken or pyknotic. Lodato thinks it remarkable that vision is not more affected by these changes in the ganglion cells.

Cattaneo ('00) studied the functional and chemical changes (which are slight) in the eyeballs of 3 rabbits. One eyeball (control) was enucleated before complete inanition of 6-11 days. Kammerer ('12) observed that in fasting *Proteus anguinus* the eye pigment is reduced and absorbed, which recalls a similar process in certain invertebrates (planarians and nemertine worms) as mentioned in Chapter III.

Kornfeld ('22) studied the effect of the plane of nutrition upon the rate of mitosis in the corneal cells of the larvae of *Salamandra maculosa*, which were richly fed after various periods of total inanition. The total number of mitoses per cornea drops to about 4, after total inanition for 3 or 4 days. Upon refeeding, the number does not change for 4-5 days, then increases rapidly to a maximum of about 400 after 6-14 days of refeeding. While nutrition is a condition necessary for cell division, Kornfeld thinks that hormones or other stimuli may also be necessary factors.

#### (B) EFFECTS OF PARTIAL INANITION

The types of partial inanition affecting the visual apparatus include chiefly deficiencies of protein (edema and pellagra), of salts (rickets) of vitamins (xerophthalmia, scurvy) and of water.

**Protein Deficiency.**—In Chapter V, evidence was cited to indicate that the edema frequently occurring in connection with famine and similar malnutritional conditions is in many cases probably due chiefly to protein deficiency, though often associated with other dietary defects. Lesions of the visual apparatus frequently occur in connection with the edema. Maynard ('09) observed a slight cloudiness of the cornea, with dimness of vision and evidences of increased intraocular tension in 20 cases of "epidemic dropsy." Budzynski and Chelchowski ('16) mentioned night-blindness as almost constant, generally preceding the edema. Schittenhelm and Schlecht ('19) likewise noted frequent hemeralopia and xerosis in such cases. The literature is reviewed by Maver ('20).

In **pellagra** (also probably due primarily to protein deficiency), ocular lesions may occur. According to Marie ('08, '10), these include conjunctivitis with pterygium and hemeralopia, sometimes pigmentary retinitis.

In **rickets** (deficiency of phosphorus or calcium and of antirachitic vitamin), according to Juaristi ('19), the eyes are more round and show more of the sclera, associated with changes in the fundus. In experimental rickets in rats on diets deficient in vitamin A and phosphorus, Shipley, Park, McCollum and Simmonds produced both xerophthalmia and rickets. The addition of phosphates prevents the rickets, but not the xerophthalmia (which will be considered later). In albino rats with experimental rickets, Jackson and Carleton ('22, '23) found an increase in the weight of the eyeballs (Table 2), amounting to over 40 per cent in the group with severe rickets. Possibly this increase in weight may be related to that above mentioned as occurring in young rats with general growth retarded during incomplete total inanition.

An interesting case was reported by Haigh, Moulton and Trowbridge ('20), in which a Jersey heifer, which had been on a calcium-deficient ration of silage and corn, gave birth to an undersized and maldeveloped calf, with no eyes and with hair growing from the "eye sockets."

**Deficiency of Vitamin A. Xerophthalmia.**—In the **human** species, the susceptibility of the eyes to the effects of malnutrition has long been known. In victims of the Irish famine, Donovan ('48) observed at autopsy blood-shot eyes, as noted also in death from other wasting diseases causing absorption of orbital fat. Redness and inflammation of the sclera are mentioned by Falck ('75) among the characteristic symptoms of death from starvation. In atrophic infants, Mackensie ('57) noted: "In particularly emaciated infants I have on many occasions seen the cornea of one or both eyes lose its substance, become prominent and perforate with almost no inflammation." The earliest symptom of xerophthalmia, xerosis conjunctivae, was described by Bitôt ('63) in malnourished children. Von Graefe ('66) apparently gave the first minute description of keratomalacia, which was also noted by Gama Lobo ('66), Teuscher ('67) and de Gouva ('83) in malnourished negro children in Brazil. A similar condition as a result of long fasting during the Lent Quadragesima in Russia was described by Blessig ('66), Thalberg ('83), Kubli ('87) and others. Tardieu ('80) mentioned corneal ulceration as one of the characteristic lesions in death from inanition in newborn infants, and keratomalacia in athreptic infants was also described by Koun ('03). According to Prugavin ('06), even long after the Russian famine of 1898, nearly all of the children suffered from purulent inflammation of the eyes, and much blindness resulted. The observations by Zak ('17) on "chicken-blindness" are mentioned later under "Scorbutus." Schiele ('07) found cod liver oil to be curative even when administered only to the mothers of the nursing infants affected by keratomalacia. The more recent work on human keratomalacia will be mentioned later.

The nature and significance of these eye lesions during human malnutrition were not understood until quite recently, when the subject has been cleared up by **animal experiments**. Falta and Noeggerath ('06) and Knapp ('08) observed that young rats malnourished on diets deficient in various factors (including vitamins, then unrecognized) develop a marked tendency to conjunctivitis and corneal ulceration. Knapp found *Staphylococcus* present in the conjunctiva. Freise, Goldschmidt and Frank ('15) demonstrated that this experimental keratomalacia is not contagious, however. It does not occur in rats merely underfed; hence it is not due to ordinary inanition. They found that the histological changes present the typical picture of a keratomalacia, with an early cornification of the corneal epithelium, swelling and decreased stainability of the middle epithelial cells, and inflammatory infiltration of the lower epithelial cells. The substantia propria also presents edema, vascular invasion and local areas of cellular infiltration. Severe cases may develop a perforating ulcer. The condition may be prevented or cured by the addition of 2 c.c. of milk daily to the artificial diet. Goldschmidt ('15) concluded that the efficiency of the milk depends upon its content of "noch unbekanntem, aber für das Leben notwendiger Substanzen," and that experimental keratomalacia in animals

corresponds to human keratomalacia, and belongs in the category of diseases due to partial inanition, such as scurvy and beriberi.

Some of the changes in the eyes of rats with experimental xerophthalmia are shown in Figs. 68 and 69.

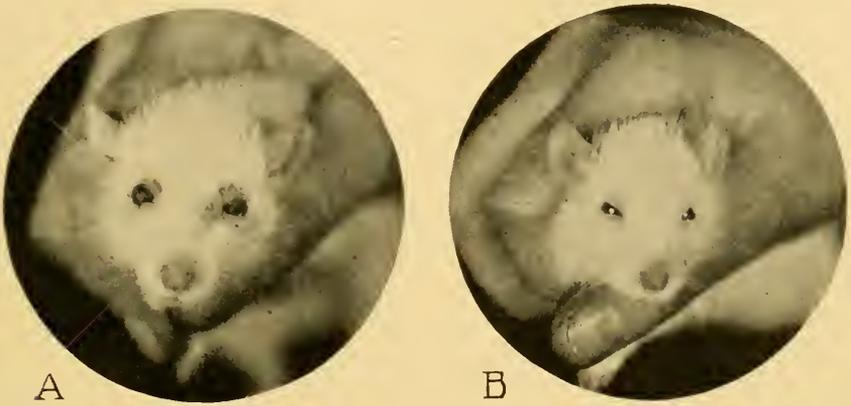


FIG. 68.—Photograph of two albino rats of the same litter, placed at 3 weeks of age on a diet deficient in vitamin A (patent wheat flour, 66 per cent; "Crisco," 20 per cent; casein, 5 per cent; yeast, 5 per cent; plaster of Paris, 2 per cent; sodium chloride, 2 per cent). In about a month, both developed xerophthalmia. This is shown in rat "A," with perforated cornea and protruding lens in the right eye. Rat "B" had a similar ophthalmia, without corneal perforation, but recovered perfectly (as shown in the photograph) in 6 days after the addition of dried spinach to the diet. (Courtesy of Professor McClendon and Miss Schuck.)

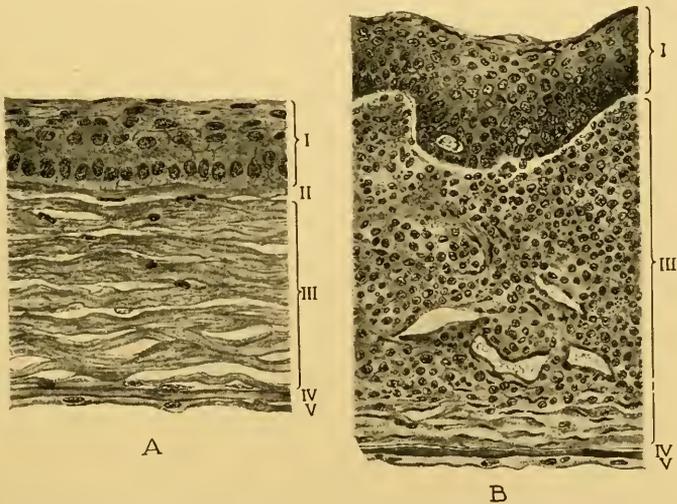


FIG. 69.—Sections illustrating the corneal changes in xerophthalmia produced in the rat by a diet deficient in vitamin A. *A*, normal cornea. *B*, stage showing moderate changes: proliferation of surface epithelium, with numerous mitoses; substantia propria invaded by blood vessels and round cell infiltration, with occasional fibroblasts; Bowman's membrane absent. *I*, surface epithelium; *II*, Bowman's membrane; *III*, substantia propria; *IV*, Descemet's membrane; *V*, posterior endothelium. (After Wason '21.)

McCullum and Simmonds ('18) (also *Jour. Biol. Chem.*, 1917, 32:181) described the condition in young rats resulting from lack of vitamin A as a type

of xerophthalmia. Bulley ('19) concluded that the xerophthalmia is due to infection, rather than to specific food deficiency, although admitting that the latter may cause a lack of resistance to the infection. Stephenson and Clark ('20) found an invasion of leukocytes to be the earliest change in the cornea of the rat, followed by edema, vascularisation, etc., which may lead to complete corneal degeneration with protrusion of the lens. They obtained various bacteria in cultures from the conjunctival sac, and concluded that "the condition directly attributable to dietetic deficiency is a predisposition to bacterial infection," leading to the characteristic lesions.

On the other hand, observations and conclusions are presented supporting the theory that the absence of vitamin A is the primary factor in experimental ophthalmia in young rats by Mendel ('20), Emmett ('20), and Emmett and Sturtevant ('20), Wason ('21), Osborne and Mendel ('21; also observed by them as early as 1913), Hess, McCann and Pappenheimer ('21), Mori ('22), Walker ('22), Yudkin and Lambert ('22, '22a) and Holm ('22); though not found (in adults ?) by Emmett and Allen ('20). Ophthalmia with similar lesions has been produced, by diets deficient in vitamin A, in the chick by Guerrero and Conception ('20) (on polished rice diet), and by Emmett and Peacock ('22) and Beach ('23); in the young rabbit by Nelson and Lamb ('20), and Nelson, Lamb and Heller ('22); in the dog by Steenbock, Nelson, and Hart ('21); in the duck by Rumbaer ('22); and in the pigeon by McCarrison ('23). There is found, however, much difference in the susceptibility to this disorder, varying according to species, individuals and diets used.

The extent of recovery upon adequate refeeding varies according to the degree of the ocular lesions. In most cases in rats complete recovery is possible, according to Stephenson and Clark ('20), but where degeneration is advanced the cornea may remain opaque. "In some cases the cornea has so far degenerated before cure is begun that the lens is forced through the aperture during life, and cure consists in the disappearance of pus and the healing over of the injured tissues."

Wason ('21) found that in rats the anatomic lesions (Fig. 69) in experimental xerophthalmia include hyalinization or necrosis of the outer layer of corneal epithelium, exudation of serum and cells into epithelium and stroma, a proliferation of blood vessels and fibroblasts, and, in advanced cases, an invasion of the anterior or (occasionally) the posterior chamber. The degree of restoration possible upon proper diet depends upon the extent of the secondary injury. The manner in which the deficiency of vitamin A renders the cornea susceptible to bacterial invasion is unknown. Walker ('22) also found a staphylococcus-like organism present, but he (like other investigators) was unable to prevent or cure the disorder by external antiseptics. He concludes that there may be some other (possibly hereditary) factor concerned.

Mori ('22) concludes that the xerosis (dryness) of the conjunctiva and cornea is the essential change produced in the eyes of rats by the deficiency in vitamin A, and that the corneal ulcers (keratomalacia) are produced by the secondary infection. He finds that the two characteristic initial changes are (1) a cornification of the outer layer of epithelial cells of the conjunctiva bulbi and cornea;

and (2) the formation of keratohyalin granules in the second layer of the epithelial cells in the conjunctiva, but not in the cornea, except at the limbus. These granules have also been described in xerosis conjunctivae in human lagophthalmos. Later stages in the rats, as in human keratitis, show alterations in the corneal epithelium, producing either an abnormal keratosis (due to the drying), or a necrosis (from interference with nutrition). The epithelial cells lose their nuclei and fuse, usually with infiltration by pus cells, and may disappear in small areas. The substantia propria shows marked edema and diffuse cell infiltration, which is denser in exposed areas. Cellular exudates also appear in the anterior chamber and iris, and perforating ulcers often develop. Mori ('23) claims that xerophthalmia and keratomalacia may be produced in rats also by diets containing abundant vitamin A, but with certain unfavorable salt mixtures.

Yudkin and Lambert ('22) found the experimental xerophthalmia of young rats presenting "watery lachrimation with a serosanguinous conjunctival secretion, becoming after a short time somewhat viscid." Early focal lesions were found always beginning in the conjunctiva, and consisting of degeneration and cellular infiltration of the epidermis, sometimes extending into the subjacent stroma. The cornea is involved later. They also find ('22a) in the **lacrimal glands** definite lesions, which appear degenerative or inflammatory in character. The lesions include variations in the size, form and staining properties of the lacrimal gland cells, which are probably correlated with functional derangement. The disturbance of lacrimal secretion may account for some of the phenomena of the xerophthalmia, particularly the characteristic drying of the cornea in the later stages.

More recent histological study by Lambert and Yudkin ('23) indicates that the changes in the lacrimal and Meibomian glands of the rat during experimental xerophthalmia are of doubtful significance. More definite degenerative and inflammatory lesions occur in the Harderian gland. Disturbances in the (probably fatty) secretion of this gland may render the conjunctiva more susceptible to infection.

Finally, Yudkin and Lambert ('23), from experiments on young white rats, concluded that:

"The earliest lesions in ophthalmia of rats resulting from deficiency of vitamin A consist in focal inflammatory lesions in the conjunctivae of the lids and nictitating membrane. The involvement of the cornea, which constitutes the most conspicuous feature of the well developed ophthalmia, is a secondary phenomenon. The characteristic corneal plaque consists of keratinized epithelium beneath which the deeper layers of epithelium are generally found intact."

"Pathologically the ocular manifestations of a deficiency of vitamin A are referable to a low grade inflammatory process, originating in the palpebral conjunctiva and spreading to the cornea. The rapidity of development and the degree of destruction probably depend in large part on the type of bacterial infection."

Certain recent observations on the effects of dietary deficiency in vitamin A upon the **human eye** remain to be considered. As previously stated, numer-

ous observers, such as Seefelder ('19) and Feilchenfeld ('20), have noted various ocular lesions resulting from malnutrition during the war. Among these lesions are conjunctivitis and keratomalacia, which we are now justified in assuming to be due to the same vitamin deficiency causing xerophthalmia in the lower animals. Hess and Unger ('19), however, found no eye trouble in 5 infants fed on a diet considered deficient in vitamin A for periods of 8 or 9 months.

On the other hand, Mori ('04), Bloch ('18, '19, '21, '24) and others have found typical eye lesions following this dietary deficiency, especially in infants. Bloch ('21) states that: "Xerophthalmia is considered a rare disease. Only amongst the negro slaves of Brazil and amongst the poorest and most ignorant inhabitants of Russia is it said to have been observed to any extent. The disease is generally described as follows: the first symptoms are dryness of the ocular conjunctiva, which becomes wrinkled and shrunken. Later on, small yellowish white spots appear, as though the conjunctiva had been dotted with paraffin wax. At this stage the disease is termed Xerosis conjunctivae. The dryness rapidly spreads over the whole conjunctiva and over the cornea, which becomes dull, uniformly hazy and insensitive. Later the cornea turns greyish and still later yellowish, until at last a more or less extensive necrosis of the cornea sets in, followed by ulceration (keratomalacia). The necrosis and ulceration may appear in the course of a few hours . . . All authors agree that the keratomalacia is due to insufficient nutrition of the cornea, and that this again is the consequence of the disorganisation of the whole mechanism of nutrition. The disease therefore occurs only amongst children who have been ailing for a considerable time and is often met with amongst infants who have been insufficiently nourished." Bloch finds this disorder, which he terms *Dystrophia alipogenica*, due to a deficiency in vitamin A. It is fairly common in Denmark, and is probably an important factor in causing permanent blindness. Bloch ('24) has recently reviewed the subject in detail. Xerophthalmia may occur in children during the late stages of various malnutritional disorders. Death may be caused by secondary infections, especially bronchopneumonia. In case of recovery, if the cornea is only partly damaged, the child can usually be saved from complete blindness. The resultant scars are always hazy and opaque.

Ross ('21) describes 4 cases of keratomalacia in infants with a dietary malnutrition corresponding closely to Czerny's "Mehlnährschaden." Both clinically and histologically the eye lesions are very similar to those produced in animals by dietary deficiency in vitamin A. A similar keratomalacia is described by Stolte ('22). Wright ('22) observed numerous cases of human xerophthalmia.

Blegvad ('24) has recently given the subject a thorough discussion, based on 434 cases of keratomalacia in children and 19 in adults (also 148 cases of xerosis conjunctivae without keratomalacia), all observed by Danish oculists between 1909 and 1920. He also gives a full review of the literature, with a bibliography of 200 titles.

**Scorbutus.**—The ocular lesions in scurvy (due to deficiency in vitamin C) are chiefly connected with the general hemorrhagic condition associated with

this disease. Thus retinal hemorrhages were reported by Jacobsthal ('00). Kitamura ('10) found retinal hemorrhage and edema, with circumscribed hypertrophy of the nerve fiber and ganglionic layers. He also cited earlier observations by Grenet, Belowsky, and Sato and Nambu, indicating the occasional occurrence of conjunctival hemorrhage in scurvy. This was also noted by Blake ('21).

A weakness of vision in the form of nyctalopia (night-blindness), or more rarely hemeralopia (day-blindness) has been noted during adult scurvy by Zak ('17), O'Shea ('18), Bierich ('19) and others. Zak stated that in Russia at Easter time, following the 7 weeks' fasting period, a visual disturbance arises, termed "chicken-blindness." There are no objective symptoms, aside from a conjunctival xerosis, and the disorder is easily curable by using fresh liver or cod liver oil. Therefore it is apparently related to the xerophthalmia above mentioned. O'Shea noted pallor of the optic disc in 3 out of 22 cases with scorbutic night-blindness. Blake ('21) describes a case of exophthalmos due to orbital hemorrhage in infantile scurvy, and cites similar observations by previous investigators (found in 49 out of 379 cases by the collective investigation of the American Pediatric Society). The ocular lesions in scurvy are included in the recent review by Hess ('20). Bessesen ('23) found the eyeballs to remain nearly constant in absolute weight, therefore appearing relatively above normal on account of the loss in body weight by scorbutic guinea pigs (Table 12).

**Aqueous Inanition.**—A few data are available concerning the effect of water deficiency (thirst) upon the visual apparatus. Schuchardt ('47) noted an apparent loss of 4 per cent in the weight of the eyeballs in pigeons with loss of 44 per cent in body weight on a dry barley diet. In a dog (initial age 76 days) with loss of 20 per cent in body weight after 4 weeks on a diet of dry biscuit, Falck and Scheffer ('54) found, in comparison with a normal control, an apparent *increase* of 19.7 per cent in the weight of the eyeballs, with a very slight increase in their water content (from 89.8 to 90.9 per cent).

In adult albino rats on a dry diet, Kudo ('21) found that in the acute thirst series, with body loss of 36 per cent, the eyeballs lose 10.2 per cent in weight; in the chronic thirst series, with body loss of 52 per cent, the eyeballs lose 13.3 per cent; and in total inanition, with body loss of 47 per cent, the eyeballs lose 13.0 per cent (Table 9). Opacity of the lens apparently caused visual disturbance in some cases; the conjunctiva sometimes appeared congested, and once hemorrhagic. In young albino rats held at constant body weight for various periods by a relatively dry diet, Kudo ('21a) found a progressive increase in weight of the eyeballs, amounting to about 71 per cent in those on the diet 9–13 weeks (Table 10). Thus during aqueous inanition the eyeballs in the adult rat lose slightly; but in the young rat they increase remarkably in weight, much as has been found during total inanition (Table 4).

Pernice and Scagliosi ('95, '95a), in an adult dog which died after 9 days on diet of dry bread, noted that the white of the eyes became slightly yellow; and the right eye, later both eyes, developed a purulent conjunctivitis.

## CHAPTER XIV

### EFFECTS ON THE HEART AND BLOOD VESSELS

The cardiac musculature, like the skeletal, undergoes atrophy and degeneration during starvation, resulting ultimately in cardiac weakness and circulatory disturbances. During partial inanition, the human heart may be either atrophied (in malnutritional edema, pellagra or thirst) or hypertrophied (in rickets, beriberi or scurvy). The blood vessels are also affected, especially in edema and scurvy. After a brief summary, the effects of inanition upon the heart will be considered under (*A*) total inanition and (*B*) partial inanition. Finally (*C*) the effects of inanition upon the blood vessels will be discussed.

#### SUMMARY OF EFFECTS ON HEART AND BLOOD VESSELS

In human adults the **loss in the weight** of the heart during total inanition appears variable, but is roughly proportional to that of the skeletal musculature and the body as a whole. As a rule, this applies likewise to atrophic human infants. In adult animals, the same rule holds, with variations; but in the guinea pig, at least, the cardiac loss appears relatively greater toward the end of starvation than at earlier periods. In young animals, the heart appears relatively more resistant during underfeeding, and in the young rat it may even increase in weight while the body weight is stationary.

The **structural changes** in the heart during total inanition (or on water only) involve a variable degree of atrophy and ultimate degeneration of the cardiac muscle. Among human adults during inanition, brown or pigmentary atrophy of the cardiac muscle fibers is characteristic, with more or less vacuolation and nuclear proliferation (sometimes degeneration). The myofibrillae become less distinct in cross striation, and fatty degeneration may occur to a variable extent. The pericardial and interstitial fat disappears, and the interstitial spaces between the cardiac muscle fibers become more extensive. In atrophic human infants, the changes appear somewhat similar, but less extensive and more variable. Pigmentation apparently does not occur as in adults. The myocardium may appear nearly normal, and in some cases the cardiac muscle fibers may even appear hypertrophied. There may also be a variable degree of interstitial fibrosis.

Among lower animals, both young and adult, the cardiac muscle during total inanition likewise undergoes a variable degree of atrophy and degeneration. During abundant nutrition there may be a considerable amount of fat stored as small droplets within the cardiac muscle fibers, especially in hiber-

nating animals. This fat is progressively consumed during inanition, although certain lipoidal granules (probably containing phospholipins) here as elsewhere in the body appear very resistant to starvation. Through fatty degeneration, on the other hand, there is apparently in some cases an increase in the amount of fat within the cardiac muscle fibers, although the question of fatty degeneration has been much disputed.

The various types of **partial inanition** also occasion cardiac changes more or less resembling those during general inanition, but with some characteristic differences. In human *malnutritional edema* (protein deficiency) the heart appears atrophic and brown atrophy has been observed. In *pellagra*, the heart is variable in size, usually atrophic, and presents a pigmentary degeneration similar to that found in starvation. In *ricketts*, the heart (especially the right side) appears variably hypertrophied, perhaps due to obstruction of the circulation from thoracic deformity. A similar cardiac hypertrophy occurs in human *beriberi* (due to deficiency in vitamin B); but in birds there is usually a marked cardiac atrophy. In both cases, there may be a variable degree of myocardial degeneration. In infantile *scurvy* there is a marked cardiac hypertrophy, which is slight or absent in guinea pigs. Slight degenerative changes may occur, occasionally hemorrhagic infiltration. During *aqueous inanition* (thirst) the heart weight undergoes changes nearly proportionate to the body weight (rat), and structural changes somewhat inflammatory in character have been observed (dog), especially in the endocardium.

The **blood vessels** during inanition likewise undergo changes which are somewhat variable in extent and character. During total inanition (or on water only) there is an apparent atrophy of the larger arteries and veins, with variably degenerative changes in all the tunics. Atrophy of the capillaries has also been observed in various regions. A primary lesion of the capillary endothelium is probably responsible for the characteristic *edema* arising from protein deficiency, and for the hemorrhagic tendency in *scurvy*. Abnormal permeability of the vascular endothelium may be due also to calcium deficiency. In *pellagra*, the dermal vessels show degenerative and sclerotic changes of primary importance. During *aqueous inanition* (thirst), congestion and degeneration likewise appear in both the capillaries and the larger blood vessels (dog and chick).

#### (A) EFFECTS OF TOTAL INANITION, OR ON WATER ALONE

The effects upon the weight of the heart will be considered first, in man and lower forms, followed by the effects upon cardiac structure.

In **human adults**, Schultzen ('63) found the heart very small and devoid of fat in a starved girl of 19 years. Curran ('74) likewise found the heart very small (5 oz.) in an old woman who died from starvation; while Bright ('77) noted a weight of  $7\frac{3}{4}$  oz. in the famous case of Harriet Staunton, with final body weight of 74 pounds. Müller ('83) stated that during emaciation the pericardial fat, like the body fat in general, is nearly or entirely consumed; and that the heart weight is decreased, though proportionately less than the body weight. In an

extensive series of 459 autopsies upon victims of the Indian famine, Porter ('89) noted that in 45 per cent of the men the heart weight was under 6 oz. (average  $5\frac{1}{8}$  oz.) and in the remaining cases it averaged only 7 oz. In 37.4 per cent of the women it was below 5 oz. (average 4.24 oz.) and in the remainder averaged barely 6 oz. For all the men autopsied, the heart weight averaged 6.17 oz. (ratio to body weight 1:196); and for all the women 5.3 oz. (ratio 1:180). As a norm for comparison, he cited Quain's (European) ratio of 1:158 for men and 1:149 for women; which would indicate a loss of heart weight in the famine victims relatively greater than the loss in body weight. This is somewhat doubtful, however. Most of the cases above childhood represented in the chart of Fig. 70 are from Porter's data.

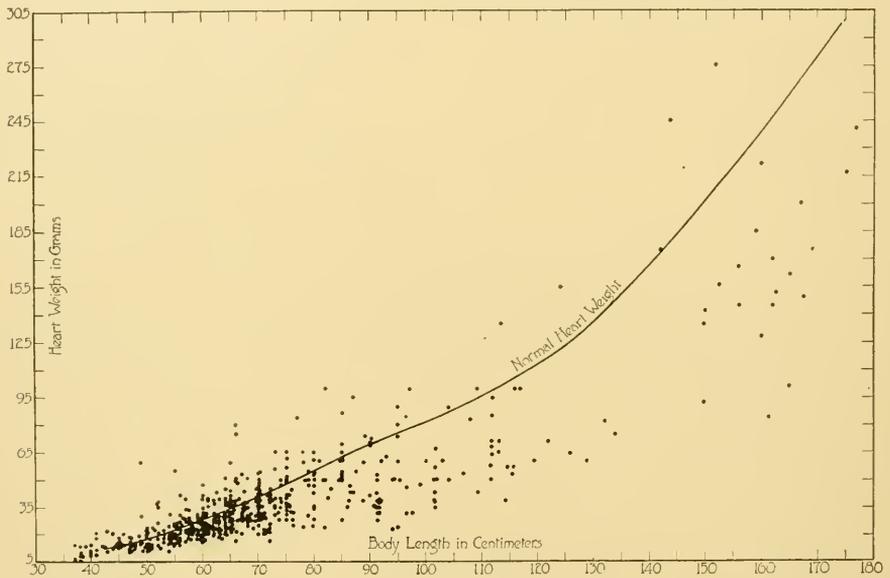


FIG. 70.—Graph showing the individual weights of the heart, according to body length, in atrophic human cases, newborn to adult, from various sources. The curve of normal heart weight is from data compiled by Prof. R. E. Scammon. It will be noted that, although there is much individual variation, in most cases the heart weight is below normal, the degree of atrophy apparently becoming greater with increasing age and body length.

Askanazy ('13) claimed that during inanition relatively the least loss occurs in the heart, brain and bones, the heart losing relatively much less than the whole body. Hirsch ('99), however, stated that in cachexias the cardiac muscle is reduced in proportion to the skeletal muscle and body weight (edemas excepted). This is confirmed by the observation of Meyer ('17), and by the extensive data of Roessle ('19).

Bean and Baker ('19) in data from autopsies at the Johns Hopkins Hospital and the Charity Hospital of New Orleans, found the average cardiac weight (excluding pathological hearts) in adults, classified according to their nutritional appearance (body weight unknown), as shown in the accompanying table.

## HEART WEIGHT IN VARIOUS CONDITIONS OF NUTRITION (BEAN AND BAKER '19)

Color and sex	No. of cases	Very emaciated, grams	Emaciated, grams	Thin, grams	Well nourished, grams	Fat, grams	Obese, grams
White, male.....	636	251	273	293	342	361	414
White, female....	385	244	266	298	353	332	340
Negro, male.....	279	201	234	258	267	323	329
Negro, female....	234	209	220	231	270	292	356

The reduction in heart weight during malnutrition is very evident from this table.

Sison ('20) found in adults during voluntary fasting a diminished area of cardiac dulness on percussion, which he thought might be due partly to increased resonance of the lungs.

The observations of Krieger ('20) indicate that the loss in adult heart weight during malnutrition from varied causes averages relatively slightly less than the loss in body weight, as shown in the accompanying table.

AVERAGE HEART WEIGHT IN VARIOUS CONDITIONS OF EMACIATION. ALL MALES, EXCEPT AS INDICATED IN GROUP I. FROM AUTOPSIES IN THE PATHOLOGICAL INSTITUTE, JENA.

IN ESTIMATING THE LOSS IN HEART WEIGHT, THE NORMAL WAS ASSUMED TO BE 0.5

PER CENT OF THE (INITIAL) BODY WEIGHT, WHICH WAS CALCULATED BY

GÄRTNER'S FORMULA FROM THE BODY LENGTH (KRIEGER '20)

Groups	Number of cases	Body weight, est. loss, per cent	Average heart weight	
			Observed, grams	Est. loss, per cent
I. Insane. No chronic organic disease	6	41.6	206.0	33.0
II. Chronic diarrhea.....	7	48.4	179.7	45.0
III. Malignant growths.....	25	38.0	221.7	33.2
IV. Chronic general infections.....	31	43.9	230.0	30.7
V. Tuberculosis.....	29	43.0	223.0	31.9
VI. Aged. Various conditions.....	20	35.8	271.0	18.3
				(29.6) <sup>1</sup>

<sup>1</sup> Making allowance for normal age change; heart assumed to be normally 0.58 per cent of the body weight in the aged.

Weber ('21) found but slight decrease in the average cardiac weight of adults autopsied at Kiel between the years 1914 and 1919, the average decreasing from 295 to 286 g. in the male and from 261 to 257 g. in the female. This is admittedly inconclusive, however, since the corresponding body weights are unavailable. Pearl and Bacon ('22), from a biometric analysis of 5,000 consecutive adult autopsies at the Johns Hopkins Hospital, conclude that in fatal tuberculosis cases there is a decrease in the absolute weight of the heart, which is probably

due to inanition. My own observations indicate a marked decrease in the weight of the heart during tuberculosis in adults, but not in children.

In **atrophic infants**, Ohlmüller ('82) found weights as shown in the accompanying table.

HEART WEIGHT IN ATROPHIC INFANTS (OHLMÜLLER '82)

Nutrition	Age	Body length, centimeters	Body weight, grams	Heart weight, grams	Heart weight, per cent of body
Normal.....	56 da.	53.5	4,149.5	27.1	0.66
Atrophic.....	56 da.	....	2,381.2	21.1	0.98
Atrophic.....	4 mo.	52.0	2,350.0	15.4	0.66
Atrophic.....	4 mo.	53.0	2,195.0	13.3	0.61

Thus apparently the heart is variable in relative weight in atrophic infants, but the lack of data concerning the previous body weight in these cases makes conclusions very uncertain.

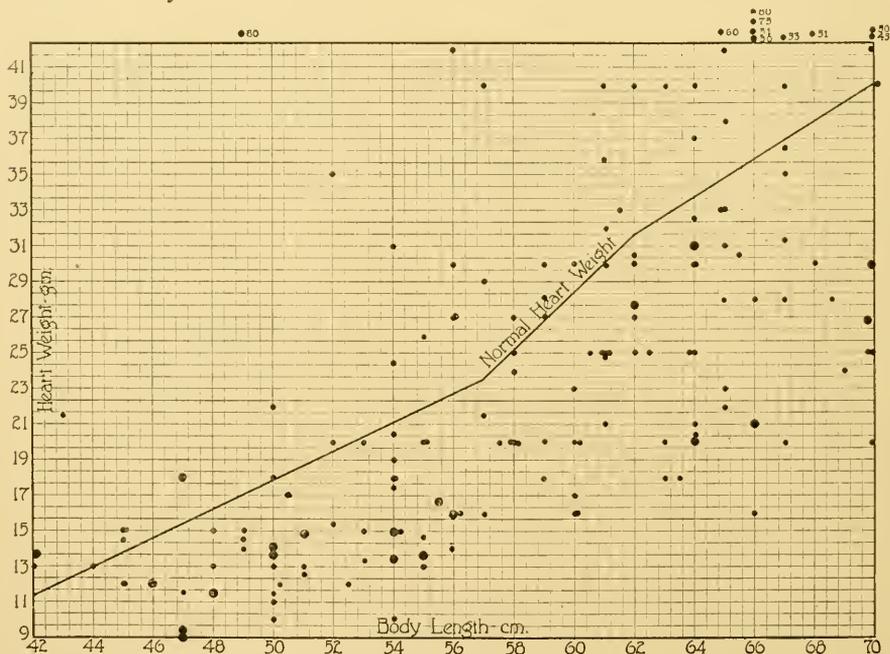


FIG. 71.—Graph showing the individual weights of the heart, according to body length, in atrophic infants. Data from various sources, the larger dots representing original Minnesota cases. The curve of normal heart weight is from data compiled by Prof. R. E. Scammon. In most cases, the heart weight appears clearly below normal, although there is much variation.

DeTommasi ('94) and Thiercelin ('04) stated that the heart is small in infantile atrophy, while Bovaird and Nicoll in an extensive series (571 autopsies, birth to 5 years of age) found the heart weight in general reduced nearly in proportion to the body weight. Lange and Feldmann ('21) concluded from fluoro-

scopic examination that in (living) emaciated infants the heart appears diminished in size; while Marfan ('21) claimed that in athreptic infants the heart, like the brain, is very resistant to inanition. Nicolaëff ('23) found the heart weight usually 20 to 40 (sometimes 50) per cent subnormal for age in famine-stricken children in Russia. Stefko ('24) noted greater cardiac atrophy in the female, especially about the age of puberty.

My own data (Tables 2 and 3) confirm the principle that in malnourished infants the heart weight approximates the normal for corresponding body weight, although markedly below the normal for the previous maximum body weight, or the final body length (Fig. 71); and especially retarded in comparison with the normal for corresponding age (Table 2). The individual data from various sources for cardiac weights plotted in Fig. 70 seem to indicate a relatively greater cardiac resistance to inanition during infancy than in later years up to the adult.

In various **adult animals**, Lucas (1826) found the heart apparently normal, but Collard de Martigny ('28) noted that it appeared small and atrophic in starved dogs and rabbits. Chossat ('43) observed that in starved pigeons the cardiac fat usually disappears, and the heart loses about 45 per cent in weight, while the loss in body weight is only about 40 per cent.

In a starved cat, Bidder and Schmidt ('52) found that, in comparison with a normal control, the heart weight had *increased* from 10.85 g. to 12.33 g., which indicates perhaps an error or abnormality. Similarly Voit ('66) found in two cats an apparent loss of only 3 per cent in cardiac weight. These observations indicating little or no loss in the heart during inanition have since been frequently cited in the literature (*e.g.*, Kitt '18), although a large number of later data lead to a different conclusion. The earlier observations are sometimes cited in support of the theory that the most active organs lose relatively least during inanition.

Manassein ('68, '69) in 47 adult fasting rabbits with average loss of 39 per cent in body weight, found a loss of 24 per cent in heart weight; and in several cases the normal weight was recovered upon refeeding. In 2 crows with loss of 36 per cent in body weight, the apparent loss in heart weight was 40 per cent. In various mammals (guinea pig, rabbit, cat and dog) and birds (fowl, pigeon), mostly on total inanition, but some with water or on incomplete inanition, Bourgeois ('70) observed an average loss of about 40 per cent in body weight. The heart was found atrophied nearly in proportion to the other musculature, with an average loss of 45 per cent, sometimes over 50 per cent. Luciani and Bufalini ('82) noted an atrophied heart in a starved dog; likewise Voit ('94), the loss in body weight being 32 per cent, and in heart weight 22 per cent. In a starved rabbit, Pfeiffer ('87) noted an apparent loss of 28 per cent in heart weight, and of 27 per cent in body weight; while in pigeons on total inanition Lukjanow ('89) found a loss of only 15 per cent in heart weight, with loss of 34 per cent in body weight.

Lazareff ('95) in a series of fasting guinea pigs, 10 in each group, with average losses of 10, 20, 30 and 36 per cent in body weight, noted corresponding losses of 4.84, 9.14, 20.97 and 33.33 per cent in heart weight. The loss in heart weight thus appears relatively greater toward the end of starvation (Table 5).

A peculiar exception was found by Kusmin ('96) in rabbits and dogs, the heart during starvation with hyperthermia (with or without water) appearing even increased in weight, which was interpreted as a functional hypertrophy. This may perhaps explain other exceptions occasionally found. Thus Weiske ('97) in 3 rabbits on water only, with body loss of 35 to 41 per cent, found an apparent decrease of about 29 per cent in heart weight in two, while in the third there was an apparent increase of 10 per cent.

Sedlmaier ('99) concluded that in starved rabbits the heart loses relatively somewhat less than the whole body; while Beeli ('08) observed an apparent loss of 72 per cent in heart weight, with loss of only 51 per cent in body weight. With losses of 34 and 36 per cent in the body weight of guinea pig and rabbit, Heitz ('12) noted corresponding apparent losses of 20 and 24 per cent in the heart weight.

Jackson ('15) found in albino rats with acute inanition an average loss of 28 per cent in heart weight (and of 33 per cent in body weight), and with chronic inanition a loss of 33 per cent in heart weight (and of 36 per cent in body weight.) (Table 4.) In fasting pigeons with loss of about 40 per cent in body weight, McCarrison ('21) noted a comparable loss in heart weight (Fig. 35). In fasting frogs with body losses varying from 10 to 60 per cent, Ott ('24) found nearly corresponding losses in heart weight in the males, but usually somewhat less in the females (Table 6).

In **young animals** during inanition, the heart usually appears somewhat more resistant. Bechterew ('95) found that in newborn kittens and puppies the loss in heart weight is relatively less than in body weight. In young albino rats held at constant body weight by underfeeding from 3 to 10 weeks of age, Jackson ('15a) found practically no decrease in heart weight; and in those underfed from birth, Stewart ('18, '18a, '19) found even an apparent increase in heart weight, up to 25 per cent. In the atrophic offspring of underfed pregnant mother rats, Barry ('20, '21) observed an average cardiac weight 8 per cent above normal (Table 4).

In underfed rats, after maintenance from age of 3 to 12 weeks, Stewart ('16) found the heart 16 to 34 per cent underweight, with apparent overcompensatory recovery (+17 per cent) after amply refeeding 4 weeks, but normal relations after refeeding 16 weeks. Jackson and Stewart ('19) noted nearly normal heart weight in rats amply refed to 25-75 g., after underfeeding from birth to 3 or 6 weeks (Table 7). The heart appeared slightly above normal in weight in young rats refed by Jackson and Stewart ('20) to adult stages after various periods of severe early underfeeding (Table 8).

Trowbridge, Moulton and Haigh ('18, '19) and Moulton, Trowbridge and Haigh ('22a) found the heart weight approximately normal for body weight in young steers of various ages, irrespective of the plane of nutrition.

**Effects on Cardiac Structure.**—The effects of total inanition (or on water only) upon cardiac structure will be considered first in man and later among infrahuman species. In **human adults**, the earlier observations (such as Donovan '48 and Müller '83) on the structural changes during inanition included merely the gross features, including disappearance of the pericardial fat, and

the "pale, soft and flabby" appearance. The first detailed microscopic study of the human heart was apparently by Hayem ('77), who observed that during inanition the heart is affected much like other (skeletal) muscles, sometimes with even more intense lesions. He found that in acute inanition, the heart muscle undergoes atrophy, with either simple granular or granulo-fatty degeneration (as found in rabbits by Manassein '69). Vitreous (waxy) degeneration is rare, but brown or pigmentary atrophy which does not occur in other muscles, may appear in the heart in all forms of cachexia. He stated that:

"Cette lésion est généralisée. L'organe devient petit; ses parois sont amincies et les cavités sont en général rétrécies, plus rarement un peu élargies (particulièrement quand il existe des lésions d'orifice); souvent elles conservent leurs dimensions normales. Le tissu musculaire en s'atrophiant prend une teinte brune spéciale, qu'on a comparée à celle d'une feuille morte; mais, quand les lésions sont très-accentuées, les parois cardiaques ont la teinte de la terre de Siemie brûlée. Le coloration feuille-morte indique une altération mixte, d'ailleurs fréquente, à la fois grasseuse ou pigmentaire. Au microscope les fibres plus ou moins nettement atrophiquées sont remplis d'amas de pigment accumulés autour des noyaux. De plus, dans quelques points, particulièrement dans ceux qui répondent à la teinte feuille-morte, on trouve des granulations grasseuses éparses, ne masquant pas habituellement la striation."

Voelkel ('86) noted a small heart with fatty degeneration in a starved man. In victims of the Indian famine, Porter ('89) found edema frequently replacing the epicardial fat. In about one-sixth of the adults, there were surface patches of a white, detachable lymphoid deposit, known as "soldier's spot." In a man who died from starvation, Stschastny ('98) noted cardiac changes, with brown atrophy, disappearance of cross-striation, and vacuolation of muscle fibers and nuclei. In a similar case, Meyer ('17) found marked atrophy of the cardiac muscle fibers, which appeared separated by extensive spaces (Fig. 59).

Krieger ('20), in various human cachexias, found brown atrophy characteristic in all except the infectious group, and most marked in tumor-cachexias. The pericardial fat usually underwent gelatinous degeneration or disappeared, but was found notably persistent in a few cases.

According to Rubner ('20), various German observers have noted a displacement of the heart resulting from the resorption of pericardial and abdominal fat. Bradycardia occurs in chronic underfeeding, as well as during certain forms of partial inanition, to be mentioned later. Reiss ('21) found sclerotic changes.

The question as to the cause and character of fatty degeneration of cardiac muscle during inanition has been much discussed, in connection with the problem of fatty degeneration in general. Krehl ('93) concluded that "Mangelhafte Versorgung der Gewebe mit O<sub>2</sub> galt als häufigste Ursache der fettigen Degeneration." For human adults, Borchers ('14) and Eyslein ('14) found no constant relation between the degree of malnutrition and the amount of fat present in the cardiac muscle fibers. This question is discussed later, in connection with the effects on lower animals.

In **human infants**, Parrot ('68), in accordance with his doctrine of visceral steatosis during inanition, claimed the occurrence of a slight fatty degeneration in

the heart in athreptic newborn. Thiercelin ('04) likewise held that the athreptic heart may undergo fatty degeneration, as in all chronic cachexias. Helmholtz ('09), however, reported negative cardiac findings, except in one case of ischemic necrosis. Mönckeberg ('12) mentioned cardiac atrophy as characteristic in cases of pedatrophy, while Nobécourt ('16) stated that slight hypertrophy occurs in some cases. Lesage and Cleret ('14) found the myocardium apparently normal in cases of congenital spasmodic atrophy.

Variot and Cailliau ('12) made a careful study of the cardiac histological structure in atrophic infants, describing three stages corresponding to the degree of malnutrition: (1) In nurslings not very atrophic; heart large. The lesions are discrete, with no atrophic muscle fibers and some even hypertrophic (up to 40-50 $\mu$ ). The muscle nuclei are slightly increased in size and number; perinuclear sarcoplasm abundant; vacuoles rare. (2) In more advanced cases, the heart still appears hypertrophied (although the body weight and stature are subnormal), but the cardiac muscle fibers are distinctly atrophic; none hypertrophic. Some fibers appear moniliform. The nuclei are proliferated and deformed. The perinuclear sarcoplasm is increased in volume, and frequently contains numerous non-fatty vacuoles. (3) In extreme marasmic atrophy the myocardial lesions are very marked, with atrophy as well as generalized vacuolation, involving the entire contractile substance. The interstitial connective tissue of the myocardium shows multiplication of nuclei and sometimes increase of fibrous tissue or enlarged interstitial spaces.

In famine-stricken children of various ages, Nicolaëff ('23) noted subepicardial edema with absence of fat. The cardiac muscle fibers appear atrophied, with loss of transverse striations in places. The sarcoplasm is sometimes vacuolated, especially near the nuclei, which appear more numerous. Nicolaëff made 61 necropsies, with histological study in 19 cases.

In **animals**, the changes in cardiac structure during inanition have been frequently and carefully studied. Manassein ('69) in fresh preparations from starved rabbits found marked histological changes in the heart muscle. The cross-striation disappears to a variable extent. Granules appear which are soluble in ether but not in acetic acid; and in marked cases large and confluent fat droplets may appear. Brown pigment granules were sometimes noted; also mentioned by Lépine ('74). In fresh cardiac muscle fibers of a starved dog, Falck ('75) noted distinct cross-striation, with diffusely scattered granules, resistant to acetic acid and caustic potash.

Zander ('79) found that in pigeons which died from inanition following section of the vagi there is a fatty degeneration of the heart muscle fibers. Eichhorst ('79) doubted the fatty character of the granules thus produced, since they failed to blacken in osmic acid. Knoll ('80) concluded that in starved pigeons the amount of ordinary fat in cardiac muscle is decreased; but there is an increase in other granules of lipoidal nature, with intermediate stages between these and true fat droplets. Popov ('85) and Ochotin ('85, '86) noted cloudy swelling, granular and fatty (?) degeneration of the cardiac muscle fibers in starving rabbits; and similar changes, with disappearance of cross-striation, were found by Isaëw ('87) in starved dogs.

Mörpurgo ('89b) noted that in starved pigeons the cardiac muscle fibers appear more or less degenerated. Measurements gave a decrease in average diameter from  $9.22\mu$  (in controls) to  $6.50\mu$  in starvation, indicating a decrease of about 50 per cent in volume. Heitz ('12) also found a marked reduction in both length and breadth of the myocardial muscle fibers in fasting rabbits and guinea pigs; likewise a decrease in nuclear size.

Coen ('90) in fasting rabbits and kittens found the cardiac and other muscle mostly well preserved, although some fibers appeared atrophic, with cloudy swelling and loss of the characteristic cross-striation. Statkewitsch ('94) noted granular, non-fatty degeneration in the cardiac muscle fibers of starved animals (cats, dogs, rabbits, pigeons); and vacuolar (rarely fatty) degeneration of the cells in the cardiac ganglia in a starved cat. Uspensky ('96) likewise described vacuolar degeneration in the cells and nuclei of the cardiac ganglia in fasting rabbits, although less marked than in other sympathetic ganglia. Kusmin ('96) noted extravasations of blood in the myocardium of fasting rabbits and guinea pigs during hyperthermia.

In *Myoxus*, *Vesperugo* and *Vespertilio*, Baroncini and Beretta ('00, '00a) found at the beginning of hibernation an enormous accumulation of fat in the interfibrillar sarcoplasm of the cardiac muscle fibers. These fat droplets decrease irregularly until by the end of hibernation the fibers are nearly or quite fat-free.

Konstantinowitsch ('03) in rabbits and Beeli ('08) in cats described during starvation a decrease in the size of the cardiac muscle fibers, with a loss of the cross-striation; the nuclei become small, irregular, and deeply staining.

Bell ('11), like Knoll ('80), recognized in cardiac (also in skeletal) muscle fine lipoidal granules, which are stainable with scarlet red, though not with osmic acid; and hence previously confused with albuminous granules in many cases. These "liposomes" he found markedly decreased in the cardiac muscle of starved rats (*Mus decumanus*). Wegelin ('13) and Bullard ('12, '16) likewise found a decided decrease or disappearance of fatty granules in the cardiac muscle fibers of fasting albino rats. Bullard ('16), however, concluded that the ordinary fatty granules are distinct from those containing phospholipins (lecithin, etc.), the latter being largely unaffected by inanition.

While a review of the chemical literature upon this problem is beyond the scope of the present work, it may be noted that chemical analyses, such as those of Rubov ('05) on dogs and Terroine ('20) on rabbit, dog and pigeon, show in starvation no very marked decrease in the cardiac fats, either the phospholipins or the neutral fats and fatty acids. The question therefore appears to be still unsettled.

### (B) EFFECTS OF PARTIAL INANITION

The effects of partial inanition upon the heart will be considered under deficiencies of protein (including malnutritional edema and pellagra); salts (rickets); vitamins, including vitamin A, vitamin B (beriberi and polyneuritis) and vitamin C (scurvy); and water.

**Protein Deficiency.**—Evidence was cited in Chapter V indicating that in both malnutritional edema and pellagra the chief factor is probably protein deficiency, although there may be other factors of importance.

**Malnutritional Edema.**—The effects upon the heart in this or allied conditions among animals have not been extensively studied (*cf.* review by Maver '20). In "cachexia aquosa" of sheep, Fröhner and Zwick ('15) stated that the heart is soft and atrophic. Hedinger ('15) mentioned not infrequent cardiac dilation in lamziekte of cattle.

In "famine edema," the condition of the heart among human victims has frequently been noted. Practically all investigators of this condition agree that bradycardia (slow heart beat) is a cardinal symptom. This suggests a cardiac lesion, although it might, of course, be of nervous or other origin. Although it is generally agreed that this edema is not to be classed with those arising from cardiac insufficiency, an atrophy or decrease in cardiac weight has been noted at autopsy by Hülse ('17, '18), Schittenhelm and Schlecht ('19), Prince ('21) and others. Paltauf ('17) reported the heart weight as nearly always below 300 g., occasionally as low as 200 g. Oberndorfer gives the weight at 180 g., and Enright ('20) states that: "The heart usually weighed only 3 to 5 oz., but in other respects was apparently normal." Mann, Helm and Brown ('20) reported the heart normal in size in 200 necropsies.

In structure, v. Jaksch ('18) and Schittenhelm and Schlecht ('19) found brown atrophy of the cardiac muscle in human famine edema. Jansen ('19a) noted pigment masses at the poles of the cardiac cell nuclei; otherwise no regressive changes. Oberndorfer ('18) reported complete absence of glycogen and fat droplets in the heart muscle. Mann, Helm and Brown ('20) noted edema or gelatinous appearance of the cardiac surface. The edema of the "auriculo-ventricular" junction, found almost constantly by Park ('18) and Menzies ('20), probably represents merely the local gelatinous metamorphosis of the epicardial fat, which has frequently been observed also in other conditions of chronic inanition.

**Pellagra.**—In general, the heart is usually found more or less atrophic in pellagra, though sometimes hypertrophied, according to the review of the literature by Marie ('08, '10), Raubitschek ('15) and Harris ('19). Thus Fraenkel ('69-'70) reported the heart hypertrophied in only 12 out of 113 cases; while it appeared atrophic or emaciated in 49. Lombroso ('92) stated that the hypertrophic appearance of the heart is often deceptive, on account of its flaccidity. Actual weights of 26 hearts of pellagrins showed 2 slightly above normal; 5 slightly below; and 19 markedly below normal. Nicholls ('12) observed in 8 cases an average cardiac weight of  $7\frac{1}{2}$  oz., the normal being 9 oz.

As to histological changes in the cardiac muscle, pigmentary atrophy was noted by Fraenkel ('69-'70) as characteristic. Lombroso ('92) found brown atrophy in 28 out of 35 cases examined, and fatty degeneration in 3. The cardiac fibers often appear abnormally separated. Brown atrophy and fatty degeneration were also found by Tuczek ('93) and Marie ('08, '10), Kozowsky ('12), and Raubitschek ('15). Kozowsky also mentions cardiac fibrosis, especially along the vessels, and pigmentary degeneration of the cardiac ganglia.

Cardiac lesions somewhat resembling those of human pellagra were found by Nicholls ('12) and Sundwall ('17) in rats and other animals fed maize and similar diets.

**Mineral Deficiency. Rachitis.**—In a dog, with a rachitoid disorder produced by a calcium-poor diet, Voit ('80) found an apparent slight hypertrophy of the heart. This was confirmed by Jackson and Carleton ('22, '23) who found a moderate hypertrophy of the heart in rats subjected to experimental rickets (Table 11). In human rickets, Cheadle and Poynton ('07) stated that the heart appears variable, but probably shares in the general malnutrition. According to Wohlaer ('11), the heart may be displaced (due to thoracic deformity), and is usually hypertrophied, especially in the right ventricle, on account of the increased labor due to the impediment to pulmonary circulation.

**Vitamin Deficiency. Vitamin A.**—Emmett and Allen ('20) and Davis and Outhouse ('21) found no definite changes in the heart of rats on diets deficient in vitamin A. The effects of this and other vitamin deficiencies have been reviewed recently by Funk ('22). Herter ('97) noted cardiac enlargement, hemorrhages, and slight "granular degeneration" in the cardiac muscle fibers of pigs during starvation, involving a deficiency in vitamin A. Meyerstein ('22) made a few observations on the heart in young white rats on diets deficient in vitamins A and B.

**Vitamin B. Beriberi and Polyneuritis.**—In human beriberi, Ellis ('98) found a marked cardiac hypertrophy, with the right side in every case much enlarged. In 125 necropsies of beriberi, the average heart weight was 13.37 oz., while in 204 controls it averaged slightly below 9 oz. Duerck ('08) noted in beriberi a variable heart weight though it was usually found hypertrophied, even in emaciated individuals. He also observed atrophic degeneration and nuclear proliferation in cardiac as well as in skeletal muscle. He stated ('08a) that the right heart is especially dilated and hypertrophied, and that the cardiac muscle shows yellowish spots and streaks of a fatty nature. In a case of acute beriberi, however, Strong and Crowell ('12) found the cardiac muscle fibers swollen, edematous, granular, and irregularly vacuolated; but not fatty. In infantile beriberi, Andrews ('12) described the right heart as greatly hypertrophied, so as to equal or exceed the left ventricle. The cardiac muscle fibers were also found hypertrophied, with congestion but no degeneration. Nagayo ('23) claims that hypertrophy of the right ventricle distinguishes human beriberi from experimental polyneuritis, in which cardiac atrophy is common.

In experimental avian beriberi, cardiac lesions have frequently been found, although Schnyder ('14) reported negative findings. In 200 fowls and 150 pigeons, Tasawa ('15) found the heart usually markedly atrophic, although the right heart (sometimes also the left) is distinctly dilated. Vedder and Clark ('12) likewise concluded that no cardiac hypertrophy, comparable to that in human beriberi, occurs in polyneuritis gallinarum (in 56 fowls). The heart may show no microscopic changes; or there may be slight edema, increased pigmentation, or incipient mucoid or parenchymatous degeneration. The cardiac lesions are described by Vedder ('13). In pigeons on diet deficient in vitamin B, McCarrison ('19, '21) observed marked decrease in cardiac weight

(Fig. 35). Findlay ('21) in 43 fowls and 41 pigeons found the heart not greatly atrophied (Table 13), and the right heart (especially the atrium) often dilated. The heart muscle appears pale and soft, with a line of edema frequently visible at the atrioventricular junction. Microscopically the myocardial cells show cloudy swelling and often beginning fragmentation. Hydropericardium occurred in 20 to 26 per cent of the birds. Very similar cardiac changes were found in inanition with water only. Hoffman ('22) in polyneuritic pigeons reported the heart "enlarged and flabby," sometimes "jelly-like." Souba and Dutcher ('22) and Souba ('23) noted a significant loss in cardiac weight in several hundred chicks on diets deficient in vitamin B. Lopez-Lomba ('23) found the cardiac weight normal in pigeons on a vitamin-free diet, excepting an early slight transient increase.

In mammals on diets deficient in vitamin B, the results upon the heart appear less striking. Schnyder ('14) found no changes in the heart muscle of mice, aside from congestion (stasis). Drummond ('18) noted enlargement of the right heart in a few black rats. Voegtlin and Lake ('19) observed slight degenerative changes in the heart of cats, dogs and rats. Emmett and Allen ('20) noted some atrophy of the cardiac muscle fibers of albino rats.

**Vitamin C. Scorbutus.**—The cardiac changes during scurvy have frequently been studied, and the literature is fully reviewed by Hess ('20). In 5 necropsies on infantile scurvy, Schödel and Nauwerk ('00) discovered a hypertrophy of the ventricles and dilation of the right heart. This was confirmed in 21 out of 31 necropsies by Erdheim ('18), who concluded that a direct ratio exists between the degree of cardiac enlargement and the intensity of the disorder. Cardiac enlargement was sometimes found even coexistent with general marasmus, and may be due to the thoracic deformity (as in rickets). Hess ('20) described and demonstrated by means of roentgenograms the enlarged heart in infantile scurvy. There is also almost always an increase in pericardial fluid.

In human adult scurvy, Sato and Nambu ('08) found the heart not especially enlarged, but the cardiac musculature often anemic and brownish, sometimes cloudy, with fibrosis. Aschoff and Koch ('19) described the enlargement of both ventricles, with possible fatty degeneration of the cardiac musculature. Comrie ('20) found the heart feeble, showing brown atrophy.

In experimental scurvy of guinea pigs, Holst and Frölich ('07, '12) frequently observed a fatty degeneration of the cardiac muscle. Lesions of the cardiac musculature were also described by Rondoni and Montagnani ('15). Findlay ('21a) found dilation but no hypertrophy of the heart in scorbutic guinea pigs. The cardiac muscle fibers show loss of striation, but no fatty degeneration. The interstitial stroma is edematous in places, with capillary congestion; and definite hemorrhagic infiltration of the heart wall was noted in 5 out of 12 cases. A slight increase in the weight of the heart in scorbutic guinea pigs was found by La Mer and Campbell ('20) and Bessesen ('23) (Table 12). A relative increase is to be expected, on account of the loss in body weight. Höjer ('24) noted atrophy of the cardiac fibers, with necrosis and tendency to calcification.

**Aqueous Inanition.**—In pigeons perishing on a dry barley diet, Schuchardt ('47) found a loss of 36 per cent in the average weight of the heart. Bowin ('80)

in rabbits and dogs on dry food found that the heart undergoes relatively less loss in weight than does the body, and retains its original water content (not confirmed by Skoritschenko '83). Pernice and Scagliosi ('95a), in a dog which died on a dry bread diet, found inflammatory changes in the heart, especially the endocardium. The perivascular connective tissue is thickened, rich in nuclei and spindle cells. The cardiac muscle fibers appear pale, less distinctly stainable and more homogeneous in appearance with indistinct striation. The myofibrillae seem thinner and less closely packed; the nuclei numerous and some showing mitosis.

Durig ('01) observed that in frogs upon withdrawal of water from the body, the organs lose unequally in weight. Excepting the brain, the heart loses less than any of the other organs. Kudo ('21) found that in adult albino rats on acute thirst experiments the heart lost 30.6 per cent in weight (body loss 36.1 per cent); while in chronic thirst experiments the heart lost 46.3 per cent (body loss 52.4 per cent). In total inanition, the results were very similar to those in chronic thirst (Table 9). In thirst experiments in which young albino rats were held at constant body weight for various periods, Kudo ('21a) found that the heart remains nearly constant in weight, with a slight increase (of doubtful significance) in the longer periods (Table 10).

### (C) EFFECTS OF INANITION UPON THE BLOOD VESSELS

Numerous scattered observations are available concerning the effects of the various types of inanition upon the blood vessels.

**Total Inanition (or on Water Only).**—Chossat ('43) gave pigeons water only until death with loss of about 40 per cent in body weight. He found an apparent decrease of nearly 30 per cent in the weight of the great vessels, but considered the result inconclusive on account of variability in the extent of removal of the vessels. Bidder and Schmidt ('52) found an apparent loss of about 38 per cent in the weight of the aorta and vena cava in a starved cat, with body loss of about 50 per cent. Strelzoff ('64) observed an apparent atrophy of the capillaries in fasting rabbits and guinea pigs, especially in the small intestine, stomach and pancreas; to a lesser extent in the liver, large intestine and muscles. The nuclei of the capillary wall apparently undergo a fatty metamorphosis, and the vessels finally disappear entirely. In starved rabbits and dogs, Mankowsky ('82) found the vessels of the spinal cord unaffected, aside from endothelial proliferation. On refeeding, a swelling of the endothelial nuclei of the cerebral vessels was noted. Poljakoff ('88) noted that in the albino rat the blood capillary plexus of the fat lobules undergoes atrophy together with the adipose tissue during inanition.

Trivus ('99) made a thorough study of the changes in the walls of ligated arteries (femoral and common carotid) in rabbits and dogs fasting various periods with losses in body weight up to 40 per cent. In general the vascular wall shows a weak inflammatory reaction. Near the ligature the leukocytes predominate over the cells of the granulation tissue; many eosinophile and pigmented cells appear. The endothelium of the intima frequently thickens, forming several layers of cells. In the tunica media, the cytoplasm and nuclei

of the muscle cells undergo vacuolation and the elastic layers are more wrinkled (due to the shrinkage of the vessel). The stellate connective tissue cells of the adventitia undergo fatty degeneration, and extensive hemorrhages into the surrounding tissue are frequent. In animals amply refed after inanition, these changes in the vascular wall have largely disappeared, excepting slight necrosis and fatty degeneration which still persisted in the cells near the ligature.

In dystrophic infants, according to Lesage ('11), the blood vessels usually appear normal in structure, although arteriosclerosis sometimes appears.

Stefko ('23) calls attention to the frequent hemorrhagic diathesis (purpura) in cases of human starvation. The condition appears to be due to degeneration in the walls of the blood vessels, which results from the impoverishment of the blood. Possibly this hemorrhagic condition should be ascribed to the exhaustion of vitamin C, as occurs in scurvy.

**Protein Deficiency.**—Many investigators of **malnutritional edema** ascribe the condition primarily to an injury of the capillary walls (Lange '17; Schittenhelm and Schlecht ('19); Maver '20; Bürger '20; Maase and Zondek '20; *et al.*). Oberndorfer ('18) considered the universal capillary congestion of significance, and Maver, Maase and Zondek mention the possibility of direct toxic injury to the capillary walls. The question is closely related to that of the rôle of the capillaries in the production of edema in general, the literature upon this topic being reviewed by Lange ('17).

Although, as previously stated, protein deficiency has usually been accepted as the primary cause of famine edema, the question has been raised as to whether this (as also other edemas) may not involve also a calcium deficiency. The work of Herbst upon invertebrates (see Chapter III) showing the effects of calcium deficiency in dissolving the intercellular cement substance has been cited in this connection; as well as in disorders such as scurvy, with characteristic capillary hemorrhages. Chiari ('10) has reviewed the evidence indicating that calcium deficiency in general tends to increase the permeability of the capillary walls.

In **pellagra** (presumably due chiefly to protein deficiency), vascular changes have been described. Fraenkel ('69-'70) mentioned pigmentation of the capillaries and fatty degeneration of the adventitia in the brain vessels. Primary degeneration and sclerosis of the blood vessels was emphasized by Marie ('08, '10), Nicholls ('12), Kozowsky ('12), Raubitschek ('15) and Harris ('19) as of importance in the pathogenesis of pellagra.

In **ricketts**, Kassowitz ('12), as previously mentioned, has long advocated the theory that the characteristic changes in the zone of enchondral ossification are primarily due to hyperemia and increased vascular proliferation in the region. This theory, however, has not met with general acceptance.

In relation to **vitamin deficiency**, vascular changes have been noted especially in connection with **scurvy** (deficiency of vitamin C), in which the hemorrhages form a constant and conspicuous lesion, and petechial extravasations have been described as occurring in nearly every organ. The exact cause of the hemorrhagic tendency is uncertain. Direct toxic injury to the capillary wall has been suggested by Sato and Nambu ('08). The possibility of a calcium-

deficit was discussed by Gerstenberger ('18), which recalls the fundamental work of Herbst (mentioned above). Bierrich ('19) thought the capillary damage might be due to the lack of some N-containing building stone in the capillary endothelium. Wallgren ('21) calls attention to the occurrence of scorbutic edema, likewise due to an abnormal permeability of the capillary walls. Endarteritis of the medium sized arteries has also been observed by Ide ('22), and Sato and Nambu state that the aorta sometimes shows sclerosis. The increased permeability of the capillary walls has been used by Hess ('14) in his "capillary resistance test" in the diagnosis of scurvy. The whole question is thoroughly reviewed by Hess ('20).

Findlay ('21a) has recently discussed the vascular changes in guinea pig scurvy, which appear to involve a primary interference with the nutrition of the capillary endothelium. The endothelium becomes swollen and degenerated, producing congestion. This occasions increased transudation of fluid through the capillary wall, and, as the intercellular substance is weakened, leads to diapedesis and characteristic hemorrhages. Höjer ('24) ascribes the hemorrhages to a weakness of the vascular wall, caused by an atrophy of the collagenous connective tissues, which is considered characteristic of scurvy.

**Aqueous Inanition.**—In a dog on dry diet, Pernice and Scagliosi ('95a) found the blood vessels generally congested (passive hyperemia) and showing degenerative changes, notably in the nervous system and viscera (especially the kidneys). Similarly in young chickens, chronic thirst involved vascular congestion in the capillaries and larger vessels. In the aorta and right carotid, marked hyperemia, small hemorrhages and round cell infiltration were noted in the tunica adventitia and tunica media, although the intima showed but slight changes. Kudo ('21a) made observations indicating an apparent increase in the weight of the aorta in young albino rats subjected to chronic thirst for various periods.

## CHAPTER XV

### EFFECTS ON THE BLOOD

The effects of inanition upon the blood are of unusual interest, not only because of its fundamental importance to the organism, but also on account of its practical use in diagnosis. Although relatively stable, the blood is found to undergo variable changes in nearly every type of inanition. The effects of inanition upon the blood will first be summarized according to its various components, and later considered in detail under (*A*) effects of total inanition and (*B*) effects of partial inanition.

#### SUMMARY OF EFFECTS ON THE BLOOD

While the blood exhibits in some respects a considerable degree of stability under various conditions of inanition, the available data appear so variable and conflicting that a summary is unusually difficult. The *variability* affects chiefly the blood cell counts, the structure of the cells rarely being appreciably modified. The blood counts are affected primarily by the water content of the plasma, which undergoes marked fluctuation under various conditions. In addition, there are also frequent and extensive changes in the differential leukocyte count, probably due chiefly to changes in the hemopoietic system. It is evident that the number of blood cells in general will vary according to the ratio between blood destruction and blood regeneration, both of which may be variably affected by inanition. In interpreting the differential leukocyte count, it must be remembered that any marked variation in the polymorphonuclears will affect the percentage count of the other varieties, independent of their absolute numbers. Other variations observed in both red and white cells may depend upon the species, age, individual and the type of inanition concerned, as well as (sometimes) imperfect technique and other unknown factors. The principal results will be summarized briefly for the separate elements of the blood under varied conditions of inanition.

The **total volume** of the blood, so far as has been accurately determined, although somewhat variable, tends to maintain its normal ratio to the entire body. Changes in distribution, however, with diminished peripheral circulation, may give a deceptive appearance of anemia in various (especially chronic) types of inanition.

The blood **plasma** is subject to various changes in chemical composition, although for a long time its losses may be restored through absorption from the various tissues. The **water content** undergoes marked fluctuations, which affect the concentration of the blood and consequently the cell counts. **Hydremia** frequently occurs, especially in later stages of inanition and in certain

chronic forms, particularly in protein deficiencies (malnutritional edema). On the other hand, anhydremia, with concentration of the blood, often occurs, especially during thirst.

The **erythrocytes** rarely show structural changes (anisocytosis, poikilocytosis), although there is evidence of their increased destruction in severe inanition, and the frequent appearance of nucleated red cells in the circulating blood indicates intensive regeneration, especially upon refeeding after inanition. During human inanition, the erythrocyte count is often within normal limits, but sometimes increased (especially in total inanition and earlier stages), or decreased (especially in chronic and late stages). In animals, the red cell count appears more frequently increased in the earlier stages of total inanition, often decreasing later. In hibernation, the erythrocyte count is variable.

Among the various types of partial inanition, in malnutritional edema (due chiefly to protein deficiency), hydremic anemia is very characteristic in both man and lower forms. The results of a dietary deficiency of iron are variable, but apparently anemia may be produced in young animals. In rickets the blood is sometimes normal, but there is usually anemia, somewhat proportional to the severity of the rickets. In vitamin B deficiency (beriberi) there is usually well marked anemia. In vitamin C deficiency (scurvy), the erythrocytes are variable; but there is usually a secondary anemia, often of the chlorotic type, with hemoglobin disproportionately low. In experimental scurvy of guinea pigs, the blood changes are usually slight. Aqueous deficiency (thirst) on dry diets usually produces in human and animal experiments an increased red cell count (in extreme cases nearly doubled) through concentration of the plasma.

The **leukocytes** likewise rarely present morphological changes, though cytoplasmic and nuclear degeneration has occasionally been noted. The **total leukocyte count** during inanition in human adults is variable, often showing an early increase, with a later decrease. In atrophic infants, it is usually increased, sometimes normal or decreased. In animals it is variable, but usually decreased. During hibernation, there is in all cases a remarkable decrease in the number of leukocytes, which apparently migrate out of the vessels. Also during malnutritional edema there is a marked leukopenia. In pellagra and rickets, leukocytosis is usually found. In human and animal beriberi, a leukocytosis has been observed in most cases, though sometimes a leukopenia. In infantile scurvy there is usually a leukocytosis, but in human adults and in guinea pigs the total leukocyte count is nearly normal. During thirst the leukocyte count is variable.

The **differential leukocyte count** is in general quite variable during inanition. In fasting human adults, the polymorphonuclear percentage is variable, usually increased at first, with decrease in later stages. The lymphocytes are also variable, usually decreased, but the eosinophiles are generally increased. In atrophic infants the polymorphonuclears frequently show a relative increase, sometimes also the lymphocytes; the other varieties are normal or variable.

In animals, starved with or without water, the polymorphonuclears are usually decreased. The lymphocytes are variable, most frequently showing a

decreased percentage, sometimes after a preliminary increase. The mononuclear and transitional forms are variable. The eosinophiles are usually normal or increased, though sometimes decreased.

During malnutritional edema, a lymphocytosis is very constant and characteristic. In pellagra, the results are variable and inconclusive. In rats on vitamin B deficiency, a marked lymphopenia has been observed. In human scurvy (especially adult) a relative lymphocytosis is usual; and a decrease in polymorphonuclears has been observed. There are no marked changes in scurvy of guinea pigs.

The **blood platelets** have been studied but little during inanition, but seem as a rule to show no marked changes. A progressive decrease in number has been found during deficiency in vitamin A. In scurvy, they are normal or increased, hence they cannot be responsible for the hemorrhagic tendency in this disorder.

**On refeeding** after inanition, the blood as a rule quickly recovers its normal condition, although a transient hydremia may occur, due to the more rapid regeneration of the plasma. Following prolonged or severe types of inanition, however, there may be a considerable delay in the recovery, doubtless due to delayed regeneration in the hemopoietic system. Regeneration of the blood is much retarded on protein-poor diets. During convalescence in human scurvy the erythrocyte count is sometimes remarkably high.

#### (A) EFFECTS OF TOTAL INANITION, OR ON WATER ONLY

After an introductory discussion, the results will be considered first in man, adult and infant, followed by a review of the results in lower animals.

On account of the intense interest in the blood, and the ease with which it may be examined, even during life, an enormous literature has accumulated upon the subject, including the effects produced by various forms of inanition. Harvey (1651), who discovered the circulation of the blood, concluded that it is to be considered a tissue of the body, rather than merely a liquid food, since it remains in quantity during starvation in man and animals.

Opinions have varied widely concerning the *extent of loss* in the blood during starvation. The earlier authors were impressed with the general appearance of anemia, both during life and at autopsy. Rokitansky ('54), for example, concluded that in starvation, or atrophy from other causes, the loss is relatively greatest in the blood, exceeding even that in the adipose tissue. A general condition of anemia at death from starvation was likewise claimed by David (1815), Collard de Martigny (1828), Tiedemann ('36), Taylor ('20), Voelkel ('86), Porter ('89) and many others. Claude Bernard stated that the diminished resistance of starved animals is doubtless due to the decreased mass of blood. On the other hand, microscopic examination revealed surprisingly little structural change, so that Carl v. Voit ('81) and others held that the blood is one of the tissues least affected by inanition. According to Heidenhain ('57), Cyr ('69), Falck ('81), Cohnheim ('89), Grawitz ('95) and most recent authors, the atrophy in total mass of the blood during inanition is, in general, proportionate to that of the whole body.

There is, however, much variation in the changes in mass and composition of the blood, varying according to species, age, individual and type of inanition, as will appear in the subsequent review of the literature. The changes in *physico-chemical constitution*, which in general lie outside the scope of the present work, are reviewed by Burckhardt ('93), Lackschewitz ('93), Weber ('02), Lewinski ('03), Tria ('11), Schulz ('12), Robertson ('13), Gerpott ('13), Ash ('14, '15), Nobécourt ('16), Trowbridge, Moulton and Haigh ('15, '18, '19), Lusk ('17), Hatai ('18), Moulton ('20) and others. In general, excepting extreme stages and variations in water content, it may be stated that the chemical composition of the blood undergoes relatively little change during inanition, its losses being largely compensated through absorption of materials stored in the various tissues and organs. Accurate analyses, however, show certain definite and characteristic changes during various types of inanition.

Special mention may be made of the *fat content* of the blood, since the fat granules (as hemokonia) are visible by the ultramicroscope. Schulz ('96, '97) found the fat content of the blood markedly increased (sometimes doubled) in fasting pigeons and rabbits. This was confirmed by Daddi ('98b) for dogs in short fasting periods, although a progressive decrease occurs in longer fasts. Further data are cited by Weber ('02), Rothschild ('15), and Greene and Summers ('16). Bloor ('14) demonstrated that in dogs the result varies according to the nutritional condition of the dog preceding the inanition. Aside from the observations of Reicher ('09), Nobécourt and Maillet ('14) and Gage ('20, '21), apparently no attempt has been made to correlate these chemical changes with the morphological structure shown by the ultramicroscope. Some possible relations between the lipemia during inanition and the deposition of lipoidal fat in certain organs will be mentioned later.

**Changes in Human Adults.**—The effects of total inanition (or water alone) upon the blood have frequently been studied in man. Morgagni (1761) found very little blood in the larger vessels of two men who died from chronic starvation. This was confirmed by Haller (1771). Dutrochet (1816) stated that the number of red blood corpuscles is increased by rich nutriment, and decreased by fasting. Donovan ('48) observed marked anemia in the Irish famine victims. Brouardel ('76) found a high red cell count and a syrupy consistency of the blood in a case of starvation from esophageal stricture. The blood changes during Dr. Tanner's fast are given by Van der Weyde ('79-'80). The digestive leukocytosis was studied by Detoma ('80). Cadet ('81) found that a 24 hour fast causes a slight increase in the number of red cells (per cu. mm.), and a decrease in the white cells and platelets. Curtis ('81) observed during a 45 day fast great variations in the number (2,370,000-6,770,000), size and form of the erythrocytes, probably due chiefly to imperfections of technique.

Hayem ('82, '89) claimed that in chronic cachexias, the loss in the total mass of blood is relatively greater than that of the whole body. The decrease in the red cell count is at first slight; later it may be extreme. The leukocyte count varies according to the cause of the cachexia. The number is usually increased; but, as likewise for the platelets, it may decrease before death. The structure of the leukocytes may also change, with cytoplasmic vacuolation and less

distinct granulation. The ameboid movement is preserved. The nuclei may appear larger and more vesicular. The differential leukocyte count is often modified.

In fasting insane patients, Andreesen ('83) found that the red cell count at first increases, later decreases. Ingestion of water causes a transient decrease, through dilution of the blood plasma. Refeeding may likewise cause a temporary decrease in the red cell count.

Senator ('87) in Cetti's 10 day fast (with loss of 11.14 per cent in body weight) found the initial red cell count 5,720,000, decreasing to 5,287,000 on the 4th day, and increasing to 6,830,000 on the 9th day. After 2 weeks of refeeding, the count decreased to 5,730,000. The leukocyte count on the 9th fast day (not observed earlier) was 4,200, the ratio to red cells being 1:1,619. On the 2nd day of refeeding, it was 12,300 (1:533). The hemoglobin, by Fleischl's hemometer, decreased from (initial) 110-118 to 85-90 on the 9th day of fasting.

Luciani ('89, '90), in the 30 day fast of Succi, noted slight fluctuations in the red cell count (usually between 4.5 and 5 millions), ascribed chiefly to variations in dilution of the plasma due to water ingestion. The leukocytes decreased from 14,536 (initial) to 861 on the 7th day; increased to 1,550 on the 9th day; with slightly higher counts later. On the whole, the blood appeared relatively resistant to change.

Von Limbeck ('92) claimed an increase in the red cell count and hemoglobin content during fasting. Lehman *et al.* ('93), in Breithaupt's fast, found an increase in the red cell count from 4,953,000 to 5,150,000 on the 2nd day; with 4,801,000 on the 6th day, and 4,812,000 on the 2nd day of refeeding.

Tauszk ('94a, '96), in a repeated 30 day fast by Succi, found (as in the previous fast) but slight variations in the red cell count (range 4,840,000-5,472,000). The form of the erythrocytes remained normal throughout. The leukocyte count decreased progressively from 9,600 on the 3d day to 4,200 on the 30th day. Differential count showed a relative increase in the eosinophiles (2.7-4.7 per cent) and in the polymorphonuclears (64.1-79.2 per cent), but a decrease in the mononuclears, including lymphocytes (33.1-16.0 per cent).

Grawitz ('95) reviewed the results of inanition upon the blood of man and animals. He concluded that there is in general a decrease in total quantity, proportional to that of the body; but relatively slight change in composition, aside from a variable degree of hydremia, which may also appear upon refeeding. Extensive reviews of the literature on the subject were likewise made by Schwinge ('98), Pashutin ('02), Benzançon and Labbé ('04), Bardier ('13), Ash ('15), and Morgulis ('23).

Cabot ('04) stated that fasting causes a temporary increase in the red cell count by concentration of the blood. In chronic malnutrition the leukocytes may decrease to 3,000. Opie ('04) found that starvation may decrease the eosinophile leukocytes to less than 0.5 per cent; but Meyer ('05) observed an increase of eosinophiles from 3.4-3.7 to 6.5 per cent in a healthy man after a fast of 24 hours.

In a 14 day fast (1 liter of water taken daily), the observations on the blood by Charteris ('07) are summarized in the accompanying table.

## BLOOD COUNTS OBSERVED DURING A FAST OF FOURTEEN DAYS (CHARTERIS '07)

Date (1907)	Hemoglobin	Leukocytes	Red cells (millions)	Differential count—percentage of					
				Poly-morph.	Lymphocyte	Large mono.	Eosino-ophile	Transi-tional	Baso-ophile
1-16 <sup>1</sup>	110	5,300	5.6	51	30.0	11.6	1	6.0	
1-17 <sup>1</sup>	...	.....	.....	62	23.0	10.0		...	
1-18	110	.....	....	75	11.7	7.0	2	4.5	
1-19	110	.....	7.2	61	23.0	9.5	2	3.0	I
1-20	108	10,000	5.6	70	18.0	8.0	2	1.0	I
1-21	108	.....	6.4	63	22.0	12.0	2	2.0	
1-22	109	11,148	6.16	70	14.0	9.0	2	4.0	
1-23	108	14,000	....	77	9.0	7.0	3	2.0	I
1-24	...	14,000	5.6	69	10.0	12.0	4	4.0	2
1-25	...	.....	....	60	26.0	6.0	5	2.0	I
1-26	103	9,000	5.6	66	18.0	9.0	5	1.0	I
1-27	98	.....	5.0	60	25.0	10.0	5		
1-29	95	10,000	....	60	18.0	16.0	3	2.0	
1-30	96	9,000	5.2	56	26.0	13.0	4	1.0	
1-31	...	.....	....	66	16.0	9.0	7	1.0	
2-3 <sup>2</sup>	93	.....	5.4	74	14.0	9.0	2	1.0	
2-4									
2-6	94	7,000	6.4	62	24.0	11.0	3		
2-8	102	7,800	5.2						

<sup>1</sup> Signifies dates preceding the fast. <sup>2</sup> Subsequent refeeding.

The blood changes appear relatively slight, aside from a moderate leukocytosis with gradual increase in eosinophiles.

Gordon observed the blood of Martin ('07), a medical student, who fasted 9 days on 24 ounces of water daily. There was no significant variation in the erythrocytes or total leukocytes, excepting a rise in the latter of 10,000 on the 2nd and 9th days. The differential count was somewhat irregular.

Benedict ('07, '08), in short fasts of 2-7 days, found a progressive fall in the erythrocyte count (with corresponding decrease in hemoglobin); and a relative leukocytosis, with a high per cent of polymorphonuclears, but a progressive fall in the total leukocyte count in the longer fasting period.

Penny ('09) records a few observations on the blood of a physician (self-experiment) fasting on water only for 30 days, as follows:

Day of fast	Red cells	White cells	Polynu-clears, per cent	Large mononu-clears, per cent	Lympho-cytes, per cent	Eosino-philcs, per cent
12th.....	6,600,000	10,000	76	12	12.0	
20th.....	7,000,000	11,000	76	18	6.0	
30th.....	6,000,000	8,800	70	20	7.5	1.5

Lustig ('11) concluded that during human fasting there is but little change in the red cell count, with a decrease in the number of leukocytes. Türk ('12)

held that the human blood is relatively resistant during fasting. There is a tendency to increase in the red cell count; and in long underfeeding a notable decrease in the number of leukocytes, especially the neutrophiles. Lazarus ('13) similarly concluded from the available evidence that total inanition in man and lower animals does not produce anemia; but in chronic inanition the results are more uncertain.

Howe and Hawk ('12) in 2 men fasting 7 days noted an initial rise in the number of polymorphonuclear leukocytes, with a decrease below normal at the end. The lymphocytes have an opposite tendency. One man showed a progressive increase in eosinophiles. Mann and Gage ('12) found an increased staining capacity in the leukocytic nuclei of man and frog, upon refeeding after a fasting period.

Gruner ('14) concluded from a review of the literature on the differential leukocyte count during starvation that the number of lymphocytes, after a preliminary decrease, remains nearly constant; while the neutrophiles show a progressive increase. He attempted to explain the blood changes in relation to those in the hemopoietic system. Schwartz ('14), in an exhaustive review of the eosinophiles, concluded that, while variable, they usually show a tendency to increase during inanition, especially in human fasting.

Ash ('14, '15) reviewed the literature on the blood changes during inanition, showing the variable and often discordant results. He also made careful daily observations on the blood (hemoglobin, erythrocyte and leukocyte count, total and differential), together with some observations on coagulation time, density, etc., in the case of Levanzin, who fasted 31 days on water only, with loss of 21.9 per cent in body weight. In general, the blood appeared very stable in composition, with fluctuations not exceeding the normal range, and no significant change in the size, form or structure of the blood cells. As shown in Fig. 72, the erythrocyte count ranged between 6 and 7 million, and the hemoglobin between 85 and 93 per cent. There was, however, a transient marked rise in the total leukocyte count, from 6,000 up to 12,400 on the 3d fast day, decreasing to nearly normal in the latter half of the fasting period (Fig. 74). The polymorphonuclear neutrophile count closely parallels the total leukocyte count (Fig. 74), rising from 60 to 79 per cent on the 3d fast day, decreasing irregularly thereafter, but about normal in the latter half of the test. There is no significant change in the lymphocytes and large mononuclears. The transitional form shows transient rises (to 5.0-6.5 per cent) on four different days (Fig. 73), and the eosinophiles show a decrease in the second half of the fasting period.

Gage ('20, '21), using the dark-field microscope, studied the fat particles (hemokonia or "chylomicrons") which appear in the blood after ingestion of fat, and gradually disappear during fasting.

Reiss ('21) reviewed the effects of malnutrition (war diet) on the blood. Lubarsch ('21a) emphasized the extensive destruction of blood corpuscles as an evident effect of the malnutrition (chiefly due to mixed deficiencies in the diet) during the war period. Stefko ('23) concludes from an extensive study that the blood during starvation may be either thickened or thinned. The thickened blood may collect in the inner organs, leaving the periphery anemic. The

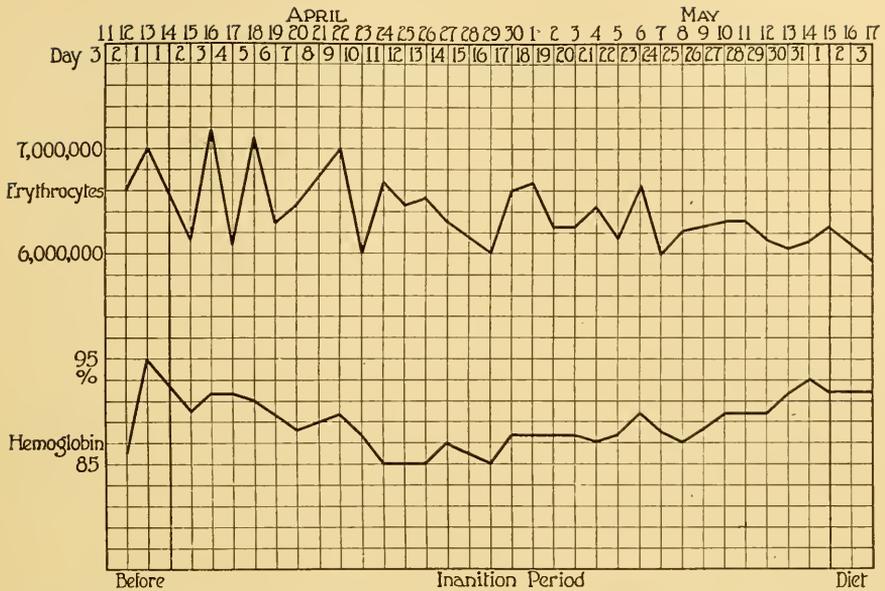


FIG. 72.—Chart showing the slight changes in the number of erythrocytes (red blood cells per cu. mm.) and percentage of hemoglobin in Levanzin, fasting 31 days on water only. (Ash '15.)



FIG. 73.—Chart showing the fluctuations in the differential leukocyte count (eosinophile, basophile and transitional forms) in the blood of Levanzin during his fast of 31 days on water only. (Ash '15.)

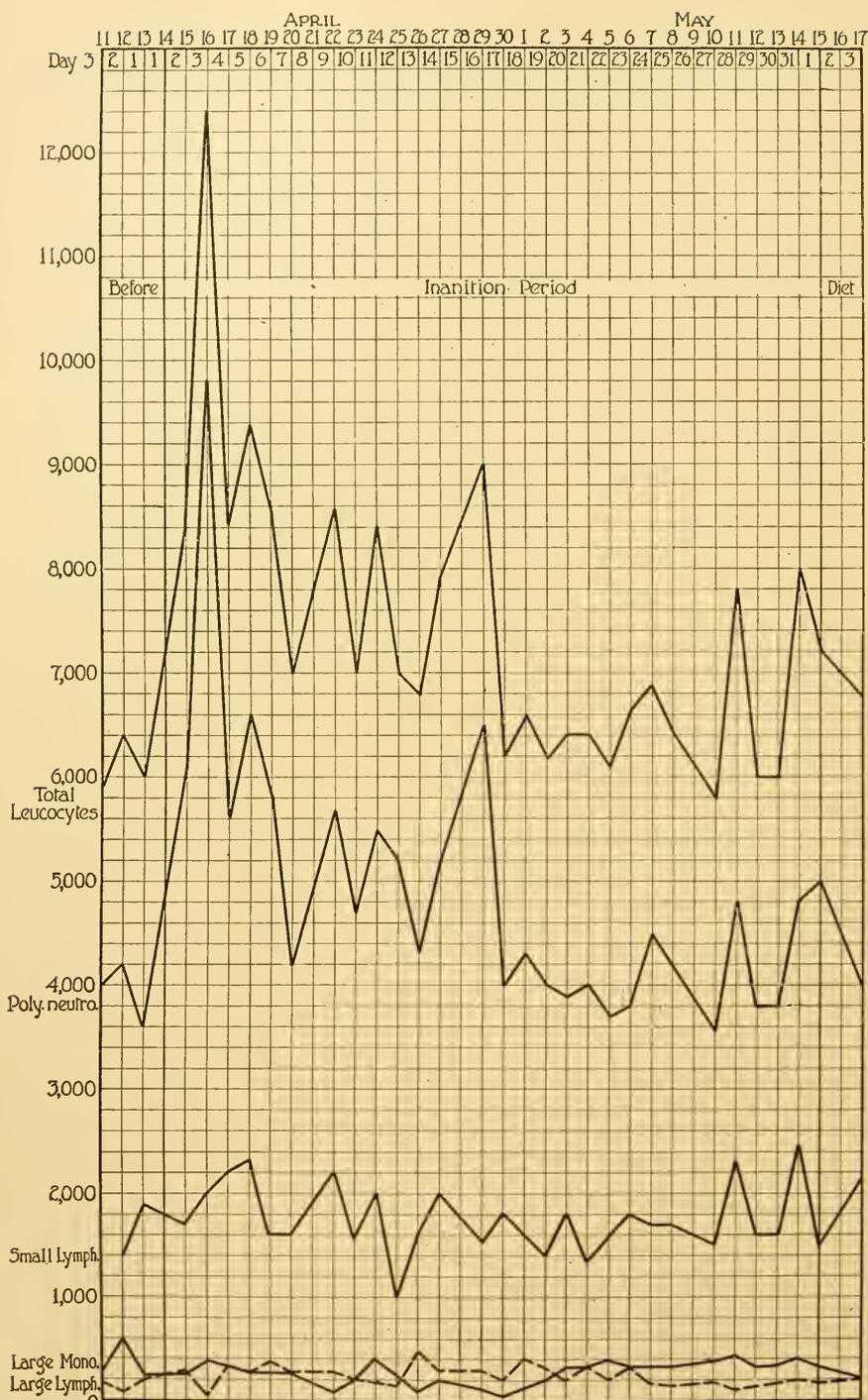


FIG. 74.—Chart showing the changes in the total leucocyte count and in the various types of leucocytes (per cu. mm.) in the blood of Levanzin during his fast of 31 days on water only. There is an initial rapid rise in the total count, with irregular decrease to nearly normal in the latter part of the fasting period. This change in the total count is apparently due to the change in the number of polymorphonuclear neutrophils, there being no significant change in the small and large lymphocytes and large mononuclear forms. (Ash '15.)

thickening is due to an excessive consumption of the plasma, resulting in a high red cell count ("Pseudopolyglobulie"). There is also a leukocytosis, with relative increase of mononuclear and transitional forms. Thinning of the blood is due to a hydremia associated with edema, and may be due chiefly to protein inanition. Further data upon this topic will be cited in connection with infantile malnutrition and also under the various types of partial inanition.

**Changes during Malnutrition in Infants.**—In considering the blood changes in atrophic infants, it must be kept in mind that pedatropy is usually the result of gastrointestinal or other chronic disorders, and in many cases represents toxic effects as well as those of chronic inanition.

Parrot ('77), who described infantile athrepsia, considered progressive leukocytosis a characteristic symptom. D'Orlandi ('99), however, found the total and differential leukocyte counts unmodified in hypothrepsia (mild or moderate uncomplicated inanition). In acute and chronic athrepsia, Cuffer ('78) observed an increased red cell count (up to 9 millions) as well as increase in total leukocytes (10,000-40,000). Cantalamassa ('92), claimed that anemia results in children who are starved as well as in cachexia from chronic diseases.

Schlesinger ('03) found that in moderate infantile atrophy there is a variable anemia, due to dilution of the plasma; but in more severe cases the anemia may be masked by loss of the plasma. In uncomplicated atrophy, the leukocyte count may be normal or below normal, with normal differential; but in gastroenteritis the blood is increased in density, with increased red cell and leukocyte count, showing lymphatic and polynuclear hyperleukocytosis. Just before death, there is a marked and rapid fall in the density of the blood, with decreased red cell count.

Thiercelin ('04) claimed marked and constant blood changes in athrepsia. At first, the blood appears concentrated; but later there is progressive anemia and the red cell count may decrease to 3 million, or even below 1 million (Luzet). The red cells are also malformed, and often nucleated. There is considerable leukocytosis. The blood is easily coagulable; hence frequent venous thromboses may occur in the brain, lungs and kidneys. Rieber ('05) noted leukopenia in 2 moderately severe cases of pedatropy, with an increase of polymorphonuclears during severe complications.

Arneth ('05) concluded that the characteristic leukocytosis found in newborn infants is not due to the deficient nutrition during that period.

In chronic athreptics, Minet ('07), found 19 showing an increased erythrocyte count (5-7 millions) due to dehydration; while only 5 showed a decrease (below 5 million). Nucleated red cells were found in 9 out of 19 cases. Progressive leukocytosis (11,000-37,000) appeared in 15 cases; and a decrease (below 9,000) in 4. A relative increase in polymorphonuclears occurred in 18 out of 19 cases; often with indistinct nuclei and neutrophile granules scarce or absent. The polynuclear eosinophiles appeared rare (0.5-1 per cent) or absent. The neutrophile myelocytes or basophiles were constant (0.2-3 per cent). Minet also noted that digestive leukocytosis occurs as in normal infants, and is sometimes very marked, especially in late stages of cachexia (confirmed by Villa '18).

Herter ('08) found a variable degree of simple anemia in infantilism resulting from chronic intestinal infection. Benjamin ('08) stated that severe infantile malnutrition causes a polynuclear leukocytosis; but in atrophy (decomposition) the lymphocytes are decreased. The eosinophiles tend to disappear and the large mononuclears are mostly replaced by younger forms.

Lenoble ('08) in a 7 months' infant convalescent from malnutrition found slight anemia. The differential count shows 77 per cent of lymphocytes and 2.3 per cent of eosinophiles, the other varieties diminished. Lesage ('11) stated that atrophic infants in general show a variable degree of anemia, and often leukocytosis (especially lymphatic).

Lust ('11) found that acute nutritional disturbances in infants usually cause a concentration of the blood, which may change to hydremia in terminal stages. In chronic malnutrition, however, the blood usually changes but slightly in water content.

Rosenstern ('11), however, concluded that in (total) complete inanition there is no change in concentration of the blood, contrary to the earlier views. The total quantity of blood decreases in proportion to the body. There is a decreased leukocyte count. In chronic malnutrition the effects are variable. There may be hydremia upon refeeding.

Nobécourt and Maillet ('14) found that the minute fat granules (hemokonion), visible in the blood through the ultramicroscope, usually decrease in number or disappear during infantile malnutrition, but reappear during recuperation when milk diet is resumed. These granules evidently correspond to the "chylomicrons" of Gage ('20, '21) above mentioned.

Nobécourt ('16) reviewed the literature of blood changes in hypotrophic and cachectic infants. The changes appear variable, with more or less anemia, but sometimes an increase in erythrocyte count. The leukocytes are also variable and may be normal, increased or decreased in number. The differential count may be nearly normal.

Meyer and Japha ('19) described 3 types of infantile anemia, associated with hydremia. These may be caused by toxic influences, constitutional weakness (aplastic anemia) or alimentary deficiencies.

Schindler ('10) thought that the increased pigmentation of the iris in malnourished infants may be hematogenous in origin, due to increased destruction of erythrocytes. The hemosiderosis observed by Helmholz ('09) and others in the liver and spleen may be similarly explained.

Bergel ('19, '21) believes that the fats and lipoids exert a specific chemotactic effect upon the lymphocytes; and that the lymphocytosis in the blood during fasting is due to the characteristic lipemia associated with the mobilization of the reserve body fat.

Marfan ('21) found the data upon blood changes in malnourished infants obscure and contradictory. In mild or moderate malnutrition (hypothrepsia) there is usually anemia with reduction in the erythrocyte count to 3 or 4 millions, the leukocytes being unchanged. But in severe stages (athrepsia) the blood is concentrated through dehydration, with erythrocyte count of 5 or 6 millions; also marked leukocytosis (up to 30,000), with relative increase of polynuclears and decrease in mononuclear forms.

Uthelm ('22) states that in Marriott's clinic the decrease in blood volume and the concentration (anhydremia) are considered important factors in the pathogenesis of athrepsia.

**Inanition in Animals.**—The changes in the blood of animals (vertebrates) during total inanition, or on water alone, will now be considered.

Morgagni (1761) observed that in a starved puppy the heart was distended with blood, but the large vessels nearly empty. Haller (1771) likewise noted a decreased amount of blood in the vessels of fasting frogs. Lucas (1826) confirmed Dutrochet (1816) as to the apparent decrease in the number of red blood corpuscles, but observed no change in the color and consistency of the blood in starved animals (various amphibians, birds and mammals). Collard de Martigny (1828) in starved dogs and rabbits always found "la presque entière vacuité du système sanguin." In rabbits of the same litter he measured the amount of blood escaped and remaining in the large vessels, finding a progressive decrease up to 11 days of starvation. Thus the blood, though concentrated, decreased in volume so that he believed death results from its insufficiency to supply the tissues. Magendie (1851-'52) likewise observed a concentration of the blood, with marked increase of solids and red corpuscles, in a stallion given water only.

Chossat ('43) in starved pigeons (loss of 40 per cent in body weight) found an average decrease in collectable blood from 12.74 to 4.88 g., an apparent decrease of 61.7 per cent. He considered the decrease in solids still greater, since the water content of the blood increases, whether water is ingested or not. Starved chickens likewise became anemic. Bidder and Schmidt ('52) observed an even greater apparent decrease of 94 per cent in the escaped blood of a starved cat, with loss of about 50 per cent in body weight. The unreliability of this method is shown by Sedlmair's ('99) observation of 54.3 g. in the weight of the collectable blood in a control cat, 1.5 g. in one starved cat, and 27.9 g. in another. Heidenhain ('57), however, by more accurate quantitative methods found the blood volume in starving mammals to decrease nearly in proportion to the body weight. His results were confirmed by Panum ('64) and Voit ('94) for the dog. Sée ('66) also concluded that during inanition the loss in blood volume is roughly proportional to the decrease in body weight, with a tendency to hydremic anemia. Bourgeois ('70), like many earlier authors, noted merely an apparent poverty of blood in the vessels of various mammals and birds, starved with or without water.

C. H. Schultz (1843) ascribed death in starved proteus, cats and dogs to oxygen deficiency caused by the marked shrinkage in the red blood cells. A similar shrinkage described by Jones ('56) and other observers was probably due to imperfect technique in the examination of the blood.

Malassez ('75) gave an extensive review of the earlier literature; and also made observations on fasting guinea pigs and frogs, indicating a decrease in the total mass of blood. Red cell counts indicate a preliminary increase, due to concentration of the blood, with a later decrease, due to hydremia. Dupérier ('78) found in a young guinea pig an increase of 500,000 per cu. mm. in the red cells in 1 day of fasting. In an adult in 4 days the red cells increased from 5,518,000 to 6,696,000, but the leukocytes meanwhile decreased from 12,000 to 5,200.

Buntzen ('79) found in fasting dogs an increased red cell count, which decreased on refeeding. Both consumption and regeneration thus appear more rapid in the plasma than in the red corpuscles. Reyne ('81) in a starving dog likewise found a progressive increase in the red cell count up to death at 25 days; but the leukocyte count showed great variation. In guinea pigs on absolute inanition up to 6 days, Cadet ('81) also found a progressive increase in the red cell count, but a decrease in leukocytes and platelets.

Nasse ('50) stated that the white corpuscles become less numerous in the blood of emaciated frogs. In starving larvae of *Rana* and *Bufo*, Cunningham ('80) found the red blood cells to undergo decolorization and fatty degeneration. Leonard ('87) noted seasonal changes in the blood cells of *Rana temporaria*. Mosso ('87) found the red blood cells of fasting frogs and tortoises more resistant to hemolysis (confirmed by Gallerani '92). Ehrlich ('91) found more eosinophiles in the frog's blood during the winter, and more mast cells upon refeeding in the spring. In starved tritons, Jolly ('01) noted that after refeeding there appear in the blood spherical erythroblasts which show mitoses. In *Amia calva* starved 20 months, Smallwood ('16) found a marked reduction in the number of red and white blood cells, but no apparent morphological changes.

In pigeons, Lukianow ('88, '89) found no marked change in the water content of the blood during total inanition. Hoffman ('22) and Palmer and Hoffman ('22), however, found in starved pigeons a reduction in the red cell count from 3.1 millions to 2.8 millions, and an increase in leukocytes from 170,000 to 280,000.

In a dog, given water alone for 43 days, Luciani and Bufalini ('82) found the blood more concentrated, with increased hemoglobin, in the earlier days; but a decrease later. Hayem ('82, '89), in a dog fasting 25 days, found the red cell count increased from 4,200,000 to 5,550,000 on the 18th day, then decreasing to 4,800,000 at the end. Kahan ('83, '84) in 6 starving dogs likewise found an increased concentration of the blood in the earlier days; later it decreased but may not fall below normal. He also noted in later stages that the red cells become smaller and crenated.

Groll ('87) and Hermann ('88) found the ratio of hemoglobin to dry substance during total inanition increasing in rabbits up to 16 days, in cats up to 22 days, and in dogs up to 21 days; but the ratio decreases in longer experiments.

Luibomudrow ('93), in 17 fasting dogs, found the red cell count stationary or increasing up to a loss of 10-15 per cent in body weight, later decreasing up to death. There are great individual variations. In 15 of the dogs, the leukocyte count decreased up to a loss of 20 per cent in body weight; later increasing, sometimes above normal. The lymphocytes decrease, both relatively and absolutely, except in the early period. The mononuclears increase from 10 to 25 per cent; and the polynuclears decrease relatively at the beginning. Eosinophiles sometimes appear although previously absent.

Lackschewitz ('93) claimed that in fasting cats the water content of the erythrocytes may vary considerably, but that of the serum remains fairly constant, contrary to the general belief.

Polétaew ('93, '94, '95) made daily blood counts in 10 dogs starved to death, 8 on total inanition and 2 on water only. During total inanition, the red cell

count increases progressively, with some fluctuations, to the end, excepting in some cases a slight decrease in the last few days. With water, the red cell count increases up to a loss of about 30 per cent in body weight, then decreases gradually, finally below the initial count. The changes in the leukocyte count, total and differential, are shown in the accompanying table (average of 8 dogs on total inanition).

LEUKOCYTE COUNTS IN STARVED DOGS (POLÉTAEW)

Stage of body weight	Total leukocytes	Lymphocytes		Transitional		Polynuclear	
		No.	Per cent	No.	Per cent	No.	Per cent
Before inanition . . . . .	13,255	1,082	8.16	455	3.43	11,718	88.41
To loss of 10 per cent. . . . .	11,016	786	7.12	451	4.11	9,779	88.77
20 per cent. . . . .	12,566	909	7.22	485	4.67	11,072	88.11
30 per cent. . . . .	12,322	629	5.10	385	3.14	11,308	91.76
40 per cent. . . . .	14,196	761	5.36	406	2.87	13,029	91.77
45-50 per cent. . . . .	14,583	916	6.28	312	2.13	13,355	91.59

Okintschitz ('93, '93a) made differential leukocyte counts on 8 rabbits during total inanition and refeeding. During inanition the relative number of lymphocytes and polymorphonuclears is progressively decreased, while the eosinophiles and "round nucleated" forms correspondingly increase. On refeeding, the normal relations are gradually reached. His results, however, have been criticised by Källmark ('11) and Schwartz ('14).

In 12 rabbits on total inanition, London ('95, '96) found that the total blood volume decreases in proportion to the body weight. Popel ('96) found a constant increase in the density of the blood in 10 rabbits and 10 dogs during total inanition. In rabbits starved 4 days, or underfed 12 days, Kieseritzky ('02) noted a concentration of the blood, with increased red cell count, which gradually decreased to normal upon refeeding. Ronsse and Van Wilder ('03) in 8 rabbits on total inanition likewise noted increase in concentration and red cell counts, although there was some tendency to decrease in the longer fasts, as shown by the accompanying table.

DAILY ERYTHROCYTE COUNT, BY RONSSE AND VAN WILDER ('03), IN FASTING RABBITS, AVERAGED FOR 3-DAY PERIODS (I-IX)

Rabbit No.	Days starved	Initial wt. grams	Final wt. grams	Average erythrocyte count (millions) in successive periods									
				Norm.	I	II	III	IV	V	VI	VII	VIII	IX
62	27	2,760	1,390	5.6	7.4	9.1	9.5	8.8	8.8	9.5	10.4	7.4	7.5
35	26	2,891	1,470	5.8	6.2	6.2	6.1	6.3	6.8	6.5	6.4	6.5	6.3,
65	24	2,907	1,615	7.4	6.95	7.7	6.6	7.1	7.6	7.2	6.8	6.6	
5	22	3,022	1,520	5.7	6.1	5.6	6.1	5.9	5.6	5.2	5.9		
59	22	2,833	1,500	5.5	5.7	5.9	6.2	7.0	7.7	6.8	6.7		
60	18	2,720	1,532	5.7	6.0	5.9	5.9	6.6	7.0	7.2			
8	15	2,577	1,402	5.8	6.0	6.2	6.1	6.3	6.8				
38	7	2,181	1,666	5.6	5.4	6.4	8.4						

In guinea pigs fasting for various periods up to 8 days, Opie ('04) found a temporary increase in the eosinophile leukocytes of the blood, followed by a decrease in relative and absolute numbers. This was ascribed to the effects on the bone marrow, although the marrow showed no marked decrease in eosinophiles. There was some diminution in the number of eosinophiles in the tissues of the lung and small intestine, and especially in the spleen. On refeeding, the number of eosinophiles appeared irregular.

Bidault ('04, '04a) noted a slight increase of eosinophiles in the blood of a horse after 1 day without food.

Cesaris-Demel ('06) observed a marked decrease in the red cells of rabbits with experimental marasmus produced by toxins. This would, perhaps, correspond to the condition frequently found in infantile athrepsia. Roger ('07), in 8 rabbits on absolute inanition, found the water content of the blood to undergo a slight increase, but dropping below normal on the 4th day. There was a marked increase on refeeding, with gradual return to normal.

In a dog starved 8 days, Keuthe ('07) noted at first a decrease in the relative number of polymorphonuclears, with an increase in lymphocytes; later the converse, with recovery on refeeding. In cats, Beeli ('08) observed during the first third of the starvation period an average red cell count of 6,950,000, and total leukocyte count of 10,000. During the last third of starvation, the red cells averaged 8,000,000; the leukocytes 5,400. No morphological changes in the blood cells were found. Schelble ('10) also made some total and differential leukocyte counts in cats during various stages of digestion and starvation.

Källmark ('11) made a careful study of the leukocytes in young rabbits (2½-6½ months old). Some were subjected to acute inanition, on water alone, for 7-14 days; others were fed barely enough to maintain body weight, 18-47 days. Considerable individual variation was found, but there usually appears, especially in acute inanition, a transient decrease in the lymphocytes and amphophiles (pseudoeosinophiles) at the beginning, and a similar increase on refeeding. These fluctuations are correlated with changes in the lymphoid organs. The acidophile and basophile leukocytes undergo no significant change in number, but the latter show rarefaction and peripheral displacement of the basophile granules. Nucleated cells occur rarely in the blood of fasting rabbits, but appear numerous upon refeeding. Argaud and Billard ('11) in 2 rabbits on total inanition noted on the fourth day a hypoleukocytosis, with inversion of the formula (3 mononuclears to 1 polynuclear).

Howe and Hawk ('12) found that 3 out of 4 dogs fasting for various periods showed a decreased polymorphonuclear count, with an increase in small lymphocytes; the fourth showed the reverse. The large lymphocytes were variable in 2; nearly constant in the other 2. The transitional, basophile and eosinophile blood cells usually appeared nearly constant. The blood became normal on refeeding. One dog on a repeated fast showed a different effect, all leukocytes excepting the large lymphocytes being nearly constant. Brasch ('12) studied the effects of various diets upon digestion leukocytosis in the rabbit and dog after 3 days of fasting.

Trowbridge, Moulton and Haigh ('15, '18, '19) and Moulton ('20) observed the composition and quantity of (escaped) blood in cattle on different planes of nutrition.

Whipple and Hooper ('18) and Whipple, Hooper and Robscheit ('20) found some regeneration of erythrocytes in dogs with anemia due to hemorrhage, even during total inanition. Protein for regeneration in this case is apparently derived from the breaking down of other tissues.

Uthelm ('21, '22) observed in fasting rabbits a decrease in the blood volume (through loss of water); but in young rabbits held at maintenance by under-feeding, the blood volume rapidly returns to normal. Ikeda ('22) studied the blood of rabbits in various stages of total complete and incomplete inanition, finding a transient increase in the leukocyte (especially the lymphocyte) count, followed by a progressive decrease. The number depends upon the rate of regeneration in the lymphoid organs. There is in the earlier stages of fasting a lipemia, which is expressed by a transient fatty infiltration of the liver and kidney. Okuneff ('22) similarly explained the deposition of cholesterin lipoids in the suprarenal cortex, liver and spleen as a result of the cholesterinemia in the blood of fasting rabbits.

Moehl ('22) found anemia (frequently pernicious anemia) among underfed horses.

Fisch and Emmel ('24) observed no significant change in the erythrocyte count of albino rats during acute inanition, but polychromasia and reticulation (normally present in a small percentage of erythrocytes) disappeared. At 108 hours of acute inanition, Streicher and Emmel ('24) found an average decrease of 31 per cent in the total leukocyte count, associated with a relative neutrophile increase, a pronounced lymphocytic decrease, and a 75 per cent decrease in the azurophile granulation in the lymphoid cells. These results differ markedly from those during lactation leukopenia, which is apparently an independent phenomenon.

Some observations upon the blood during **hibernation** have been recorded. Prunelle (1811) noted that in hibernating mammals the peripheral blood tends to collect in the central portion of the body (confirmed by Baroncini and Beretta '01). Valentin ('38) found the total blood volume relatively unchanged in the hibernating marmot. He also discovered ('65, '81) that the white corpuscles have nearly disappeared from the blood, which he ascribed to stasis in the lymph stream. He also noted a decrease in the size and number of the red blood cells. Quincke ('82) observed a decrease of about 30 per cent (to  $3\frac{1}{2}$  millions) in the red cell count; these cells being normal in form, but of various sizes, some containing yellow droplets.

In the hibernating hedgehog, Carlier ('92) found the red cell count unchanged or increased. The leukocytes, however, undergo a remarkable decrease from 18 or 20 thousand down to 1-3 thousand. They emigrate out into the connective tissue, being found abundant in the gastric mucosa and submucosa.

Pappenheim ('01) observed no anemia in the blood of hibernating spermophiles, and no degenerative changes in the red bone marrow. Argaud and Billard ('11) induced dormice to hibernate in summer by starvation. After 10 days

only a few leukocytes, and these of the mononuclear type, were found in the blood.

Polimanti ('13) found in the hibernating marmot an increased red cell count, due to concentration of the blood; but a decrease in leukocytes. Rasmussen ('16) and Rasmussen and Rasmussen ('17) in hibernating marmots found but little change in the relative blood volume, or in the red cell and platelet counts. The number of circulating leukocytes is reduced about one-half. On feeding and drinking after awakening, the normal blood count is restored, but no digestion leukocytosis is found.

### (B) EFFECTS OF PARTIAL INANITION

The effects of partial inanition upon the blood will be considered under deficiencies of protein (including malnutritional edema and pellagra), salts (including rachitis), vitamins (including beriberi and scurvy), and water. The malnutrition during infantile atrophy is doubtless frequently a mixed deficiency, involving one or more forms of partial inanition, although it was classified under total inanition in the previous section.

**Protein Deficiency.**—For reasons previously given, malnutritional edema and pellagra are classified under protein deficiency, although their etiology is still somewhat uncertain.

Various earlier experiments (Verdeil '49, Subbotin '71, *et al.*) upon the dog with bread or similar protein-poor diets indicated a production of anemia. Voit and his school held that the hemoglobin content of the blood varies according to the protein content of the diet. Von Hösslin ('82), however, found but little difference in the blood of dogs on protein-rich or protein-poor diet.

Morozoff ('97) concluded that in man a meatless diet causes an increase in red cell count, but a decrease in the leukocytes.

Boycott and Chisholm ('11) observed marked variation in the normal red cell count for rats, with no significant change on various (especially protein-poor) diets causing marked loss in body weight.

Whipple and Hooper ('18) and Whipple, Hooper and Robscheit ('20) found that the regeneration of blood in dogs following hemorrhage is much less with a diet of sugar, gliadin or casein, than with a diet containing hemoglobin, gelatin or meat. No single amino-acid appears to determine the blood regeneration. Geiling and Green ('21) likewise found that in rats blood regeneration after hemorrhage is markedly retarded on diets poor in protein, vitamins or salts. Rubner ('19) stated that the lowered birth rate in Germany during the war was probably due to the lack of protein in the diet which prevented normal regeneration of the red blood cells, thereby interfering with normal menstruation and fertilization.

During malnutritional edema, anemia is almost constantly observed. This was noted by Vacker ('71) in the malnourished children during the siege of Paris. During the recent world war, hydremic anemia associated with edema was observed by Woltmann ('16), Budzynski and Chelchowski ('16), Maase and Zondek ('17), Lange ('17), Landa ('17), Knack and Neumann ('17), Gerhartz

('17), Jansen ('18), Bürger ('20), Enright ('20), Mann, Helm and Brown ('20), Lubarsch ('21a) and Tallquist ('22).

As to the detailed blood changes associated with this edema, Woltmann described anisocytosis, polychromatophilia, marked leukopenia and lymphocytosis. Budzynski and Chelchowski found the hemoglobin reduced 50 per cent, but only slightly decreased red cell count; also a definite leukocytosis, mainly due to increase in lymphocytes, which equalled or surpassed the polymorphonuclears. Eosinophilia was almost constant. Maase and Zondek found decreased hemoglobin (50-70 per cent), red cell count (3-4 millions) and leukocytes (4-5 thousand); with marked increase of lymphocytes (up to 45 per cent) and large mononuclears and transitionals (11-25 per cent). Gerhartz noted a tendency to low leukocyte count. Jansen found the red cell count 1.5-4 millions; and leukopenia (below 5,000) in 60 per cent of the cases, with relative lymphocytosis (30-55 per cent). Schittenhelm and Schlecht ('19) also noted a relative lymphocytosis. Bürger observed variable counts; the red cells usually slightly decreased (4 millions) and the leukocytes usually normal. Enright found a typical count of erythrocytes 3.5 millions (hemoglobin 60); leukocytes 4,000; polymorphonuclears 36, lymphocytes 48, and mononuclears 16 per cent; eosinophiles normal. Tallquist claimed that the increase in mononuclears is not a specific symptom, although lymphocytosis is characteristic. Lubarsch found a marked destruction of erythrocytes, with hemorrhages into the connective tissues, resembling scurvy. In famine edema in Russia, Abel ('23) described a slight decrease in erythrocyte count, and moderate leukopenia with decrease in neutrophiles and occasional lymphocytosis.

Hydremic anemia has also been noted in various animals on protein-poor diets; by Friedberger and Fröhner ('08) in draft oxen and horses; by Fröhner and Zwick ('15) in sheep and cattle; by Hoare ('15) in sheep, cattle and pigs; and by Hutyra and Marek in various domestic animals. Kohman ('20) produced edema with anemia in rats by an aqueous diet poor in protein and fats; and her results were confirmed by Maver ('20) in rats, dogs and guinea pigs.

In **pellagra**, Marie ('08, '10) concluded that secondary anemia is apparently frequent, though not constant. Leukocytosis is infrequent, probably due to complications. The differential count is uncertain, but there is probably an increase of large mononuclears. Findlay ('20) stated that although observers in Italy and Roumania have reported an increase in large mononuclears, this has not been generally confirmed. Thus Bardin ('13) and Hillman ('13) in America noted a definite increase in the small lymphocytes. Woodcock ('18) found some lymphocytosis in Turkish war prisoners, but Paton ('18) obtained a normal differential leukocyte count. In Armenian refugees, Findlay noted an increased total leukocyte count, with a relative increase in lymphocytes and decrease in neutrophiles. Huck ('23) has recently given an extensive review of the literature on the subject (including several references in addition to those above mentioned). He concludes that in all stages of uncomplicated pellagra the blood picture shows a secondary type of anemia, with normal leukocyte and platelet counts. The differential count shows an increase in lymphoid elements

in severe pellagra, with increase of polymorphonuclear eosinophiles during convalescence.

The effects of a dietetic deficiency of **iron** upon the blood structure have attracted much attention, on account of the iron content of hemoglobin. Since the loss of iron from the body is slight, however, but little is needed in the food except during growth. Von Hösslin ('82) in young, growing dogs on diets very deficient in iron found at first a decrease in hemoglobin with but slight loss in the total mass of blood; but later a decrease also in the blood volume. Similar experiments with variable success in the production of anemia in animals on iron-poor diets were made by Hall ('94, '96); by Kunkel ('95), Tartakowsky ('04) and Stoeltzner ('09a) in puppies; by Häusermann ('97), in man, rats, rabbits and kittens; by Abderhalden ('00) in rats, rabbits and guinea pigs; by Schmidt ('12) in white mice; and by Brinchmann ('21) in guinea pigs. Lazarus ('13) opposed Immermann's doctrine that inanition causes the purest type of hypoplastic anemia. He concluded that the anemic appearance (pale skin and mucosae) is often deceptive, and that a qualitative dietetic deficiency, especially of iron, is more important than a quantitative deficiency. Happ ('22) found that well balanced diets, deficient in iron, do not produce anemia in the rat in the first generation, although slight anemia may occur in the second generation.

In human **ricketts**, Comby ('01) stated that the blood is usually found normal, though sometimes simple or splenic anemia occurs (with enlarged spleen). According to Cheadle and Poynton ('07), there is usually a simple anemia, proportionate in general to the severity of the ricketts. The leukocytes are usually increased, and nucleated red corpuscles occur. The extreme anemia associated with an enlarged spleen is probably due to a syphilitic complication. Wohlaue ('11) reviewed the literature, indicating usually alteration of the blood in ricketts, but the data are variable. Heubner says the erythrocytes may sink to 2 or 3 millions, with leukocytosis up to 20 or 30 thousand; the changes being somewhat proportional to the severity of the ricketts. Poikilocytosis, nucleated red cells and megalocytes may occur. Kuttner's findings were similar. Schiff and Widowitz, however, in rachitis with severe digestive disturbances found a condition of chlorosis, with marked decrease of hemoglobin without corresponding decrease in the red cell count.

In adult osteoporosis, due to chronic dietetic deficiency in protein, calcium and phosphorus, Alwens ('19) found the hemoglobin below 80 in 16 cases, with the red and total white cell count within physiological limits. There was lymphocytosis in 13 cases, and eosinophilia in 7. Happ ('22) concluded that diets producing rachitoid changes in the rat may also produce anemia, if the diet is prolonged, and also in the second generation.

The effects of **oxygen deficiency** are of interest in this connection. Albitzki ('84) reviewed the earlier work on this topic. The blood changes include deformity and destruction of the erythrocytes, which are decreased in number. Granules (probably from degenerated red cells) are found in the blood and urine; hemoglobinuria, nasal hemorrhages and bloody diarrhea occur. Askanazy ('13) mentioned blood stasis and ecchymoses as a result of oxygen-deficit, with

anemia in chronic asphyxia. Martin, Loewenhart and Bunting ('18) obtained a progressive hyperplasia in the red marrow of the long bones in rabbits, which probably represents a compensatory hypertrophy of the hemopoietic tissue. The literature on oxygen deficiency is reviewed by Morgulis ('23).

**Vitamin Deficiency.**—The effects of a deficiency in vitamin A upon the blood appear slight. Hess and Unger ('19) found no anemia in 5 infants fed 8 or 9 months on a diet deficient in vitamin A. Cramer, Drew and Mottram ('21a) and Happ ('22) likewise observed no anemia in rats with diets thus deficient. Cramer, Drew and Mottram ('22), however, noted a progressive decrease in the number of blood platelets (thrombopenia) in the rat. Bedson and Zilva ('23, '23a) failed to confirm this, finding no marked decrease in the platelet count.

Upon diets deficient in **vitamin B**, the results are more striking. In human **beriberi**, Takasu ('03) found in infants a decreased erythrocyte count (range of 2,400,000–4,800,000 in 17 cases), but nearly always an increase in leukocytes (range of 9,000–34,000 in 15 cases). In chronic cases there is an increase in the mononuclear leukocytes. Chun ('17) observed an increase of about 100 per cent in the leukocyte count. Findlay ('20), however, claimed that in beriberi there is a decrease in the total leukocytes, though not in the lymphocytes or neutrophils. Nagayo ('23) claims that human beriberi differs from experimental polyneuritis in that anemia is not present and lymphocytosis is frequent.

The work of Breaudat ('10) was inaccessible.

In 200 chicks and 150 pigeons with experimental polyneuritis, Tasawa ('15) noted general anemia as a striking symptom. Weill, Arloing and Dufourt ('22), in pigeons on polished rice diet, likewise found a rapid and progressive decrease in the red cell count and hemoglobin, with a tendency to considerable leukocytosis. Hoffman ('22) found that even in normal pigeons there is a marked individual variation in the blood cell counts (erythrocytes 2.4–4.0 millions; leukocytes 40,000–320,000), so conclusions as to changes must be guarded. In 13 normal pigeons the erythrocytes averaged 3.1 millions per cumm., the leukocytes 170,000; in 7 latent polyneuritic, erythrocytes 2.5 millions, leukocytes 220,000; in 16 severe polyneuritic, erythrocytes 2.2 millions, leukocytes 260,000; in cured polyneuritic pigeons, erythrocytes 3.4 millions; leukocytes 390,000. These results appear to agree with those of Weill, Arloing and Dufourt, and also to those (previously cited) for general inanition in the pigeon.

Suski ('23) obtained somewhat different results with adult pigeons (300–380 g.). On vitamin-free diet (autoclaved rice, wheat protein, lard and salt mixture) there was marked loss in body weight, slight loss in average erythrocyte count, and some irregularity in differential leukocyte count (absolute leukocyte counts not given). With the addition of butter and orange juice to the diet (deficient in vitamin B only), there was similar decrease in body weight, increase in average erythrocyte count (from 4,140,500 to 4,780,000), and in relative polymorphonuclear count (from 48 to 50 per cent) with corresponding decrease in lymphocytes and transitional forms.

In a dog on polished rice diet with symptoms of polyneuritis, Brucco ('20) observed a fall in the hemoglobin content and the erythrocyte count.

In rats on diets deficient in vitamin B, Drummond ('18) found (in the "black variety of *Mus norvegicus*") no significant change in total or differential blood counts. Cramer, Drew and Mottram ('21, '21a), however, observed a marked decrease in lymphocytes (lymphopenia) in the circulating blood of rats, associated with a general atrophy of lymphoid tissue throughout the body. Prompt recovery occurred upon administration of vitamin B. Happ ('22) concluded that although deficiency in vitamin B does not produce anemia in the rat, "Diets so deficient in water soluble B as to produce polyneuritis diminish leucopoietic activity and cause a severe leucopenia with a shift to the right in the Arneht formula." Weitbrecht ('22) found in young rats on vitamin-free diets (also deficient in iron) a tendency to anemia of chlorotic type. In all his experiments there was a reduction in the number of leukocytes (especially lymphocytes), with nuclear changes in form. This lymphopenia is ascribed to a general atrophy of the lymphatic apparatus.

The blood changes in **scurvy** have been studied frequently, on account of the hemorrhagic tendency characteristic of this disorder. In infantile scurvy, Fraenkel ('06) found a simple anemia, with decreased hemoglobin and erythrocyte count, leukocytosis and appearance of nucleated red blood cells. Nobécourt, Tixier and Maillet ('13-'15) concluded that the anemia arises from myeloid lesions, and recovery is sometimes long delayed. Hess and Fish ('14) in infantile scurvy found the hemoglobin very low (35-70), although the red cell count may be normal or slightly below. There is usually a leukocytosis (10,000-40,000). The blood platelets vary within normal limits. Brandt ('19) found the hemoglobin nearly normal, the erythrocyte and platelet count sometimes increased, the total and differential leukocyte count nearly normal (sometimes lymphocytosis).

In **human adult scurvy**, Sato and Nambu ('08) found a marked hydremic anemia. In 54 cases, the hemoglobin averaged 31.8 per cent; the red cell count 2,409,323; leukocytes 6,856. In 19 convalescent, the hemoglobin averaged 50.7; erythrocytes 3,539,947; leukocytes 7,405. The differential count was nearly normal; blood-platelets somewhat increased. In convalescent scorbutics, Wassermann ('18) noted cases where the erythrocyte count rose to 6 or 7 millions; the hemoglobin to 110 or 120 per cent. Aschoff and Koch ('19) and Bierich ('19) described the hemorrhages and histological appearances during absorption of the extravasations. Comrie ('20) found secondary anemia and lymphocytosis, with the following average in 50 cases; hemoglobin 55 per cent; erythrocytes 4,080,000; total leukocytes, 7,510; polymorphonuclears 45 per cent; large lymphocytes 20 per cent; small lymphocytes 29 per cent; mononuclears, 2 per cent; eosinophiles 4 per cent. Hausmann ('22) also made differential counts in scurvy, noting a reduction in the neutrophiles. Hess ('20) concludes that in general the blood-picture in scurvy resembles that of chlorosis, with hemoglobin decreased proportionately more than the number of erythrocytes. The variations reported in total and differential leukocyte count may depend upon various stages, degrees of severity, or complications in the cases studied.

In **experimental scurvy** of the guinea pig, no marked blood changes have been observed. Jackson and Moore ('16) found no appreciable leukocytosis.

Herzog ('21) obtained negative results as to erythrocytes, total and differential leukocyte count, and blood platelets. Findlay ('21a) found only a slight decrease in the erythrocyte count. Bedson ('21) in guinea pigs and monkeys (also one human) found but slight variation from the normal in the red cells, leukocytes (total and differential) and platelets. He reviews the literature showing contradictory results on the platelets. Only Mouriquand ('21) obtained more positive results, finding a decrease in the red cell count from 5,518,000 (hemoglobin 80 per cent) to 3,250,000 (hemoglobin 65) in 24 days, with anisocytosis and poikilocytosis. On giving orange juice, the red cells increased to 5,201,000 (hemoglobin 60) on the 28th day; with complete recovery and 5,406,000 red cells (hemoglobin 90) on the 37th day.

**Effects of Water Deficiency.**—According to Lorenzen ('87), a decrease in drink to reduce body fat was recommended by Plinius, and in the 19th century by the French physician, Dancel. The method was rediscovered by Oertel, who ascribed obesity to excessive water consumption. He explained the effect of thirst through decrease of the water-content in the blood, producing a concentration of the red corpuscles which was supposed to increase the oxidation of the body fat. Denning ('99), however, found but slight increase in the human red cell count or hemoglobin during thirst (up to 1 week). Naegeli ('12) stated that the blood may become concentrated, with abnormally high red cell count, as a result of thirst, or of loss of body fluid through diarrhea, etc. Rubow ('20) concluded that in dry diet cures the effects are partly due to the resultant concentration of the blood, the water content of which may be reduced 8–12.5 per cent. Marriott ('20) holds that diarrhea in infants may give rise to a toxic condition, with anhydremia, largely due to the general desiccation of the body and measured by the concentration of the blood. In a recent review, Marriott ('23) concludes that thirst causes anhydremia with impairment of the circulation, resulting in marked functional disturbances throughout the body. Through loss of water from the blood plasma, the blood is greatly concentrated, and the red cell count may be doubled. Destruction of red cells also occurs in severe cases, with resultant delay in recovery after water is administered.

Among **animals**, the effects of thirst upon the blood have often been studied. Falck and Scheffer ('54), in a dog fed dry bread found the water content of the blood decreasing from 86.11 to 82.83 per cent. Bowin ('80) in dogs and rabbits on a relatively dry diet (meat or vegetables) found the red blood cell count nearly normal for 4 or 5 days, then becoming progressively higher, reaching nearly double (8,544,000) on the 13th day.

Gürber ('89) noted that while in a frog kept in a moist place the erythrocyte count decreased from 836,000 to 516,000 in 6 days, in another frog kept in a dry place it increased from 865,000 to 1,352,000 in 5 days. Durig ('01) found a smaller increase of 3–16 per cent in the red cell count of frogs losing 13–35 per cent in body weight by desiccation.

Pernice and Scagliosi ('95a) found in a dog fed dry bread the red cell count increased somewhat during the first 4 days, from 5,177,000 to 7,409,000, with corresponding hemoglobin increase from 65 to 105. Later the red cell count decreased to 4,712,000 and the hemoglobin to 55, on the 11th day, shortly

before death. The leukocyte count, on the contrary, decreased from 12,400 to 9,300 on the 4th day, then steadily increased to 41,850 shortly before death. In 3 young chickens fed dry maize, there was found a progressive erythrocyte count during the 8 or 9 days up to death, the increase in the 3 cases being from 3,131,000 to 3,596,000, from 3,069,000 to 4,092,000, and from 3,007,000 to 4,185,000, respectively. The hemoglobin values were practically doubled (45-55 up to 90-100). The leukocyte count was variable, showing a final decrease in the first case (12,400 to 4,650) and increases in the other 2 (4,650 to 17,050 and 10,850 to 13,950).

In 2 dogs fed dry meat powder mixed with fat, Straub ('99) found the dry content of the blood increased from 22.03 per cent (average) to 24.49 per cent. Blix ('16) obtained a reduction of 11 per cent (maximum) in the water content of the blood in rabbits by fasting and thirst. Keith ('22) studied the dilution of the blood and the changes in hemoglobin and red cell counts in dogs which were given water after total inanition for periods of 2-4 weeks.

## CHAPTER XVI

### EFFECTS ON THE LYMPH AND LYMPHATIC GLANDS

Changes in the lymphoid tissue of the bone marrow have already been described in Chapter VII, with the skeleton. The lymphoid tissue of the alimentary canal, spleen and thymus will be considered along with these organs in later chapters. The present chapter deals with the lymph and lymph glands in general. Although the characteristic involution of the lymphoid tissue during malnutrition usually results in atrophy of the lymph nodes, they often appear swollen (especially in rickets, beriberi and scurvy), perhaps chiefly through secondary infections in conditions of lowered resistance. After a brief summary, the details will be presented under (*A*) effects of total inanition, and (*B*) effects of partial inanition.

#### SUMMARY OF EFFECTS ON THE LYMPH AND LYMPHATIC GLANDS

During total inanition the quantity of lymph apparently increases during the first third of the fasting period, but gradually decreases later, with changes in composition.

The lymphatic glands during inanition appear variable in **size**. In emaciated human adults they are in many cases extremely atrophic, but in others they appear normal in size or even enlarged (probably from secondary infections). Enlargement appears more frequent in atrophic infants. In fasting animals, the results are also variable, although marked atrophy of the lymph glands appears characteristic. During partial inanition, changes in the size of the lymph glands likewise appear somewhat inconstant, but enlargement appears characteristic in rickets, beriberi and scurvy, especially in the mesenteric nodes, often probably due to secondary infection.

**Microscopically**, the lymphatic glands during inanition usually show a very characteristic atrophy of the lymphoid tissue, even in cases where a decrease in the size of the gland as a whole may be offset by a distension of the blood vessels and lymph sinuses. In general, there is a marked diminution in the number of lymphocytes (by emigration), which renders the less affected stroma (reticulum) and trabeculae very prominent. The lymphoid nodules and cords are reduced in size, and mitoses are decreased in number or absent. Numerous phagocytic cells are found, often containing pigment derived from excessive destruction of erythrocytes (especially in regions of hemorrhage in scurvy). An increased number of phagocytes and plasma cells has been noted during hibernation. Retterer's claim that lymphatic glands may be transformed into hemolymph glands by inanition lacks confirmation. Secondary infections may occasion inflammation, however, and occasionally even suppuration of the lymphatic glands, especially in scurvy.

Cirrhosis of the lymph glands has been noted in pellagra. The lymphoid tissue appears especially sensitive to a dietary deficiency of fat, while in rickets a general lymphoid hyperplasia appears characteristic. A deficiency in vitamins (especially of vitamin B) tends to cause a general atrophy of the lymphoid tissue, associated with lymphopenia in the circulating blood. During chronic thirst, the changes in the lymph nodes resemble those typical for inanition in general, with hyperemia and lymphoid atrophy.

Although there are numerous variations, the changes in the structure of the lymphatic glands during inanition in general resemble those found in the other lymphoid organs, including the bursa of Fabricius ("cloacal thymus" in birds), bone marrow (considered with the skeleton) and the thymus, spleen and intestinal lymphoid structures (to be considered in later chapters).

Upon adequate **refeeding** after inanition, the lymphatic glands in general recuperate promptly, showing rapid increase of weight, associated with active mitosis and recovery of normal structure in the lymphoid tissue.

#### (A) EFFECTS OF TOTAL INANITION, OR ON WATER ONLY

The effects will be considered first in man, adult and infant, and then in the lower animals.

The observations upon the effects of inanition on the lymphatic system of the **human adult** appear rather scarce. In autopsies upon emaciated victims of the Madras famine (226 men, 155 women and 78 children), Porter ('89) found the mesenteric lymph glands nearly normal in size in about a third of the adults and five-sixths of the children (57 men, 37 women and 51 children). They were enlarged and swollen (probably chiefly through infections) in 36 men, 6 women and 11 children, and were extremely atrophied in 73 men, 74 women and 2 children. Pigmentation of the glands was noted in 12 men, 8 women and 2 children. In 12 cases (4 men, 4 women, 4 children) of extreme emaciation without evident complications, the mesenteric glands appeared about normal in size in 1 man, 3 women and all 4 children; much enlarged in 1 man; and atrophied in 2 men and 1 woman.

In an adult man who died of starvation (60 days on water only) with loss of about 40 per cent in body weight, Meyer ('17) carefully studied the lymph nodes, 18 hours post mortem. "The inguinal lymph nodes were barely palpable on both sides, and all except the medial nodes, which were slightly reddish, were pale. The mesenteric nodes were small and pale, but numerous. The pre-vertebral nodes formed a chain of soft, flat, pale bodies, and the only very red specimens were a pair of iliac nodes, one on each side. That on the right was  $1 \times 0.5$  centimeters and only a few millimeters thick. That on the left was very much smaller. There was nothing noteworthy about the rest of the nodes of the entire body. Some of the right bronchial nodes were calcified. The cisterna chyli contained a little yellowish fluid."

Microscopic examination revealed the following:

"Iliac Nodes.—The parenchyma especially of these lymph nodes is very much depleted and some portions of the nodes are comprised of the collapsed

coarser framework merely. Germinal centers are absent and large trabeculae and large sinuses are especially evident. Some of the latter contain granular detritus. Few degenerated cells are found, however, although some yellow pigment is present. Only a few polymorphonuclear leukocytes are seen, but a good many acidophile cells with finely granular protoplasm and round vesicular nuclei are present. The parenchyma is so depleted that one can actually count the cells in sections ten microns thick in most portions of the sections. The nuclei of the lymphocytes contain few chromatin granules, stain lightly, and look more transparent than usual, some of them appearing as empty vesicles.

“Prevertebral Nodes.—The prevertebral nodes seem somewhat better preserved, but show some polychromatophilia. They, too, contain no germinal centers, phagocytes, or giant cells. Large cells with a large, oval, vesicular nucleus, which look as though they might have an endothelial origin, are usually numerous. These cells are contained in both sinuses and parenchyma. These portions contain large acidophile cells and masses of degenerated erythrocytes.

“Bronchial Nodes.—The bronchial nodes are not so depleted as might be expected, but show considerable pneumonokoniosis. They contain almost nothing but small lymphocytes. Some portions of the abdominal lymph nodes are wholly depleted, being represented merely by a folded mass of trabeculae and connective tissue.”

It may be noted, however, that Retterer ('02b) found that lymph glands of human adults examined 24 hours post mortem may show as an artefact the rarefaction of the lymphoid tissue and other changes resembling those produced in the lymph glands of animals by inanition.

The lymph glands during **infantile malnutrition** have been frequently studied. Baginsky ('84, '84a) and Fede ('98) noted atrophy of the intestinal follicles and lymphoid tissue; but Mattei ('14), on the contrary, found evidence of hyperactivity, as will be shown later, in the chapter on the alimentary canal. Moldenhauer ('99) noted hyperemia and increase of stroma in the mesenteric nodes of athreptic infants. Thiercelin ('04) described the axillary and inguinal lymph glands in athreptic infants as swollen (secondary infection ?) and the mesenteric glands as slightly hypertrophied.

Among 1,000 New York primary school children, 6–12 years of age, of whom 40 per cent were malnourished, Sill ('09) observed that 90 per cent had “adenoids,” 40 per cent hypertrophied tonsils, and 4.5 per cent tubercular cervical lymph nodes. In another series of 210 markedly malnourished children, 75 per cent had enlarged cervical glands, and of 101 tested for tuberculosis, 55 gave a positive (von Pirquet) reaction. Schelble ('10), however, found no significant histological changes in the mesenteric glands from 17 cases of pedatropy, 9 of which were fixed shortly after death.

Among the **lower animals**, data concerning the effects of inanition upon the lymphatic system are more numerous. From experiments on several dogs and rabbits of various ages and sizes, which were subjected to absolute inanition for variable periods up to death, Collard de Martigny (1828) concluded that:

“Durant le premier tiers environ du temps de l’abstinence, la quantité de la lymphe est très considérable, et augmente d’autant plus, que l’animal est à jeun depuis plus longtemps. Dans les deux autres tiers du temps de l’abstinence, la quantité de la lymphe diminue graduellement. Quelques heures avant la mort, le canal thoracique n’en contient que très-peu. Les vaisseaux lymphatiques des diverses régions du corps se vident de lymphe d’autant plus tard comparativement qu’ils s’en étaient remplis moins lentement. Généralement la vitesse avec laquelle la lymphe parcourt des vaisseaux est très-peu considérable. Elle augment d’autant plus, que la quantité de ce fluide devient plus forte. Elle diminue graduellement, à mesure que la lymphe est en moindre proportion dans le système lymphatique. Durant la période de son augmentation en quantité, la lymphe devient graduellement plus riche en matière colorante, en caillot et en fibrine. La lymphe est d’autant moins coagulable, colorée et fibrineuse, dans la reste de la durée de l’abstinence, que la mort et moins éloignée.”

Tiedemann ('36) found that with the decrease in blood volume during inanition, there is an increased activity of the absorbent system, so that the fluids of the serous and joint cavities are diminished.

Bourgeois ('70) stated that the results of Collard de Martigny as to the lymph during inanition were confirmed by Magendie and Bouchardat. In numerous fasting mammals, Bourgeois found “Les ganglions lymphatiques sont très-developpés, quelquefois injectés, surtout dans l’abdomen.”

The observations of Cunningham ('80), Hofmeister ('87), Erdely ('05) and Holthusen ('10) on the atrophic changes in the intestinal lymphoid tissue during inanition will be considered in the chapter on the alimentary canal.

In 6 severely starved young and adult rabbits, Morpurgo ('88, '89, '89a) noted atrophic changes in the intestinal lymphoid tissue (to be mentioned later) and also in the lymphatic glands. The cervical and mesenteric glands appear reduced in size and consistency. The lymphoid cells are greatly decreased in number, in both the superficial and the deeper lymph spaces. The medullary cords are very slender and poor in lymphoid cells. Mitoses persist, however, both in cortex and medulla, in the places where mitoses normally occur. “Leur nombre est certainement diminué; et il me semble aussi que la substance chromophile était devenue plus rare.” The intercellular “tingible bodies” of Flemming were observed.

In similar rabbits refed 4 or 5 days after inanition Morpurgo ('90) found the number of lymphoid cells in the mesenteric lymph glands, especially in the medullary cords, more numerous. The lymph vessels still appeared to contain relatively few cells, however. Numerous mitoses were found in both cortex and medulla, and they appeared larger in diameter than during starvation. Phagocytes and “tingible bodies” of Flemming appeared less numerous.

Retterer ('02) subjected adult guinea pigs to total inanition, and during the first 5 days found the lymphatic ganglia grey in color, with dilated lymph sinuses free from red cells. In animals starved to death in 7 days, however, the small peripheral ganglia appeared reddish; the central ganglia appeared grey on the surface, but the medulla was reddish, with sinuses containing numerous

red corpuscles. He also found all the ganglia with blood-filled sinuses in a dog emaciated by repeated hemorrhage and inanition, although this was not observed in a cat after 12 days of total inanition. Retterer concluded that the ordinary lymph glands may be changed into hemolymph glands by inanition.

In a more detailed histological study of the lymphatic glands from the fasting animals, Retterer ('02a) found the sections appearing spongy and rarefied. The medullary cords and lymphoid follicles appear less distinct than normally. The reticulum loses its affinity for hematoxylin, but stains deeply with the acidophile stains. In the lymphoid masses, the lymphoid cells have become separated by the cytoplasmic atrophy, and the stroma, though also atrophic, becomes distinct as granular filaments. The atrophy of the lymphoid tissue is accompanied by enlargement of the peripheral and central lymph sinuses, which contain free cells of various types: (1) numerous chromatic nuclei of 4 to 7 $\mu$ ; (2) leukocytes; (3) cells with clear, unstained cytoplasm and irregular margins; (4) cytoplasmic masses with several nuclei. In many of the free cells, the cytoplasm has undergone "dégénérescence hémoglobique" (phagocytosis of red corpuscles?). The nuclei of the lymphoid cells are poor in nucleoplasm, and the chromatin may become fragmented so as to simulate mitosis (as claimed by Morpurgo). In summary:

"En un mot, l'atrophie qui suit l'abstinence prolongée se traduit dans le ganglion lymphatique par la rarefaction du tissu et la transformation du protoplasma commun et continu en cellules libres ou leucocytes. La macération, les agents mécaniques ou chimiques conduisent au même résultat."

According to Hammar ('09), unpublished observations by Hellman show that the lymphoid tissue in general undergoes "accidental involution" during inanition, though not so marked as in the thymus. The changes during inanition in the weight of the bursa of Fabricius (a lymphoidal appendage of the cloaca in birds) were observed by Jolly and Levin ('11) for the pigeon, chicken and duck. With a loss of 30-37 per cent in body weight, the bursa lost 48-77 per cent, or about the same as the thymus and spleen. On refeeding pigeons 8-15 days after starvation for 8 days, with increase of 28 per cent in body weight the bursa of Fabricius increased 102 per cent, which was relatively greater than the increase in the spleen (53 per cent), but less than that in the thymus (246 per cent).

The distribution of fat in the lymph nodes during inanition was studied by Holthusen ('10). Holmström ('11) noted an increased deposit of lipoidal granules in the lymph nodes, chiefly in the sinus reticulum, of fasting rabbits. Normal conditions were restored after a week of refeeding.

Jolly ('11) studied the histological changes in the bursa of Fabricius (or "cloacal thymus") in pigeons during inanition. As in the involution of the thymus, there is an atrophy, especially in the cortex, due to emigration of lymphocytes. "Les modifications histologiques que nous venons de décrire consistent donc essentiellement en une disparition graduelle des lymphocytes avec conservation du bourgeon épithélial qui forme la trame de la substance médullaire. Cette involution rappelle celle qui est due à l'âge, mais elle n'est pas définitive. Si on laisse mourir l'animal, elle n'a pas le temps d'aboutir à

l'atrophie scléreuse; si on renourrit l'animal, le follicule se repeuple en lymphocytes en peu temps et se reconstitue."

In the lymphatic glands, Jolly ('14) found the changes during inanition less marked than in the spleen and bursa of Fabricius (above noted). Two puppies 1 month old were given water only for periods of 6 and 8 days, respectively, with 2 normal controls. The loss in body weight was 27.1 per cent; in the cervical and popliteal ganglia, 41.3 per cent; mesenteric ganglia, 56.9 per cent; thymus, 68.1 per cent; spleen, 73.5 per cent. In a rabbit of 6½ months, starved 7 days, the loss in body weight was 23.5 per cent; popliteal ganglia, 38.8 per cent; vermiform appendix, 43.2 per cent; mesenteric ganglia, 52.5 per cent; spleen, 62.8 per cent; and thymus, 87.9 per cent.

The histological changes correspond to the degree of loss in weight. The lymphocytes become scarce, the reticulum distinct. The cortex of the lymphatic glands is less affected than the medulla. The follicles become smaller, and persist long (as in the spleen), but finally disappear. The terminal lesion is a sclerous atrophy. Cells containing blood-pigment, etc. occur in both lymph-glands and spleen. Mitoses progressively diminish in number, but disappear in only extreme stages. Other lymphoid organs, such as the vermiform appendix, tonsils and bone marrow, are similarly affected. The effects are more marked in the lympho-epithelial organs (thymus, bursa of Fabricius) than the lympho-lymphatic (ganglia) or hemo-lymphatic (spleen, bone marrow). The effects appear progressively greater in the following order: peripheral ganglia; tonsils; mesenteric ganglia; bone marrow, appendix; spleen; bursa of Fabricius; thymus. The lymphoid nuclei supply nitrogenous and phosphorized materials for the starving organism (Jolly '24).

Howell ('14) found that in dogs starved 48 hours the lymph shows but little evidence of chyle-fat, and also a great decrease in the number of lymphocytes, in comparison with the milky lymph an hour or two after feeding.

Ikeda ('21, '22) studied rabbits in various stages of acute and chronic inanition, and upon refeeding. During starvation the mesenteric and peripheral lymph nodes, in addition to atrophy and fatty changes, show degenerative changes in the parenchyma. The lymph follicles of the vermiform appendix, besides the degenerative process, may show also regenerative activity, with mitosis of the lymphocytes. In the mesenteric glands during inanition, there is fat in the parenchyma, but not in the sinuses as extracellular fat. Animals with well developed lymphatic system and richly lymphocytic blood are much more resistant to inanition. Ikeda considers it probable that at a certain period of inanition (related to the consumption of fat?) there is a vigorous demand for lymphocytes, emphasized by an increased transport of lymphocytes from the hemopoietic system into the blood, with compensatory regeneration in the hemopoietic organs.

The observations of Lefholz ('23) as to the relations between the diet and the amount of lymphoid tissue will be mentioned later, under partial inanition.

**Hibernation.**—The lymphatic glands in the hibernating hedgehog were studied by Carlier ('92). The germinal centers become inactive, with but few mitoses. The phagocytes become very numerous, occurring in the lymph-sinuses and throughout the gland, excepting the germinal centers and the

fibrous tissue. They are large and occasionally multinucleated. The cytoplasm contains numerous yellow or brownish pigment granules (iron-containing), also fragments of degenerated tissue cells and of erythrocytes, etc. The macrophages become less numerous after hibernation and are distinct from the phagocytic giant cells of the spleen. During hibernation there is also an increase in plasma cells of the lymph nodes, which nearly disappear elsewhere, excepting in the tongue.

### (B) EFFECTS OF PARTIAL INANITION

A few observations have been recorded upon changes in the lymphatic glands during deficiencies of protein, fats and carbohydrates, salts, vitamins and water.

During **pellagra** (classified as a protein deficiency), Kozowsky ('12) noted hyalin changes in the blood vessels of the lymph-nodes. Harris ('19) noted cirrhosis of the lymph-nodes, with increased pigment and decreased parenchymatous elements.

In human **malnutritional edema**, Schittenhelm and Schlecht ('19) found the mesenteric lymph glands somewhat swollen.

In rats with edema produced by diets deficient in protein and fats, Kohman ('20) found usually a congestion of the lymph glands, especially the cervical glands.

Lefholz ('23) continued the work of Settle, who noted an apparent hypertrophy of the lymphoid organs of kittens on a diet rich in fat and calories. The palatine and pharyngeal tonsils and especially the intestinal (aggregated) follicles were found to become nearly twice as large on diets high in protein or sugar and also in calories; while if the excess calories are given in the form of fat, these organs become nearly 3 times the normal size. The mesenteric lymph glands also appear larger on a diet rich in fat than on one rich in sugar or protein. Other lymphoid organs (spleen, thymus and cervical lymph glands) show no constant response to variations in diet. There is some evidence indicating a reciprocal relationship in the size of these organs, so that if one is unusually small, the other will be large, thus making a tendency to uniform total amount of the lymphoid tissue.

In human **ricketts**, enlargement of the mesenteric lymph glands was observed by Whistler (1645) and (slightly) by Glisson (1650). Seibold (1827) noted hardening of the lymph glands at autopsy. Dickinson ('69), Comby ('01) and Cheadle and Poynton ('07) found the lymph glands often swollen, and Jenner ('95) found "albuminoid infiltration" of these and other organs. Woh-lauer ('11) concluded that the lymph glands are usually swollen (especially the cervical, axillary and inguinal); although Frölich ascribes the swelling to infectious complications. Pfaundler ('22) states that in ricketts the lymphoid tissue is markedly hypertrophied throughout the body. No data were found concerning the lymphatic glands in experimental ricketts of animals.

**Beriberi.**—According to Cyr ('69), Tiedemann produced in animals by faulty diet a disease resembling beriberi, in which the lymphatic glands appeared swol-

len. McCarrison ('21) noted atrophy of the lymphoid structures in the intestines of polyneuritic pigeons. In monkeys on autoclaved rice diet, although the lymphoid nodules in the colon were frequently swollen, the lymphoid cells of the intestinal mucosa in general were greatly reduced in number. The mesenteric glands, especially those of the colon were invariably much enlarged (from toxic absorption).

Cramer, Drew and Mottram ('21, '21a) found that diets deficient in vitamins (especially vitamin B) produce in rats and mice a marked atrophy of lymphoid tissue throughout the body, associated with lymphopenia in the circulating blood. Peyer's patches become very atrophic, and the ordinary lymph glands, even though not macroscopically decreased in size, are found histologically almost free from lymphocytes. "They consist almost entirely of endothelial cells and large empty lymph-spaces." They hold that there is a specific relation between vitamin B and the nutrition of lymphoid tissue.

In human beriberi, Strong and Crowell ('12) found no enlargement of the superficial, cervical or mesenteric lymph glands. The mesenteric glands were small. Tasawa ('15), however, mentioned hypertrophy of the gastrointestinal lymphatic apparatus as characteristic of human beriberi. Nagayo ('23) states that lymphatic hypertrophy is a characteristic distinguishing human beriberi from experimental polyneuritis, in which lymphatic atrophy occurs.

In human **scurvy**, Lind (1772) frequently observed swollen and purulent axillary and mesenteric lymph glands. Sato and Nambu ('08) found the mesenteric glands often hemorrhagic, especially when intestinal ulcerations were present; also an increase of intestinal lymphoid tissue. Aschoff and Koch ('19) likewise noted that the inguinal lymph glands frequently showed blood in the peripheral lymph sinus, or hematogenous pigment in the stroma. "Weiterhin ist ein häufiger Befund der Sinuskatarrh der Lymphdrüsen; die Sinus sind erweitert und vorwiegend mit abgestossenen und verfetteten Sinusepithelien prall ausgefüllt, doch tritt die Beteiligung von Leukozyten ganz zurück. Auch Oedem der Lymphknoten wird öfters beobachtet."

Jackson and Moore ('16) observed swollen axillary and inguinal lymph nodes in experimental scurvy of guinea pigs. Hess ('20), however, who has recently reviewed the subject, concludes that this enlargement probably occurs only in advanced cases complicated by general infection. As a rule, the enlargement is confined to nodes draining areas where hemorrhage has occurred. On section such nodes appear reddish or brownish on account of the contained blood pigment; sometimes the peripheral sinus is distended with pigment-laden cells. Where secondary infection has occurred, extensive necrosis of the glands may result, especially in the mesenteric nodes when severe intestinal lesions are present. Höjer ('24) describes lymphoid atrophy in advanced cases.

**Thirst.**—In a dog which died after 11 days on a diet of dry bread, Pernice and Scagliosi ('95a) found the lymph nodes all hyperemic, with distended blood vessels. The lymphoid cells are less numerous, especially in the medulla, so the septa appear thicker and the reticulum more distinct. The intestinal lymphoid areas are also hyperemic. Similar changes were noted in the lymph glands of 3 young chickens on dry maize diet.

## CHAPTER XVII

### EFFECTS ON THE SPLEEN

The spleen, like the lymphatic system in general, usually undergoes atrophy during conditions of inanition and malnutrition. The splenic enlargement sometimes found is in most cases to be ascribed to complications, such as tuberculosis, syphilis or other infections. After a brief summary, the effects of inanition upon the spleen will be considered in detail under (*A*) effects of total inanition and (*B*) effects of partial inanition.

#### SUMMARY OF EFFECTS ON THE SPLEEN

As to the changes in the **weight** of the spleen during inanition, the great normal variability makes it often difficult to reach conclusions. In general, however, it is clear that during total inanition (likewise on water only) in human and animal adults the spleen shares in the marked atrophy of the lymphoid organs. The relative loss in the spleen weight is usually greater than the loss in body weight, often twice as great; but the spleen loss may be slight in the early stages of inanition (guinea pig). In emaciated human adults, the spleen is sometimes enlarged on account of complicating infections, such as tuberculosis or syphilis.

In the **young**, the results are more variable. In some cases there is a definite decrease in the weight of the spleen, in others the inherent growth impulse may overcome the tendency to atrophy during inanition. In atrophic human infants, syphilis or other infections also may produce marked splenic enlargements.

During **hibernation** and subsequent inanition, the changes in the weight of the spleen appear very irregular.

Upon ample **refeeding** after inanition, the normal weight of the spleen is promptly restored, sometimes apparently with a transient over-compensatory regeneration.

During the various forms of **partial inanition**, the changes in the weight of the spleen are variable. In human pellagra and famine edema, the spleen usually appears atrophic, but sometimes hypertrophied. In human rickets the spleen usually presents an enlargement of doubtful significance (often due to complications). In experimental rickets of rats, the spleen is irregular in weight. In human beriberi, the spleen is usually enlarged; whereas in animals on diets deficient in vitamin B there is a very marked and constant splenic atrophy. In human and animal scurvy, the spleen is variable in weight; usually enlarged, but often within normal range, or even subnormal in the early stages. During thirst, there is a very marked loss in the weight of the spleen, comparable to that during total inanition.

During inanition in general, the **structural changes** of the spleen, though varied in degree and character, usually present certain characteristic features.

In the somewhat exceptional cases of splenic enlargement, there is often congestion and general hyperplasia. In the more characteristic decrease in the size and weight of the spleen, the atrophy takes place in the parenchyma, but not in the stroma. The capsule and trabeculae thus become relatively more prominent, giving a variable degree of fibrosis and sclerosis.

The atrophy affects especially the lymphoid tissue, so that the Malpighian nodules and pulp-cords become variably reduced in size and indistinct. The lymphoid cells decrease in number and size. The nuclei tend to be slightly decreased in size and the number of mitoses is greatly diminished. In the sinuses and red pulp, the erythrocytes are variable in amount, giving in some cases an appearance of congestion; in others, of anemia. Correlated with the increased destruction of erythrocytes, there is a variable degree of hemosiderosis. Granular masses of pigment occur both extracellular and intracellular (in the endothelium and macrophages of the pulp-cords). Nucleated erythroblasts may also appear.

During the various types of **partial inanition**, the structural changes in the spleen in general resemble those noted for total inanition. Where splenic enlargement occurs, there is usually congestion and a variable degree of general hyperplasia. In the more frequent diminution in size of the spleen, there is a relative fibrosis, with marked atrophy of the pulp (especially of the lymphoid structures) and a variable increase in pigmentation and hemosiderosis. Sometimes the changes appear inflammatory in character, and hemorrhages rarely occur (infantile beriberi, scurvy, thirst). It may furthermore be noted that these changes are not peculiar to inanition, but occur also in many other conditions affecting the spleen.

Upon adequate **refeeding** after inanition of any type, the spleen in general makes a prompt recovery in normal structure as well as in size. Abundant mitoses accompany the proliferation in the lymphoid tissue during recuperation from its atrophic condition.

#### (A) EFFECTS OF TOTAL INANITION, OR ON WATER ONLY

The changes in the weight of the spleen in man and animals will be reviewed first, followed by the changes in structure.

**Changes in Weight.**—The normal weight of the spleen is so exceedingly variable that conclusions as to changes are often difficult. From a review of the literature, Willien ('36) concluded that the spleen is small and firm after inanition. At the autopsy of a 19 year old girl who had died from starvation, Schultzen ('62, '63) noted a very small spleen—"Lien perparvus, 3½" longus, 2½" latus, 1⅛" crassus." Curran ('74) found the weight of the spleen only 1 ounce in a greatly emaciated, starved old woman. Bright (*et al.*) ('77) stated that the spleen in a case of starvation was considerably below normal weight; but at 4½ ounces (about 130 g.) it was not much subnormal for an initial body weight of 121 pounds (final weight 74 pounds).

Casper-Liman ('82) found a very small spleen at death from starvation, but opposed Tardieu's view that this is a characteristic sign of medicolegal impor-

tance. In a large man, who died from voluntary starvation, Voelkel ('86) described the spleen as "auffallend klein (10 cm. lang, 5 cm. breit, noch nicht ganz 2 cm. dick)." Cohnheim ('89) held that during starvation the relative loss in the weight of the spleen is next to that of the adipose tissue.

Porter ('89) recorded the weight of the spleen among native victims of the Madras famine, as shown in the accompanying table.

WEIGHT OF THE SPLEEN IN VICTIMS OF THE MADRAS FAMINE (PORTER '89)

No. and sex	Average weight (and range) in ounces	Average ratio to corresponding body weight
	<i>Spleen hypertrophied</i>	
16 men.....	11.4 (7-20 $\frac{5}{8}$ )	1:125
9 women.....	8.7 (6-12 $\frac{7}{8}$ )	1:127
	<i>Spleen of normal size</i>	
22 men.....	4.8 (4-7)	1:258
17 women.....	4.0 (3-6)	1:279
	<i>Spleen atrophied</i>	
135 men.....	2.3 (all under 4)	1:540
97 women.....	1.83 (all under 3)	1:558

The normal weight of the spleen in native Indians was not known, but Porter concluded that its loss in weight was relatively greater than that in any other organ.

Marked atrophy of the spleen was likewise noted by Formad and Birney ('91) in two cases of death from starvation.

Düschmann ('00) also held that the spleen is very small in starvation, reduced one-half or more; and Aschoff ('13) stated that the spleen loses in relative as well as absolute weight. Meyer ('17) found the spleen weight only 53 g. in a man who died after 60 days on water only.

The data by Krieger ('20) for the weights of the spleen in emaciated adults (infections excluded) are summarized in the accompanying table.

WEIGHT OF THE SPLEEN IN EMACIATED ADULTS (KRIEGER '20)

Condition in group	No. of cases	Normal weight estimated, grams	Observed weight average, grams	Percentage loss in weight
I. Insane, without chronic organic disease.....	8	150	80.0	46.6
II. Chronic diarrhea.....	5	150	96.0	36.0
III. Malignant growths.....	22	150	108.6	27.6
IV. Various cases in aged.....	14	{ 150 123 <sup>1</sup>	78.0	{ 48.0 36.5 <sup>1</sup>

<sup>1</sup> Making allowance for normal decrease in weight of the spleen after age of 50.

It will be noted that the estimated loss in spleen weight varied from 27.6–48 per cent in the various groups, which is approximately the same as the average loss in corresponding body weight.

Weber ('21) compared the weight of the spleen as found in 1,257 autopsy records at Kiel for the years 1914–1918. Unfortunately no body weights were available. Comparing the period of good nutrition (1914–1915) with that of subnutrition (1916–1918), the average weight of the spleen shows a slight decrease in the males from 156.5 g. to 137 g.; and in the female from 141.5 g. to 128 g. From 50 necropsies in cases of death from starvation, Stefko ('23) concludes that there is a loss in both relative and absolute weight of the spleen.

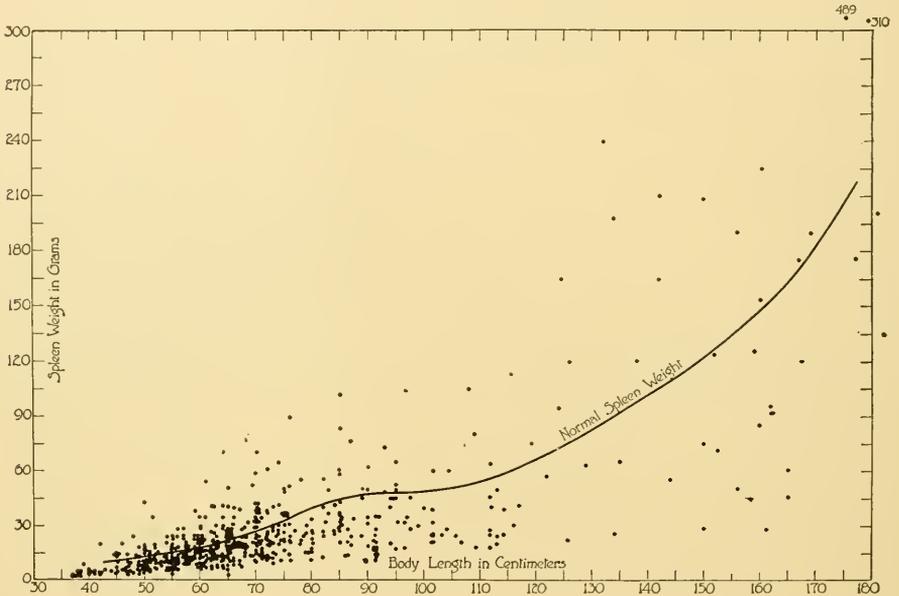


FIG. 75.—Graph showing the individual weights of the spleen, according to body length, in atrophic human cases, newborn to adult, from various sources. The curve of normal spleen weight is from data compiled by Prof. R. E. Scammon. Great individual variation is evident, but in most cases the weight is below normal.

Sison ('20) in 4 adult males on voluntary fasting observed a decrease in the splenic area of dullness on percussion, which he ascribed partly to a decrease in the size of the spleen, and partly to increased tympany of the overlying lung margin.

Bean and Baker ('19) from a study of a large series of organ weights at autopsy concluded that the weight of the spleen varies directly with the degree of general nutrition of the body (body weights not available). Pearl and Bacon ('22), however, from a statistical study of the ratios between the weights of various organs at autopsy found an indication of an increased absolute weight of the spleen in fatal tuberculosis, which usually produces marked emaciation of the body.

In Fig. 75, representing a field graph of the spleen weight in emaciated individuals (from various sources), under 20 years of age, arranged according to

body length, it will be noted that in those above 120 cm. in body length, there is no very marked tendency to subnormality in the weight of the spleen. Many of the enlarged spleens are probably due to syphilis, tuberculosis, or other complications, however. Among the children (Fig. 76), the splenic atrophy is more striking, but here also the weight is often above normal.

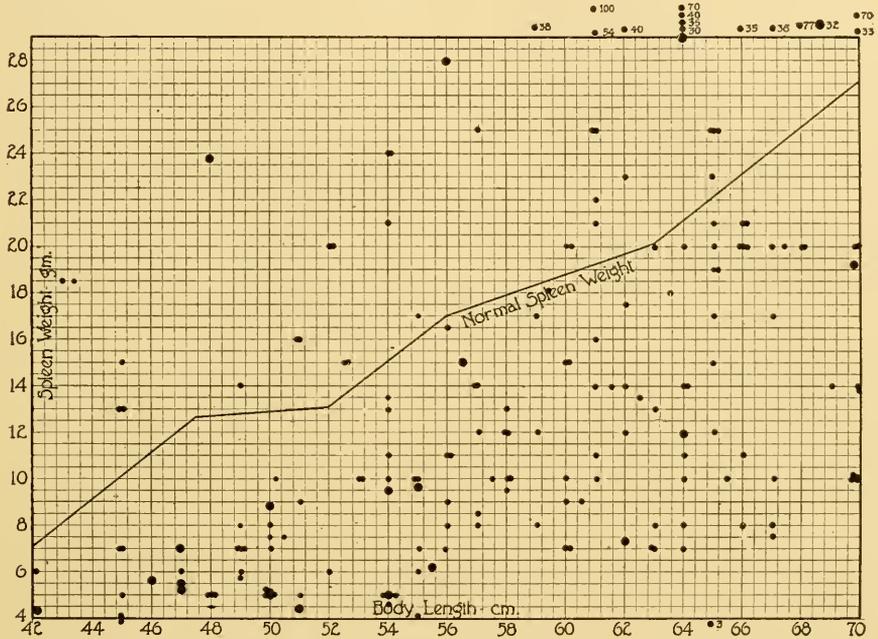


FIG. 76.—Graph showing the individual weights of the spleen, according to body length, in atrophic infants from various sources. The larger dots represent original Minnesota cases. The curve of normal spleen weight is from data compiled by Prof. R. E. Scammon. Most of the cases are clearly below normal, although there is great individual variation.

**Children.**—Ohlmüller ('82) observed a weight of 6.8 g. in the spleen of an atrophic infant of 8 weeks (body weight 2,381.2 g.), while in a "normal" infant of the same age (body weight 4,149.5 g.) the spleen weighed 20.2 g. Unfortunately the previous weight of the atrophic infant is not stated. De Tommasi ('94) and Thiercelin ('04) concluded that in atrophic infants the spleen is small. Bovaird and Nicoll ('06) from weights at 571 autopsies on children of various ages (newborn to 5 years) at the N. Y. Foundling Hospital concluded that the spleen "has no apparent relation to the size or state of nutrition of the child." Mattei ('14) likewise concluded that the spleen in atrophic infants is very irregular in weight, though often small. In 7 cases below 3 months of age he found the spleen ranging between 5 and 10 g., body weight 2,260–3,100 g. (previous body weight not given).

Lesage ('14) found a weight of 8 g. in the spleen of an atrophic infant of 4 months (normal 15 g.). Nobécourt ('16) and Marfan ('21) concluded that in general the spleen is relatively small in malnourished infants. In famine-stricken children of various ages, Nicolaëff ('23) found the spleen 48–51 per cent subnormal in weight according to age.

From the original data in Table 3, it will be observed that the weight of the spleen in atrophic infants is exceedingly variable. Of the cases above normal, only No. 11 can be excluded on account of syphilis. All the cases in which the age, body length, maximum and final body weights and weight of the spleen in atrophic infants were available are summarized in Table 2. Known syphilitic cases have been excluded. Thus it is apparent that, compared with the normal for final body weight, the spleen averaged 9.5 per cent above normal (or 5.6 below normal in the Minnesota series alone). Compared with the normal for the maximum body weight during life, the spleen averaged 14.9 per cent below normal; and for height, 20.5 per cent below normal. For age, the spleen averaged 31.3 per cent below normal (18.1 per cent for the Minnesota series alone). Thus in this series the average loss in weight of the spleen appeared somewhat less than that in the body as a whole.

On the other hand, from the field graph of all cases of spleen weight according to body length in atrophic infants, as shown in Figs. 75 and 76, it appears that in most cases the spleen weight is decidedly subnormal, according to body length. Doubtless if all complications (especially infections) tending to produce splenic enlargement could be excluded, the average weight of the human spleen during inanition would appear still lower.

Among **animals**, a more uniform loss of weight in the spleen has frequently been observed during inanition. A remarkably small size of the spleen in dogs and rabbits on total inanition was noted by Collard de Martigny (1828). In pigeons on total inanition with average loss of about 40 per cent in body weight, Chossat ('43) found an average loss of 71 per cent in the weight of the spleen. Similarly, Bidder and Schmidt ('52) found an apparent loss of 72 per cent in a cat with loss of about 50 per cent in body weight.

Manassein ('68, '69) also noted profound atrophy of the spleen in animals starved with or without water. Thus in 47 adult rabbits with average loss of 39 per cent in body weight, the spleen lost 65 per cent. In 8 young adult rabbits ( $3\frac{2}{3}$  months old) with average loss of about 33 per cent in body weight, the spleen lost 52 per cent. In 3 young rabbits (23-25 days old), with body loss of 35 per cent, the spleen lost 38 per cent. An apparent loss of 74 per cent was observed in the spleen of 2 starved cats, and of 79 per cent in 2 starved crows. On fully refeeding 5 rabbits after a severe fasting period, the spleen had recovered normal weight.

Bourgeois ('70) found in general the spleen atrophied to less than half its normal size in various starved mammals and birds, with or without water. A small spleen in dogs on total inanition or water only was noted by Carville and Bochefontaine ('75), Luciani and Bufalini ('82) and Mankowski ('82). In 6 fasting rabbits, with or without water, Skoritschenko ('83) found with average loss of 43.7 per cent in body weight an apparent loss of 26.5 per cent in spleen weight.

In 20 pigeons on absolute inanition, compared with 20 controls, Lukianow ('89) found an average loss of 34 per cent in body weight and of 58 per cent in the spleen, with no appreciable change in water content. In a dog fasting 22 days with loss of 32 per cent in body weight, Voit ('94) found the spleen slightly

heavier than in a normal control of the same litter (probably an individual variation). In newborn kittens on acute inanition (water only), Bechterev ('95) noted a relative increase in the weight of the spleen in kittens, but a decrease in puppies.

In 4 groups of guinea pigs (10 in each group) starved without water by Lazareff ('95), with average losses of 10, 20, 30, and 36 per cent in body weight, respectively, the corresponding losses in the weight of the spleen were 0, 31, 37 and 44 per cent (Table 5). Thus apparently the spleen is at first resistant, but loses greatly in the second period. Kusmin ('96) noted that, of the various organs, the spleen, liver and intestine suffered the greatest relative loss in rabbits and guinea pigs, with or without water, at ordinary or elevated temperatures. In 3 rabbits on water only with loss of 35-41 per cent in body weight, Weiske found a loss of about two-thirds in the fresh weight of the spleen, and slightly more in the dry weight. A similar loss in spleen weight was observed by Quattrochi ('01) in underfed puppies with loss of about 25 per cent in body weight.

Miescher ('97) noted during the migratory fast of the Rhine salmon an enormous decrease in the size of the spleen, which becomes reduced to stroma, with loss of blood and atrophy of the lymphoid cells.

Beeli ('08) found apparent losses up to 83 per cent in the weight of the spleen in 4 cats starved (water only) with losses up to 51 per cent in body weight. Jolly and Levin ('12a) in birds (pigeon, fowl, duck) starved 4-9 days without water found an apparent average loss of 60 per cent in spleen weight; body loss 30 per cent. In the guinea pig, they found the spleen loss 52 per cent, body loss 36 per cent; and in the rat, spleen loss 46 per cent, body loss 26 per cent. Jolly ('14) in 2 puppies, 1 month old, on water 6-8 days, with body loss of 27 per cent, noted an apparent loss of 73.5 per cent in the spleen weight, which was relatively greater than the loss in the thymus (68.1 per cent), or lymphatic glands (41-57 per cent). In 2 rabbits, 6½ months old, with loss of 23.5 per cent in body weight, the spleen lost 63 per cent, which was less than the thymus loss (88 per cent) but greater than that of the lymphatic glands (39-53 per cent).

Giannelli ('16) reported a marked decrease in the size of the spleen and other viscera in the teleost, *Tinca vulgaris*, after 5 months without food.

In adult albino rats on acute inanition (water only), Jackson ('15) found, with body loss of 34 per cent, an apparent average loss of 51 per cent in the weight of the spleen; while in a series on chronic underfeeding, with loss of 36 per cent in body weight, the spleen lost only 29 per cent. The great individual variability in the size of the spleen was emphasized.

In underfeeding experiments upon younger, growing albino rats, the effects upon the spleen weight appear variable (Table 4). In experiments on rats beginning at 3 weeks of age, Jackson ('15a) found an average loss of 42 per cent in the spleen of those underfed (at constant body weight) to 10 weeks of age, whereas in longer experiments the spleen showed but slight apparent loss. Stewart ('18) in rats severely underfed from birth found at 3 weeks an apparent loss of 49 per cent in the spleen weight; while in those underfed up to 10 weeks there was an apparent *increase* of 24 per cent in the spleen. In another series

held at birth weight for 16 days, there was an average increase of 38 per cent in the spleen weight. Barry ('20, '21) likewise found the spleen 34 per cent above normal weight in the newborn (stunted) offspring of severely underfed pregnant albino rats.

Upon refeeding albino rats after underfeeding from 3 to 12 weeks of age, Stewart ('16) found rapid recovery of normal spleen weight within a few days. There was apparently even an excessive (over-compensatory) growth of the spleen during the first 2 weeks of refeeding, but after 4 weeks the spleen weight became normal. The results of Jackson and Stewart ('19) likewise indicated an over-compensatory growth in the spleen after a short period of ample refeeding, with a tendency to lag behind later (Table 7). In such rats refed to adult stages after early periods of underfeeding, Jackson and Stewart ('20) found the spleen varying in different groups from 12.6 per cent below normal to 11.8 per cent above normal weight (Table 8). These differences are probably insignificant, in view of the great normal variability in the weight of the spleen.

In young steers held on various planes of nutrition, including those markedly retarded in growth by underfeeding, Moulton, Trowbridge and Haigh ('22a) found the spleen weight in general nearly proportional to the body weight in all cases.

In pigeons subjected to acute inanition (water only) with loss of 38.7 per cent in body weight, Findlay ('21) found an average loss of 60 per cent in the spleen weight (Table 13). In chronic underfeeding, the spleen lost 71 per cent.

Inlow ('22) in 2 fasting dogs ("fed a half-day's ration every third day") with losses in body weight of 31.9 and 46.2 per cent, respectively, noted a corresponding (estimated) shrinkage of 60 and 86 per cent in the spleen. The initial size of the spleen was measured directly by means of a laparotomy at the beginning of the experiment and compared with the findings at necropsy. Inlow concluded that similar losses in spleen and body weight following ligation of the pancreatic ducts are likewise due to the resultant inanition.

In frogs (species?) which had lost two-thirds of their body weight by starvation, Blumenthal ('04) found the spleen reduced to a diameter of 1 millimeter. Gerhartz ('06) found in female *Rana esculenta* a spleen weight of 0.028 g. in a normal frog with body weight of 47.5 g. In one starved 3 months in a warm room, with body weight of 35 g., the spleen weighed only 0.001 g.; and in another starved 4½ months, body weight 40 g., the spleen was extremely small (pin-head size). Ott ('24) in an extensive study on *Rana pipiens* during torpidity and at various stages of inanition, up to a loss of 60 per cent in body weight, found the average spleen weight very irregular in the various groups and in the sexes (Table 6), so that he was unable to draw any general conclusion.

A. L. Gaule ('93) and J. Gaule ('01) noted seasonal changes in the weight of the frog's spleen. Valentin ('57) found only a slight apparent loss (about 10 per cent) in the spleen of the hibernating marmot. Pappenheim ('01) even claimed that in spermophiles the spleen during hibernation becomes greatly enlarged. Thus during the seasonal changes, including hibernation, the weight of the spleen appears very irregular.

**Changes in Structure.**—The effects of total inanition (or on water only) upon the structure of the spleen will be reviewed first in man, adult and infant; later in the lower animals.

In the victims of the Madras famine, Porter ('89) noted in the usually atrophic spleen a variable thickening of the capsule and usually a deficiency in the pulp, with pigmentation in a few cases. In a man of 30 years who died from voluntary starvation, Stschastny ('98) observed in the spleen a pronounced atrophy, with scarcely recognizable Malpighian bodies, hyalinization of vessels and trabeculae, numerous eosinophile cells, hemoblasts in mitosis, and considerable pigmentation with hemosiderin. In a similar case, Meyer ('17) found the Malpighian nodules nearly obliterated, only a few barely distinguishable. The splenic sinuses were not evident, but erythrocytes (no nucleated forms) were abundant in the parenchyma. Only a few giant cells and phagocytes were found, although pigment was relatively abundant. The staining reactions of the cells were normal, though somewhat faint.

In extensive material from cases of starvation (age 1-63 years) Stefko ('23) finds hyperemia of the spleen, with atrophy of the lymphoid follicles, but increase in the reticulum and trabeculae.

As to the changes in the spleen of **malnourished infants**, Moldenhauer ('99) noted a relative increase in the stroma. Lucien ('08) found the spleen in athreptic infants firm and sclerotic. The Malpighian nodules were apparent, though small. In general, the histological changes were less marked than in the thymus and other organs. Helmholz ('09) in atrophic infants noted extensive pigmentation in the spleen, though no relation was found between the intensity of the pigmentation and the severity of the disease. The (iron-containing) pigment usually occurred in large intercellular masses as well as in fine intracellular granules. The Malpighian nodules were usually free from pigment. In general, the spleen presented relatively few erythrocytes, and relatively conspicuous fibrous tissue. Schelble ('10), on the other hand, found no significant histological changes in the spleen of atrophic infants.

In cases of congenital spasmodic atrophy of infants, Lesage and Cleret ('14) described perivascular sclerosis, with secondary fibrous trabeculae pervading the parenchyma. Mattei ('14) during athrepsia found the splenic capsule and trabeculae somewhat thickened. The white pulp of the spleen appears more abundant at first; later the red pulp gradually replaces the white, which persists only in the Malpighian nodules. Siderosis was found constant, with active red cell destruction in the macrophages of Billroth's cords. Nobécourt ('16) reviewed the literature, emphasizing the splenic siderosis, which accompanies the hepatic siderosis, as found by Triboulet, Ribadeau-Dumas and Harvier ('10), Helmholz and others. "La pulpe rouge de la rate est incrustée de blocs pigmentaires plus ou moins volumineux. Les sinus et les cordons de Billroth sont la siège d'une macrophagie active avec nombreuses figures de destruction globulaire, de sorte qu'il paraît évident que tout le fer mis en liberté provient de la destruction des globules rouges." The large vessels appear congested, but the venous sinuses appear nearly normal. Marfan ('21) stated that the splenic and hepatic siderosis found in athreptic infants is a

macrophagic reaction to the increased erythrocytic destruction in the anemia associated with the condition.

In famine-stricken children of various ages, Nicolaeff ('23) described the spleen as firm in consistence, with atrophy of the pulp and increase of fibrous trabeculae. Some edematous cases showed hyperemia or hemorrhagic infiltration, with atrophy of the lymphoid tissue, early hyalin degeneration and increased amount of brown pigment. Splenic and hepatic hemosiderosis was likewise observed by Stephani ('23).

In starved **animals**, Tiedemann ('36) found the blood vessels of the viscera in general, including the spleen, contracted and empty, hence giving the organs a pale or greyish tint. Falck ('75) in starved dogs found the spleen "braunroth, glänzend, schlaff, fein gerunzelt und blutleer."

Morpurgo ('88, '89), in rabbits starved 5-13 days, described the spleen as atrophic and anemic, with relative enlargement of the trabeculae and reduction of the lymphoid tissue in the Malpighian nodules and pulp cords. Mitoses occur in the normal adult rabbits, but become rare during inanition. Giant cells were observed in the spleen of a starved rabbit 15 days old. In rabbits refed 5 days after starvation for 10 days, Morpurgo ('90) found the spleen somewhat increased in size but still subnormal in weight. The pulp appeared relatively increased (compared with the starved condition), and the venous spaces and trabeculae correspondingly decreased. The histological structure resembled the normal. Mitoses were abundant in the pulp and especially in the center of the lymphoid nodules.

Coen ('90) noted the changes during starvation (with or without water) in 3 rabbits and 1 kitten. The spleen shows marked atrophy of the splenic pulp, rendering the connective tissue trabeculae very prominent. The Malpighian nodules are poor in lymphoid cells. The veins appear distended. Some small hemorrhagic foci occur, with both extracellular and intracellular hematic pigment, occurring chiefly just beneath the capsule, more sparsely in the splenic pulp. Blumenthal ('04) found the histological structure fairly well preserved in the spleen of starved frogs. Opie ('04) observed a marked decrease in the number of eosinophiles in the spleen of fasting guinea pigs, as stated in Chapter XV. Cesaris-Demel ('06) noted pigmented granules in the cells and connective tissue of the spleen in rabbits with marasmus produced by bacterial infections.

In 4 starved cats, Beeli ('08) found that the atrophy of the spleen is caused by decrease in the pulp. The trabeculae remain unchanged in size, and therefore become relatively very prominent and closely arranged, though inconspicuous in the normal spleen. The Malpighian nodules are also reduced in size and closer together. In some places, the blood capillaries (sinuses) are dilated. The nuclear diameters of the lymphoid cells in the Malpighian nodules were measured and tabulated according to size and frequency distribution, showing a tendency to progressive decrease in nuclear size during inanition.

In birds (pigeon, fowl, duck), guinea pigs and rats fasting for various periods, Jolly and Levin ('12a) noted atrophy of the lymphoid tissue, especially in the Malpighian nodules, the pulp otherwise being unaffected. Refeeding

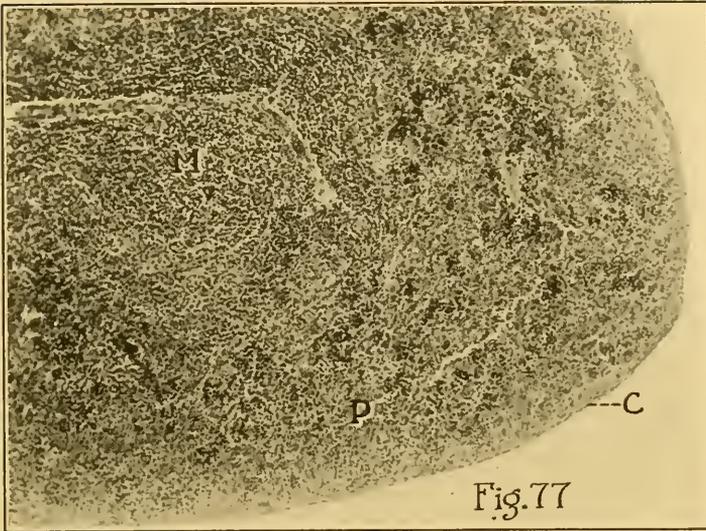


FIG. 77.—Photograph of a portion of a section of the spleen from a normal albino rat (Mo. 9), female, age 4 months. *M*, a splenic nodule (Malpighian corpuscle) with central arteriole, cut longitudinally. *P*, red pulp, with intermingled lymphoid pulp-cords. *C*, capsule. Trabeculae are scanty. Zenker fixation; hematoxylin-eosin stain.  $\times 90$ .

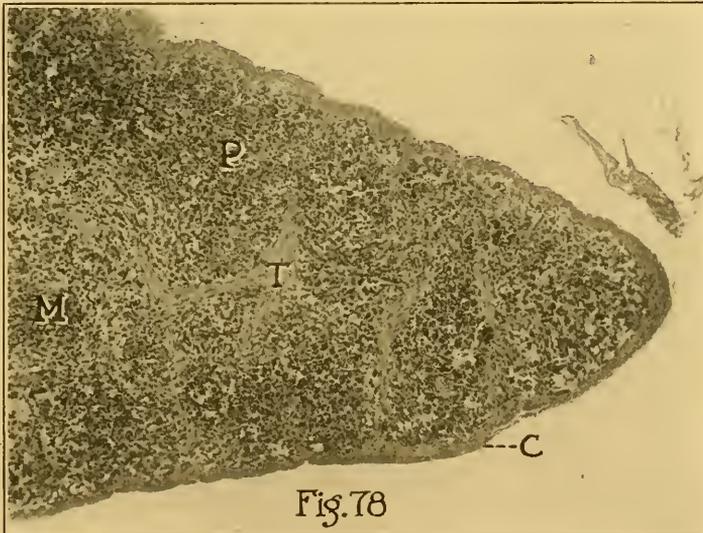


FIG. 78.—Photograph of a portion of a section of the spleen of a male albino rat (S. 18), body weight reduced from 196 to 121 g. (loss of 38 per cent) in 8 days on water only. Spleen greatly atrophied (weight 0.115 g.). Splenic pulp (*P*) reduced in amount. *M*, rudimentary splenic nodule (Malpighian corpuscle). Capsule (*C*) and trabeculae (*T*) appear relatively hypertrophied. There is a somewhat diffuse pigmentation, which is not evident in the photograph. Zenker fixation; hematoxylin-eosin stain.  $\times 90$ .

restores the normal structure in about 15 days, probably by mitoses of the remaining lymphocytes. Jolly ('14) concluded that in fasting puppies and rabbits the effects in the spleen are greater than those in the lymphoid organs generally, excepting the thymus (and the bursa of Fabricius in birds). In guinea pigs subjected to acute (complete) or chronic (incomplete) total inanition, Rondoni and Montagnani ('15) found the spleen greatly reduced in size by atrophy of the lymphoid tissue in the splenic pulp and Malpighian nodules. The trabeculae and supporting tissue become more prominent, being relatively, if not absolutely, increased in amount.

In 3 albino rats starved on water only, Sundwall ('17) found in the spleen: "prominent capsule; trabeculae appear very much thickened; extreme congestion; reduction in areas to complete disappearance of Malpighian follicles as a result of the congestion, and hyperplasia of endothelial cells; the latter are filled with red blood cells and pigment hemoglobin and hemosiderin." Asada ('19) found congestion of the blood vessels and striking pigmentation of the spleen in rabbits after 10 days of total inanition.

Inlow ('22) described the capsule of the atrophic spleen in starved dogs as shrunken and thinned, with compact structure, hyalin appearance and few nuclei. The trabeculae become more conspicuous through comparatively greater atrophy of the parenchyma. The cytoplasm of the pulp cells and supporting tissue has largely disappeared, so the pulp nuclei are closely packed. The number of lymphocytes outside the Malpighian nodules is markedly decreased; cells of large size predominate. The Malpighian nodules and their germinal centers appear more definitely delimited. The larger blood vessels appear normal; the splenic sinuses are smaller, but distinct. The free blood pigment in the pulp is increased in amount. The atrophic changes in the spleen appear roughly proportional to the length of the inanition and the loss in body weight.

In the fasting rabbit, Okuneff ('23) described a diminution in the number of the lymphoid splenic cells; but they remain unchanged in size and mitochondrial content.

Figures 77 and 78 represent the histological changes in the spleen of the albino rat during acute inanition.

Papers dealing with chemical changes (especially water-content) of the spleen during general inanition include those of Lukianow ('88) in pigeons, Tonninga ('93) in rats and rabbits, and Roger ('07) in rabbits. Those concerning changes in fats and lipid content include Terroine ('20) and Okuneff ('22).

During **hibernation**, Aeby ('75) studied the chemical changes in the spleen of the marmot. Mann ('16) noted marked congestion of the spleen in the hibernating gopher, *Spermophilus tridecemlineatus*. According to Mann and Drips ('17), this congestion reaches a maximum in a few days, persists about 40 days, then gradually subsides.

#### (B) EFFECTS OF PARTIAL INANITION

The effects of partial inanition upon the spleen will be considered under deficiencies of protein (including pellagra and famine edema), of salts (including rickets), of vitamins (including beriberi and scurvy), and of water (thirst).

**Effects of Protein Deficiency.**—The reasons for including pellagra and malnutritional edema under protein deficiency were given in Chapter V.

**Pellagra.**—According to Fraenkel ('69-'70) the spleen appeared subnormal in weight in 23 out of 30 cases. Lombroso ('92) found it atrophic in 41 and hypertrophied in 12. Babes and Sion ('00) likewise found the spleen usually atrophic, except in malarial cases. Nicholls ('12, '13) in 8 negro pellagrins noted an average weight of only 3 ounces for the spleen. Raubitschek ('15) and Harris ('19), from a comprehensive review of the literature on the pathology of pellagra, concluded that the spleen is usually decreased in size, though sometimes enlarged.

As to the structural changes in the spleen during pellagra, Fraenkel ('69-'70) noted hyperemia, more rarely pigmentation. Tuczek ('93) found atrophic changes and abnormal pigmentation, which are also included in the review by Marie ('08, '10). Kozowsky ('12) described thickening of the trabeculae, venous congestion and hyalinization of the small arteries. An increase in the fibrous tissue (sclerosis), especially of the blood vessels, and marked hematogenous pigmentation of the spleen are mentioned by Nicholls ('12, '13), Raubitschek ('15) and Harris ('19).

The weight of the spleen in human **famine edema** appears somewhat variable. Paltauf ('17) observed a range of 70-235 g. Atrophy of the spleen was reported by Hülse ('17) and Oberndorfer ('18), the latter finding weights as low as 50 g. Enright ('20) found the spleen enlarged only in cases complicated by malaria; otherwise small, sometimes weighing only 3 ounces. Mann, Helm and Brown ('20) reported the spleen normal or shrunken in 200 necropsies. Prince ('21) found the spleen usually slightly increased in volume.

As to the structure of the spleen in famine edema, Oberndorfer ('18) described it as sclerotic; the pulp anemic and atrophic; color dark reddish brown; follicles small but distinct. Enright found the consistency of the spleen normal except in the malaria cases, when it appeared hard and pigmented. Fracassi ('22) noted splenic fibrosis.

In guinea pigs on maize diet (mixed deficiency of protein, vitamins and salts), Rondoni and Montagnani ('15) obtained a sclerosis and sometimes hyperemia of the spleen. Rondoni ('19) found that the spleen formed 0.14 per cent of the body in maize-fed guinea pigs (normal 0.12 per cent), indicating a slight increase in relative weight.

In monkeys, pigs and albino rats on corn-oil cake, maize and similar diets (mixed deficiencies of protein, etc.) producing emaciation, Sundwall ('17) found the spleen intensely congested, showing hemosiderosis, and sometimes amyloidosis and hyalin changes; proliferation of endothelial cells of the pulp, containing red blood cells and pigment; and reduction in size of the Malpighian bodies.

In pigeons and monkeys on diets with mixed deficiency of protein, vitamins, etc., McCarrison ('19b, '21) found marked atrophy of the spleen, especially in the pigeons.

Lefholz ('23) found that in kittens the spleen shows no consistent response to variations in the protein, fat or sugar content of the diet (thus, like the thymus

and lymph glands, differing from the tonsils and other lymphoid structures of the alimentary canal).

In human **ricketts**, enlargement of the spleen was noted by Whistler (1645), Seibold (1827) and many subsequent observers; but its significance has been much disputed (*cf.* reviews by von Starck '96 and Sasuchin '00), being frequently attributed to syphilis or other complications. Von Starck ('96) found at Kiel a splenic enlargement ("Milztumor") in 53 out of 113 autopsies of rachitic children (57 per cent), but it also occurred in 77 out of 148 non-rachitic (52 per cent). A palpable "Milztumor" was also found in 68 out of 110 living rachitic children, which is said to agree approximately with the findings by Rehn at Frankfort (64.8 per cent), and by Kuttner at Berlin (73.3 per cent). Nevertheless, von Starck concluded that the splenic enlargement is merely a frequent complication, and not due to the same cause as the ricketts. Sasuchin ('00) found splenic enlargement in 12 out of 16 cases, the exceptions showing general emaciation. Comby ('01) found the spleen usually enlarged in ricketts. Vincent ('04) claimed that it is moderately enlarged in the progressive stage, but not permanently. Cheadle and Poynton ('07) stated that the rachitic spleen is sometimes enlarged; while Stöltzner ('03, '09) found no significant change (aside from complications). Pfaundler ('22) states that in ricketts the spleen is often enlarged.

Wohlauer ('11), from original observations and a review of the literature on human ricketts, concluded:

"Ein besonderes Verhalten zeigt die Milz. Sie ist stets vergrößert manchmal in excessivem Grade, bis zum Sechs und Achtfachen ihres normalen Masses (Heubner). In leichten Fällen lässt sie sich am Lebenden nicht nachweisen, da auch die aufgetriebenen Därme die Untersuchung erschweren. Wir fürchten uns zu wiederholen, es muss aber gesagt werden, dass auch hier wieder die Meinungen geteilt sind (v. Starck, Müller, Kuttner, Fox, Ball, M. Cohn, Stöltzner, Monti). Mit dem Ablauf der floriden Erscheinungen verschwindet der Milztumor, der sich meistens bei Kindern im zweiten Lebensjahr findet."

In rats with experimental ricketts, Shipley, Park, McCollum and Simmonds ('21) found the spleen apparently atrophic in some rats, more or less enlarged in others. McCollum, Simmonds, Shipley and Park ('21) noted that the spleen is frequently greatly enlarged; while McCollum, Simmonds, Kinney, Shipley and Park ('22) state that the spleen is enlarged in some cases, but usually not above normal. These conclusions were apparently not based on actual weights. Jackson and Carleton ('23) found the weight of the spleen so irregular and variable in rachitic rats that no conclusion could be drawn, although in most cases the average was below that in the controls (Table 11).

But few observations upon the histological changes in the spleen during ricketts are available, and these are all in the human species. Sasuchin ('00) concluded that the changes are very characteristic, appearing early and in many cases proportional to the intensity of the rachitic symptoms. The most marked changes are proliferation of the connective tissue, constriction of the arterial lumina, inflammatory appearances and atrophy of the Malpighian bodies. The lesions resemble those in lues and tuberculosis, but these diseases were carefully

excluded. These changes may affect the hemopoietic function of the spleen and be related to the anemia occurring in rickets, as was also emphasized by Saricinielli ('03). He found at first a hyperplasia of the splenic pulp followed by a progressive proliferation of the connective tissue stroma, which gradually replaces the parenchyma. Pfaundler ('22) holds that during rickets there is a marked swelling of the lymphoid organs throughout the body. The spleen is often enlarged, due to hyperplasia of pulp and follicles.

**Vitamin Deficiency.**—In some cases previously cited, such as infantile atrophy, the effects are probably due in part to vitamin deficiencies. We may consider these under the three well known vitamins—A, B and C.

Deficiency of **vitamin A** alone has apparently no marked effect upon the spleen, according to experiments on rats by Emmett and Allen ('20) and Cramer, Drew and Mottram ('21a). Davis and Outhouse ('21) noted frequent congestion of the splenic sinuses, but no degenerative changes. Meyerstein ('22) made a few observations on the spleen in young white rats on diets deficient in vitamins A and B.

**Vitamin B.**—In 125 cases of human beriberi, Ellis ('98) found the average weight of the spleen 9.27 ounces, in comparison with 6.28 ounces in 204 dying from other causes, thus indicating a hypertrophy of the spleen in beriberi. Strong and Crowell ('12) noted some congestion of the spleen, with relatively small follicles. Andrews ('12), in 18 necropsies of infantile beriberi, likewise found the spleen very hyperemic, and even hemorrhagic; but with no increase of splenic tissue. Nagayo ('23) claimed that splenic passive congestion distinguishes human beriberi from experimental polyneuritis.

In experimental beriberi (or polyneuritis) produced in pigeons by polished rice diet (deficient in vitamin B), Funk and Douglas ('14) mentioned atrophy and degenerative changes in the spleen, among other organs. Tasawa ('15) studied the effects in about 150 pigeons and 200 fowls, finding the body emaciated and the spleen always atrophic; capsule wrinkled and thickened, and trabeculae conspicuous; the pulp atrophic and the follicles scarcely visible. "Ein Bild wie die gewöhnliche Stauungsmilz ist überhaupt nicht zu sehen." Emaciation of the body and atrophy of the spleen were likewise noted by Mackenzie ('15) in pigeons and by Drummond ('16) in young chickens.

Voegtlin and Lake ('19), in cats, dogs and rats with polyneuritis produced by deficient diets, noted in the spleen degenerative changes similar to those (above mentioned) found by Sundwall ('17), but less extensive.

As previously mentioned, McCarrison ('19, '19a, '21) found that a diet of milled and autoclaved rice gives rise to an atrophic degeneration of the spleen and other organs in pigeons and monkeys. Atrophy of the lymphoid tissues in general was observed. Brucco ('20) noted evidences of regenerative activity in the spleen and bone marrow of dogs on a polished rice diet. Findlay ('21) found a loss of 65–67 per cent in the spleen of fowls and pigeons with beriberi (Table 13). Lopez-Lomba ('23) noted a brief increase preceding the marked decrease in the weight of the spleen in adult pigeons on vitamin-free diet.

Cramer, Drew and Mottram ('21) found in mice and rats that the spleen, like the lymphoid tissue in general, undergoes a specific and profound atrophy

upon dietary deficiency of vitamins (especially vitamin B), the result being similar to that produced by the Roentgen rays and radium.

In chickens with polyneuritis from dietary deficiency of vitamin B, Souba ('23) found the spleen markedly subnormal in weight, the loss being relatively exceeded only by the testes. In experimental avian beriberi, Korenchevsky ('23a) also found splenic atrophy, but persistence and even hypertrophy and hyperplasia in the germ centers of the nodules.

**Vitamin C.**—In human scurvy, Sato and Nambu ('08) found the spleen enlarged in tuberculous cases; otherwise normal in size. Much granular pigment was noted, and subcapsular hemorrhage in 1 of 13 autopsies. Aschoff and Koch ('19) found the spleen generally normal in size, not enlarged in uncomplicated cases. Histologically they found manifold changes (especially pigmentary), generally secondary in character. Congestion was observed, but no hemorrhages.

Jackson and Moore ('16) found the spleen frequently enlarged in scorbutic guinea pigs. Hess ('20) has reviewed in detail the literature on human and animal scurvy, indicating that the spleen is usually enlarged and congested, showing pigmentation, and sometimes hemorrhage and hyperplasia. Höjer ('24) describes lymphoid atrophy, siderosis, occasional hemorrhages and necrosis.

Bessesen ('23) found the weight of the spleen variable at different stages of scurvy in the guinea pig. In the early stages, the spleen showed a loss in weight; but after the appearance of definite scorbutic symptoms, it appeared hypertrophic, being 35–56 per cent above normal weight (Table 12).

**Water Deficiency.**—In a dog 76 days old, on dry diet with loss of 21 per cent in body weight, Falck and Scheffer ('54) noted an apparent *gain* of 9 per cent in the spleen (probably an individual variation), in comparison with a litter-mate control. Bowin ('80) found that in dogs and rabbits on dry diet, with loss of about 50 per cent in body weight, the losses in the various organs were similar to those in total inanition. The spleen lost relatively more than the body as a whole.

Pernice and Scagliosi ('95a) studied the effects of a dry diet upon the spleen in 1 dog and 3 young chickens. In the dog, the spleen at autopsy appeared small and dry, with wrinkled, thickened capsule and hypertrophied trabeculae. The pulp was atrophic, dark brown in color, with sharply demarcated follicles. Many cells were in mitosis. Small, subcapsular hemorrhages occurred. In the chickens, the spleen was likewise atrophic. The thickened capsule in many places showed round cell infiltration. In the pulp just beneath the capsule were numerous hemorrhages of various size, around the Malpighian bodies, which appeared very atrophic. The arteries showed inflammatory changes. The pulp was scanty, with many pulp cells in mitosis.

In adult albino rats on a relatively dry diet, Kudo ('21) found in acute thirst experiments, with average loss of 36 per cent in body weight, a loss of 66 per cent in the spleen; in chronic thirst experiments, with loss of 52 per cent in body weight, a loss of 73 per cent in the spleen; and in one rat with neither food nor water, with loss of 47 per cent in body weight, a loss of 63 per cent in the spleen (Table 9). In young albino rats (1 month old) held at constant body weight by relatively dry diets for various periods the spleen shows a marked loss (36–48 per cent) in all but one group, in which one exceptionally large spleen reduced the average loss (Kudo '21a) (Table 10).

## CHAPTER XVIII

### EFFECTS ON THE THYMUS

The thymus is an organ characteristic of the growth period, and is of especial interest in pediatrics on account of its pronounced tendency to atrophy in all conditions of inanition or malnutrition. Following a brief summary, the effects of inanition upon the thymus will be considered in detail under (*A*) total inanition, and (*B*) partial inanition.

#### SUMMARY OF THE EFFECTS ON THE THYMUS

The weight of the thymus responds so promptly and extensively to conditions of malnutrition as to justify fully Simon's designation of it as a "barometer of nutrition." In this respect, it is rivalled only by the adipose tissue. The loss is relatively far greater than that in the whole body. In both man and lower animals the **loss in thymus weight** usually reaches at least 75 per cent before death from acute inanition (total complete, or on water only); and in chronic forms (incomplete total) may reach 90 to nearly 100 per cent, though it is doubtful whether it ever completely disappears as sometimes stated.

The thymic atrophy during inanition occurs at every age, but is especially notable in the young, where the thymus is both relatively and absolutely larger than at later ages. The persistent growth tendency found during inanition in many of the organs during infancy does not appear in the thymus, although its loss in the newborn rat appears relatively less than at later ages.

The characteristic thymic atrophy appears not only in the various degrees of total inanition, but also in most forms of partial inanition, as well as in many other conditions (exhaustion, disease, etc.), and is designated by Hammar as "accidental involution," in contrast with the normal "age involution" of the thymus.

In most cases the degree of thymic atrophy appears closely correlated with the general malnutrition of the body; although certain exceptions occur, in which the thymus may be large in spite of general emaciation. This is found in some cases of infantile atrophy, and has been claimed in human rickets, but is of doubtful significance.

**Recovery** of the normal thymic weight usually occurs promptly upon refeeding, unless the inanition has been extremely severe. There is some evidence indicating persistent subnormality in the thymus of rats permanently stunted by underfeeding, but this is still somewhat uncertain.

The **histological changes** in the thymus during inanition are equally striking and characteristic. The resultant involution affects all parts of the thymus; but especially the lymphoid tissue, which here (as elsewhere throughout the body) undergoes a pronounced atrophy. Although there are numerous variations in

the details, the typical process appears very similar in all types of inanition, including hibernation and various diseases involving malnutrition. There is a marked decrease in the number of mitoses, but not complete cessation, except perhaps in extreme stages. The number of lymphocytes becomes very greatly reduced, chiefly through emigration into the adjacent tissues and vessels, but partly (especially in later stages) by degeneration of lymphocytes, with phagocytosis by the reticulum cells. The reticulum is much more resistant, and assumes a somewhat epithelioid, embryonal appearance, recalling the "reduction" phenomena among certain invertebrates. The reticulum presents a progressive increase in lipoidal content, with degenerative changes in the later stages.

The atrophy first and foremost affects the cortex, which becomes rarefied by the "delymphoidisation," and lighter than the medulla in stained sections, producing the so-called thymic "inversion." Later the differentiation between cortex and medulla disappears. The Hassall's corpuscles are relatively resistant, but also ultimately undergo atrophy and cystic degeneration, and in extreme stages may disappear entirely.

In contrast with the striking atrophy of the parenchyma, the fibrous stroma is relatively more resistant, and becomes more prominent, giving an appearance of fibrosis or sclerosis in the capsule and interlobular septa. There is usually a prompt disappearance of the ordinary adipose content, thus differing from the typical age involution of the thymus. Although relatively more resistant, the fibrous stroma also decreases progressively in absolute volume, so that in extreme stages the thymus is reduced to a small mass of vascular fibrous tissue, containing only indistinct remnants of the parenchyma.

Unless the inanition has been extremely severe, there is prompt **regeneration** of the thymus upon ample refeeding. The remaining cells undergo rapid mitosis; the reticulum cells regenerate new Hassall's corpuscles in the medulla, and become infiltrated with lymphocytes in the cortical region (as during normal development). Thus the normal structure is ultimately restored, excepting extreme cases where permanent injury may result.

#### (A) EFFECTS OF TOTAL INANITION, OR ON WATER ONLY

The literature upon the "accidental involution" of the thymus has been thoroughly reviewed by Hammar ('06, '10, '21) and is also included by Biedl ('16, '22). For convenience, the effects of total inanition will be discussed first in the human species; later in the lower forms.

The earliest observation upon **human** thymic atrophy was apparently by Verheyen (1710) who noted its occurrence in persons subjected to strenuous activity ("qui corpus vehementer exercent"). As in the case of most organs, however, the earlier observations upon the human thymus during inanition concerned chiefly the weight or size, together with the gross appearance, in various cachectic conditions. Thus Meckel (1810, 1820) observed that the general nutritive condition of the body greatly affects the rapidity with which the thymus atrophies. In a weak, malnourished child of 2 years, he found the thymus "fast ganz geschwunden, saftlos, weich, viel kleiner als bei einem

wohlgenährten 6 jährigen." Similar observations were made by Haugsted (1831).

Simon ('45) stated: "I think it extremely probable that the thymus may within a few days, if not hours, vary remarkably in the same individual, according to the immediate state of the general nutrition. Its size seems to be, *caeteris paribus*, if I may venture to use the phrase, a barometer of nutrition and a very delicate one."

Hérard ('47) found great variation in the weight of the thymus, even aside from the nature of the disease causing death. "La constitution de l'enfant, son état de maigreur ou d'embonpoint, semblent être les principales conditions qui influencent ces variations." Ecker ('53) likewise noted a decreased size in the thymus during malnutrition.

Friedleben ('58) made extensive and careful observations on the weight of the thymus in the well-nourished and malnourished, and concluded: "Das relative Gewicht der Thymus stellt sich im Säuglingsalter bei akuten Krankheiten um viermal, in chronischen um zwölfmal niedriger als der normalen Thymus; in der ersten Kindheit bei akuten Prozessen fünfmal, bei chronischen sechsmal; in dem Knabenalter bei akuten Krankheiten viermal, bei chronischen neunmal niedriger als in gesunden Individuen." Friedleben's animal experiments will be mentioned later.

Thaon ('72) similarly found that at death from traumatism or acute diseases the thymus is always large; while in chronic disorders with malnutrition the thymus is largely consumed.

Seydel ('94) emphasized the medico-legal importance of the thymus weight, claiming that thymus atrophy, accompanied by extreme emaciation and without signs of organic disease, is a sure sign of death from inanition. Hansen ('94) weighed the thymus in 108 cases, with results similar to those of Thaon ('72). He opposed Seydel's claim that the thymus may totally disappear in conditions of extreme exhaustion. Filomusi-Guelfi ('95) questioned the importance of thymic atrophy as a sign of death from starvation, since it occurs in all chronic diseases or conditions involving malnutrition.

Farret ('96) confirmed Thaon's finding of thymus atrophy in athreptic infants, with 27 tabulated cases. He concluded that the thymus is functionally related to the nutrition and development of the organism. He cited the case of Durante, who found in a cachectic infant an atrophic thymus (1.5 g.) showing an intense sclerosis which he thought might have caused the fatal condition.

The atrophy of the thymus during inanition, especially in its medico-legal aspect, is discussed by Dwornitschenko ('97), von Mettenheimer ('98) and Dün-schmann ('00). Von Mettenheimer (like Simon) considered the weight of the thymus as the best index of nutrition of the body, its atrophy being comparable to that of the adipose tissue. He described the occurrence of fibrosis and degeneration of Hassall's corpuscles, and held that thymic atrophy is the cause of pedatropy. Ghika ('01), however, maintained that the thymic atrophy is the effect, rather than the cause, of athrepsia.

Stokes, Rurah and Rohrer ('02) and Rurah ('03), like previous observers, found a marked and constant atrophy of the thymus (average weight 2.2 g.) in a

series of 18 malnourished infants. They also studied the histological changes in the thymus, finding a general fibrosis, with thickening of the capsule and interlobular connective tissue. Hassall's corpuscles increase in size and undergo hyalin degeneration. A later stage shows "almost entire disappearance of the lymphoid structure of the lobule and an increase in the reticular endothelium."

Dudgeon ('05) studied the weight and structure of the thymus in 15 cases of primary infantile atrophy and in 41 cases of secondary atrophy. He concluded that the atrophy of the thymus is closely associated with the general wasting of tissues. Histologically, the most characteristic changes in the atrophic thymus include: fibrosis, usually well marked, with thickening of the outer coat of the blood vessels; atrophy of the lymphoid corpuscles, which are replaced by endothelial cells, connective tissue cells and small "giant cells;" all varieties of degeneration in Hassall's corpuscles. The average weights found by Dudgeon are as shown in the accompanying table.

WEIGHT OF THE THYMUS IN INFANTS WITH VARIOUS CONDITIONS OF NUTRITION (DUDGEON'05)

Source	No. of cases	Average wt. of thymus, grams
Primary atrophy.....	15	2.680
Secondary atrophy (tuberculous).....	26	3.065
Secondary atrophy (non-tuberculous).....	12	2.605
Acute diseases.....	32	5.440
Fetal specimens.....	10	6.53 (or 4.575)
"Sudden death." "Found dead".....	16	25.011

Somewhat similar thymus weights were recorded by Fortescue-Brickdale ('05), who found the average in 12 marantic infants to be 2.45 (1.3-4.8) g.; in 9 tuberculous children, 1.9 to 10 g.; in 9 chronic emaciated (non-tuberculous), 3.14 (1-4.7) g.; in 20 acute diseases, 5.7 g.

Hammar ('05, '06) made an extensive and thorough study of the involution of the thymus, a continuation of his earlier animal experiments (to be mentioned later). Hammar introduced the term "accidental involution" to indicate the atrophy caused by malnutrition or other abnormal factors, in contrast with the normal "age involution" of the thymus. The establishment of a reliable norm of growth in weight made it possible to measure precisely the degree of atrophy at any stage of postnatal development. The amounts of parenchyma and stroma in both cortex and medulla were also measured, making possible a quantitative measurement of the histological changes.

In general, Hammar found that the process of atrophy in the "accidental" involution is characterized by a subnormal amount of parenchyma, which, in the cortex, may disappear entirely. The stroma is also reduced, but to a lesser degree; it therefore becomes relatively more abundant, but there is no true fibrosis or sclerosis. There may be a "paradoxical" adipose deposit in the stroma of the atrophic thymus, even in infants where normally no fat occurs. In the parenchyma, the lymphocytes becomes variably decreased in number;

sometimes nearly all disappear. "Die Retikulumzellen legen sich dabei dichter an und bilden häufig sogar Komplexe, die ihr ursprüngliches epitheliales Aussehen mehr oder weniger wiedergewonnen haben. Auch sie fallen einer Degeneration allmählich anheim, welche allerdings von dem normalen durch Hypertrophie der Zellen eingeleiteten und zur Bildung Hassall'scher Körperchen führenden Prozess deutlich zu trennen ist." Hassall's corpuscles persist in the earlier stages of inanition, becoming relatively prominent; later they are variable, sometimes disappearing.

Bovaird and Nicoll ('06) studied the weight and gross structure of the thymus in 571 autopsies on children up to 5 years of age. In general, the loss in thymus weight (80 or 90 per cent, in extreme cases) is relatively greater than in body weight; but there are exceptional cases indicating that factors other than the extent of malnutrition may influence the weight of the organ. The greatest loss of thymus weight occurs in marasmus, diarrheas, and similar chronic exhausting disorders. The atrophic involution includes actual absorption of thymic tissue, which becomes fibrous and fatty, as during the normal age involution.

Thompson ('07) in 20 cases of infantile marasmus found the average weight of the thymus 2.472 g. (range 1.0-4.75). There is marked histological atrophy of the lymphoid tissue, and increase of interlobular connective tissue, as described by Dudgeon. Hassall's corpuscles become prominent and the differentiation between cortex and medulla usually disappears.

Naegeli ('08) held that the disappearance of the medullary cells of the thymus during inanition indicates that these are large lymphocytes, rather than epithelial in character.

Lucien ('08, '08c), in fatal cases of athrepsia, found an average thymus weight of only 0.97 g. (range 0.05-2.50), indicating an average loss of over 80 per cent. Grossly the thymus appears reddish, with a firm, fibrous consistence. The histological changes are variable, with 4 progressive stages: (1) Early involution, with retention of the distinction between cortex and medulla; little change in structure, aside from increased perilobular connective tissue and dilation of blood vessels. (2) The cortico-medullary distinction disappears; lymphocytes equally distributed throughout, but the medulla is more vascular and contains more Hassall's corpuscles. (3) The peripheral (cortical) zone becomes clear, filled with irregular "epithelioid" cells, and the lymphocytes become more concentrated in the central (medullary) zone, making an *inversion* of the lobular structure; Hassall's corpuscles numerous throughout almost the entire lobule, appearing simple or compound in structure, and in various stages of evolution or degeneration, sometimes hyalin, cystic or calcified. (4) The most extreme stages show the thymus converted into a fibrous tract, with numerous thick-walled vessels; vestiges of the thymic lobules appear as scattered small lymphoid nodules; sometimes a few degenerating Hassall's corpuscles are still visible.

Feldzer ('10) and Tixier and Feldzer ('10) concluded that the thymic atrophy in athrepsia is probably secondary, rather than primary in character. The regressive process is a sclerosis, distinct from the normal adipose age

involution, and presents 5 stages: (1) Moderate fibrous proliferation, especially interlobular; blood vessels strongly congested; differentiation of darker cortex and lighter medulla not well marked; cells show mitoses; Hassall's corpuscles polymorphic, but not abnormal. (2) The congestion and cellular hyperplasia become decreased; interlobular connective tissue increased; lobular reticulum more apparent, with sclerosis extending from vessels and septa; distinction between cortex and medulla has disappeared; the various cell types tend to homogeneity; lymphocytes, macrophages and eosinophile myelocytes become rare; Hassall's corpuscles numerous and polymorphic. (3) The thymic lobules become fragmented by sclerotic bands, proceeding especially from the perivascular connective tissue; sometimes the normal lobular topography appears inverted, the cortical zone through rarefaction and sclerosis becoming clearer than the medulla; lymphocytes with opaque nuclei predominate; a thin zone of mononuclears appears around the Hassall's corpuscles, which are still numerous, but sometimes cystic. (4) The thymus is now largely fibrous, with small, irregular lobules; homogeneity of cell types still more evident; cell activity restricted to a small zone around Hassall's corpuscles, which are chiefly cystic and sometimes united into irregular masses. (5) Thymus now presents a fibrous (collagenous) mass, poor in cells, with a few cell islands as remnants of the thymic lobules; in the thickened reticulum appear a few pycnotic lymphocytes; usually no traces of the Hassall's corpuscles remain.

Tixier and Feldzer hold that the thymic sclerosis is comparable to that occurring during inanition in other (especially the lymphoid) organs.

The effects of inanition upon the thymus in atrophic infants are reviewed by Lesage ('11) and Mönckeberg ('12), who considered the thymic involution as an effect, rather than a cause. Schridde ('13, '21), however, contends that the atrophy of the thymus is a real factor in infantile malnutrition, or a *circulus vitiosus*, inanition causing a sclerous atrophy of the thymus, which in turn intensifies the malnutrition. Schridde also described an increasing amount of fatty granules in the reticulum cells of the cortex; and a disappearance of the lymphocytes and eosinophile leukocytes during the progressive sclerosis. Plasma cells rarely occur (contrary to some authors).

Crémieu ('12) claimed that the involution of the thymus by inanition, X-rays, etc., is fundamentally similar to the normal age involution. "Il ne s'agit que de deux modalités différents d'un processus uniforme: l'envahissement conjonctif. D'un côté, le tissu conjonctif reste sec; de l'autre, il se charge de vesicules adipeuses."

Matti ('13) gave an extensive review of the work on thymic involution in man and animals.

Hornowski ('13) found the weight of the thymus usually varying directly with the general nutritive condition in the newborn. Lesage and Cleret ('14) emphasized sclerosis during athrepsia as the characteristic change, occurring to a variable degree in all organs, especially in the thymus.

Mattei ('14) gave a careful description of the changes in the atrophic thymus of athreptic infants, his findings being in general agreement with those of Lucien and Feldzer. He concluded that "Le tissu propre de l'organe présente

deux modifications importantes: *l'inversion thymique* et la *sclérose marquée*, les deux altérations se rencontrent dans le même organe à différents degrés, suivant les cas." He described epithelioid cells and giant mononuclear cells as abundant in the cortex during thymic inversion, with peripheral invasion of the lobule by adipose tissue.

Nobécourt ('16) reviewed the changes in the thymic atrophy of malnourished infants, following in general the findings of Lucien, Feldzer and Mattei. He noted that the nature of the thymus atrophy has been explained in three ways: (1) as a primary cause of the general malnutrition (Farret, Durante, v. Mettenheimer); (2) as a simple, secondary atrophy, comparable to that occurring in other organs during inanition (Friedleben, Clark, Ghika, Seydel, Sokoloff); and (3) as due to toxic or infectious causes (Tixier, Feldzer, Martel, Marfan).

Hart ('17) described the thymus in a starved child of 3 years, complicated with "eine floride Rachitis leichten Grades." The thymus weighed 5 g. Frozen sections stained with Sudan showed no sclerosis, but numerous peripheral cells with vesicular nuclei filled with fatty droplets of variable size, and some cells with complete fatty degeneration. In the center of the lobules, Hassall's corpuscles contained fatty detritus, but cells with fatty degeneration were rare. The cells in the septa were mostly fat-free. The ordinary stains (hematoxylin, etc.) showed the typical inversion of the lobule, with lighter cortex and darker medulla.

Hammar ('21) has recently reviewed the problem of thymus involution, including the accidental involution caused by disease, pregnancy, X-rays, and especially inanition. In congenital pyloric stenosis and in infantile pylorospasm, accurate measurements showed the thymic parenchyma reduced 80 per cent. In general, the cortex is more labile, being rapidly reduced by wholesale emigration of lymphocytes, which infiltrate the adjacent interstitium and vessels. The medulla also becomes richer in lymphocytes. The number of mitoses is greatly reduced; but a few persist, especially in the reticulum cells. The distinction between cortex and medulla apparently disappears, although fat stains show abundant fat droplets appearing in the cortical reticulum. The medulla may become relatively richer in nuclei, producing the "inversion" of the French authors, which appears oftener in illness than in starvation.

During inanition-involution, according to Hammar, the medulla remains unchanged longer than the cortex, but later decreases in size by general atrophy (and some degeneration) of the individual medullary cells. Hassall's corpuscles are more resistant, hence become *relatively* more numerous, although there is a slow decrease in *absolute* numbers. In extreme cases the parenchyma may decrease to 1 or 2 per cent of the original amount, and the thymus presents only narrow strips, poor in lymphocytes, and in which Hassall's corpuscles may disappear entirely. During Röntgen involution, the lymphocytes do not emigrate, but disintegrate *in situ*. There are also some variations in the process of involution in different diseases, but in general the process resembles that of inanition-involution. (Hammar '17, '18, '20, '21.)

In famine-stricken children of various ages, Nicolaëff ('23) found the thymus 90-98 per cent subnormal in weight, compared with Hammar's norm for age.

The atrophied thymus was found reduced to fibrous cords, with small islets of gland tissue. Similar data are reported by Stefko ('23a). Stephani ('23) noted fat in the thymus cells of atrophic infants.

Keilmann ('23) studied the thymus in 86 nurslings and 73 children of the second year (no individual data). Unlike most previous investigators, he was unable to find any regular relation between thymus weight and the character of the disease causing death. He found both high and low thymus weights in all conditions, and therefore doubts whether the thymus weight can be accepted as an index of nutrition. He cites the observations of the Italians, Oliari and Spolverini (*cf.* abstracts in *Arch. f. Kinderh.*, 65:124-130) in support of this conclusion. Keilmann's observations upon the histological changes in the



FIG. 79.—Graph showing the individual weights of the thymus, according to body length, in atrophic infants from various sources. The larger dots represent original Minnesota cases. The normal curve is from data compiled by Prof. R. E. Scammon. The profound atrophy of the thymus during malnutrition is evident, the weight being above normal in only 2 out of about 300 cases.

thymus are likewise in disagreement with those of previous investigators. He noted the so-called "inversion" of cortex and medulla in 4 cases, but did not find a disappearance of the lymphocytes accompanying the process of fibrosis. He claims that Hassall's corpuscles are usually greatly increased. He admits that low thymus weights are in part due to emaciation, but holds that they are not always pathological, since the norm is usually put too high.

My own observations upon the weight of the thymus in atrophic infants, in opposition to the conclusions of Keilmann, show clearly the marked effect of malnutrition upon the thymus weight, confirming the findings of most previous observers. In the 15 cases shown in Table 3, the thymus weight ranged from 0.1-5.8 g. (the latter in a slightly rachitic infant of 6 months). The normal for the newborn is about 13 g., increasing with age (see Fig. 79).

In a series of about 40 cases (about half of which represent original observations upon Minnesota cases), in which complete data were available, the average loss in thymus weight in atrophic infants has been calculated upon various bases, as shown in Table 2. Thus in comparison with Scammon's norm for the corresponding final body weight, the thymus averages 71.8 per cent. below normal for the entire series, or 75.8 per cent below for the Minnesota data alone. Compared with the normal for the maximum body weight reached during life, the thymus weight averages 80.7 per cent subnormal. Compared with the norm for corresponding height, the thymus loss is 80.6 (80.4) per cent; while for age the thymus appears 82.6 (84.4) per cent subnormal.

The marked depression of the thymus weight in malnourished infants also appears clearly in Fig. 79, a field graph representing all available cases in which the body weight was 20 per cent or more subnormal according to body length, irrespective of the cause of death. The large dots represent original Minnesota data. Out of nearly 300 cases, only 2 appear above normal, and the profound atrophy in nearly all cases is clearly evident.

Among the **animals**, the effect of unfavorable environment upon the thymus has long been known. Wharton (1659) found that the strenuous labor to which young oxen were subjected when yoked causes a marked atrophy of the thymus. Gulliver (1842) similarly observed that "in overdriven lambs the thymus will soon shrink remarkably and be nearly drained of its contents, but will become as quickly distended again during rest and plentiful nourishment."

Friedleben ('58), in addition to the above mentioned observations on the human thymus, starved young puppies for 12 hours, 40 hours and 14 days, respectively, and demonstrated that the thymus atrophied relatively more than the liver, spleen or the entire body. In the longest experiment, the thymus was reduced to a mere trace, while the body lost 45.7 per cent in weight. Manassein ('69) included some data indicating a marked loss in the weight of the thymus in fasting young rabbits, but he makes no comment thereon.

Hofmeister ('92) pointed out the similarity between the hunger involution of the thymus and that in other lymphoid tissues, and thought there is a relation between this and the blood lymphocytes. Voit ('94) noted, in dog starved 22 days, almost complete disappearance of the thymus, which weighed 31 g. in a normal litter control.

During fasting or hibernation in frogs, Ver Eecke ('99) found a loss of 75 per cent or more in the weight of the thymus. The atrophy involves both cortex and medulla. There is a rarefaction of the lymphoepithelial tissue (including the concentric corpuscles), which is more marked in the medulla. Persistence of the connective tissue gives an appearance of pseudosclerosis.

We come now to the work of Hammar and his co-workers, who introduced more accurate methods of histological analysis, which have contributed largely to the rapid recent progress in our knowledge of the thymus problem in man and animals. Hammar ('05a) first described the changes as found in rabbits and frogs subjected to inanition, and also in pathological cases in animals and man. The rabbit's thymus may lose half its weight in 3 days of fasting. The mitoses decrease rapidly in number (especially in the cortex) and soon disappear. The

lymphocytes of the cortex become greatly reduced in number through migration into the surrounding connective tissue, especially around the blood vessels and lymph vessels. There may also be migration into the medulla. The emigration of the lymphocytes leaves the cortical reticulum more prominent and the surface cells may become epithelioid in appearance (as in embryonal stages). The distinction between cortex and medulla is lost, and degenerative changes appear in the remaining cells. There is at least a relative increase in the interlobular connective tissue and the vascular stroma, but it is uncertain whether there is an actual sclerosis, as described especially by the French authors. The myoid cells and Hassall's corpuscles undergo variable, regressive changes, sometimes disappearing. In the teleost fish, *Labrus rupestris*, starved 23-31 days, Hammar ('09) described a reduction to one-sixth in the weight of the thymus, and histological changes similar to those found in higher vertebrates.

Hammar's pupil, Jonson ('08, '09), made a series of accurately controlled experiments upon young rabbits on acute inanition (water only) or chronic underfeeding (maintenance of constant body weight); also a series refed after inanition. In 4 weeks of chronic inanition, the thymus weight decreased to about  $\frac{1}{30}$  and the parenchyma to about  $\frac{1}{65}$  of the normal. In 9 days of acute inanition, the thymus was reduced to  $\frac{1}{4}$  and the parenchyma to  $\frac{1}{10}$  normal weight.

Of the parenchyma, the cortex suffered the greatest reduction—to  $\frac{1}{12}$  in 2 weeks of underfeeding and to  $\frac{2}{9}$  in 5 days of acute inanition. In later stages the cortex has usually disappeared. The cortex atrophies chiefly by emigration of the lymphocytes into the lymph spaces (and veins?). The persistent reticulum cells gradually assume an epithelioid appearance, undergoing degenerative changes only in the later stages. The number of mitoses in the entire thymus was reduced from 28,500,000 to 6,500,000 in 4 days of acute inanition, and from 10,500,000 to 3,100 in 4 weeks of chronic inanition. The persistent mitoses were chiefly in the reticulum cells. Hassall's corpuscles showed a varied resistance. The unicellular forms disappeared (by simple atrophy?) even in the second week of underfeeding, while the multicellular corpuscles were reduced (partly by degeneration) from 139,200 to 16,100 in 4 weeks. During acute inanition, the unicellular forms decreased from 170,000 to 44,000, and the multicellular from about 741,500 to 352,700. The interstitial (fibrous) tissue was reduced to about  $\frac{1}{8}$  normal weight in 4 weeks of underfeeding; with a smaller loss in acute inanition. The interstitial fat is completely resorbed, and the interstitial fibrous tissue assumes a loose, edematous appearance.

Jonson's refed rabbits made a rapid recovery, showing a distinct increase in the weight of thymus and parenchyma even in 2 days, and nearly normal conditions in 3 weeks. "Die Zunahme des Parenchyms wird in erster Linie durch Einwanderung von Lymphocyten aus den Lymph- (und Blut-) Wegen bedingt, wozu frühzeitig eine nicht geringe Zunahme von Mitosen in Lymphocyten und Retikulumzellen hinzukommt." The cortex regenerates first. Differentiation of the typical structure in the medulla, with regeneration of Hassall's corpuscles (by hypertrophy of the reticulum cells), begins only after 2 weeks of refeeding. The interstitial fibrous stroma recuperates rapidly, and fat cell groups begin to appear even after 2 days of refeeding.

Källmark ('11), in connection with his study of the effects of inanition upon the blood of young rabbits, also made some observations upon the lymphoid organs, including the thymus. In an initial control of 3 months, the thymus weight was 3.15 g.; after 19 days of underfeeding (at maintenance), 0.3 g.; after 28 days of underfeeding, plus 2 days on water only, 0.17 g.; after 31 days of underfeeding, 0.20 g.; and in a final, full fed control, 4 months old, 3.45 g. The blood lymphocyte count does not show much change, but there is a transient decrease at the beginning of inanition, which is ascribed to the atrophy of the lymphoid tissues of the body in general. There is also a transient increase in the blood lymphocyte count upon refeeding, indicating an over-compensatory regeneration in the lymphoid organs.

Jolly and Levin ('11) studied the effects of inanition upon the weight of the lymphoid organs in the pigeon, chick, duck and guinea pig. In the birds, with loss in body weight of 30-37 per cent, the thymus lost 51-80 per cent, which is relatively greater than the loss in the bursa of Fabricius (48-77 per cent), or spleen (53-67 per cent). In young fasting guinea pigs, the thymus and spleen showed similar losses. In pigeons, the thymus also made the most rapid recovery in weight. In a later paper ('11a), they showed that in all these animals the histological process of involution in the thymus during inanition is similar to that described by Hammar and Jonson. The diminution in weight is due chiefly to loss of the cortex, which is caused primarily by emigration of the lymphocytes, with decrease in mitosis and some loss by phagocytosis. Degenerative changes are described in the cortex and medulla; also the regenerative process upon refeeding (in pigeon and guinea pig). The degenerative and regenerative changes, especially in Hassall's corpuscles, are more fully considered in a later paper ('12).

Holmström ('11, '12) found lipoidal granules stainable with scarlet red in the reticulum cells of normal newborn rabbits. These granules, which are independent of the ordinary interstitial fat, become more numerous with age, and also during malnutrition. Crémieu ('12) noted in 2 malnourished kittens a sclerous atrophy of the thymus, like that produced by the X-rays, etc. Levin ('12) described the typical process of involution in the thymus during inanition, and the recovery upon refeeding. In underfed tadpoles of *Rana fusca*, Dustin ('13a) observed an atrophy of the thymus, with cessation of mitosis and transformation into small cells with pycnotic nuclei.

The extensive monograph of Salkind ('15) includes several inanition experiments on the thymus. Puppies of various ages and underfed to various degrees showed an atrophic thymus, with the cortex reduced to a narrow zone of lymphocytes and the medulla large and vascular. Mitoses are greatly decreased in number. The stroma cells show evidences of phagocytosis. Mast cells are numerous. Thus underfeeding depresses the secretory activity of the thymus (production of lymphocytes); but increases the phagocytic activity, and ultimately causes sclerosis. In rats one month old without food or water, signs of "delymphoidisation" appear in 12 hours, with pycnosis in the follicular centers and phagocytosis of lymphocytes by the reticulum cells. This process continues and at 3 days there is an inversion, the cortex becoming light and the

medulla darker in appearance. The formation of Hassall's corpuscles from the epithelioid cells continues. At 4 days, "delymphoidisation" is complete and there is but slight distinction between cortex and medulla. Mitoses have entirely disappeared; Hassall's corpuscles become cystic and are destroyed by eosinophiles. Recovery of the rat upon refeeding is impossible at this stage, but occurs after 2 days of starvation. The process of "relymphoidisation" is somewhat slow, mitoses appearing rare after 48 hours of refeeding. At least a week is required to re-establish the normal lymphoid structure. A chick

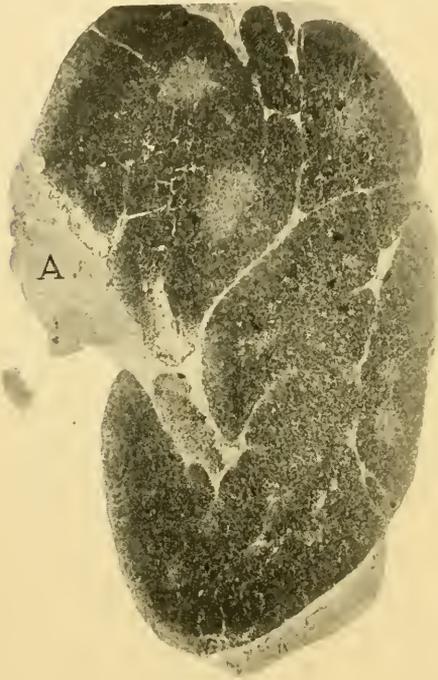


FIG. 80.

FIG. 80.—Photograph of a cross section of the thymus in a normal albino rat (S. 2) at 3 weeks of age. The gland is mostly cortex, the few light areas representing the medulla. The capsule and interlobular septa are thin. A, perithymic adipose tissue. Zenker fixation; alum-hematoxylin stain.  $\times 22$ .

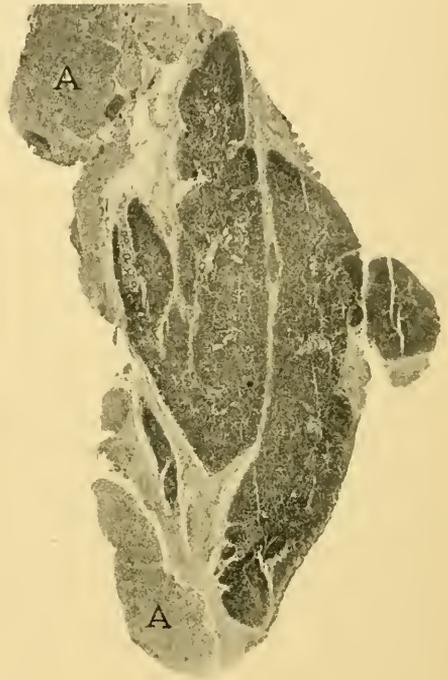


FIG. 81.

FIG. 81.—Photograph of a cross section of the thymus in an albino rat (S. 11) held at constant body weight by underfeeding from 3 to 10 weeks of age. The thymus is greatly reduced in size, and the distinction between cortex and medulla obliterated. The capsule and interlobular septa are relatively thickened. Some masses of atrophic, perithymic adipose tissue (A) are included in the section. Zenker fixation; alum-hematoxylin stain.  $\times 22$ .

(a few days old) after 12 hours' starvation showed beginning "delymphoidisation," similar to that in mammals. Lizards starved 1-5 weeks also showed the typical thymic involution, but a teleost fish ("Chat de Mer") showed no appreciable change in 6 days.

Some of the changes observed in the weight of the thymus of the albino rat during inanition by Jackson and his co-workers are shown in Table 4. In rats underfed from the age of 3 weeks to 10 weeks, Jackson ('15a) noted a loss of about 90 per cent in the thymus. In rats underfed from birth for various

periods, Stewart ('18, '19) found a smaller loss (30-80 per cent); and in the stunted offspring of severely underfed pregnant rats, Barry ('20, '21) found the thymus only 21 per cent subnormal in weight.

The reduction in the thymus of underfed young albino rats is shown by Figs. 80 and 81.

Upon refeeding rats underfed from 3 to 12 weeks of age, Stewart ('16) found the thymus still somewhat subnormal after 2 weeks; but after 4 weeks it appeared 50-70 per cent above normal, possibly indicating an over-compensatory growth. In rats underfed from birth to 3, 6 or 10 weeks of age, and subsequently refed to 25, 50 or 75 g. body weight, Jackson and Stewart ('19) found the thymus variable, but in most cases still slightly subnormal in weight (Table 7). In rats similarly refed to maximum (adult) weight, after earlier periods of underfeeding, Jackson and Stewart ('20) found the thymus still subnormal in weight in 3 of the 4 groups (Table 8). The evidence would seem to indicate a permanent dwarfing of the thymus in most cases, although the great normal variability renders the results uncertain.

Trowbridge, Moulton and Haigh ('18) and Moulton, Trowbridge and Haigh ('22a), in steers on different planes of nutrition, found that the thymus ("heart sweetbread") averages higher in weight in fat animals, but the reduction in the poorly nourished is much less than might be expected from the results of inanition in other species.

McCarrison ('19b, '21) gave organ weights indicating a great loss in the weight of the thymus in pigeons during starvation as well as on various deficient diets. Findlay ('21) found total disappearance of the thymus in starved pigeons and fowls (Table 13).

Ikeda ('22) in fasting rabbits found that the thymus atrophies more rapidly than the other viscera, due chiefly to emigration of lymphocytes, but also to degeneration of the parenchyma. Okuneff ('22) observed large amounts of isotropic, and especially of anisotropic, lipoids in the thymus of rabbits starved until the ordinary reserve fat was assumed to be exhausted.

Several observations indicate that the thymus undergoes a typical involution during **hibernation**. A winter-atrophy of the thymus was noted by Ver Eecke ('99) in the frog (species?); and by Schaffer ('08) in the mole. A similar process, with the typical involution changes during hibernation, was described by Aimé ('12, '12a) for chelonians (*Emys vittata*, *Clemmys leprosa*, *Testudo mauritanica*). The annual regeneration is apparently by a process of budding, the epithelioid buds being later invaded secondarily by small thymic cells, which form the cortex (as in normal development). Dustin ('13) observed a seasonal involution in adult amphibia, *Rana fusca* and *Bufo vulgaris*. Mann ('16), however, found apparently no uniform change in the thymus of hibernating spermophiles (*Spermophilus tridecemlineatus*).

#### (B) EFFECTS OF PARTIAL INANITION

These will include changes in the thymus during various partial dietary deficiencies, especially in rickets, beriberi, scurvy, and thirst (aqueous inanition).

Lefholz ('23) found that the thymus, spleen and cervical lymph glands of kittens showed no consistent response to dietary variations in the amounts of **fat, sugar and protein**, although the tonsils and lymphoid structures of the alimentary canal generally were markedly affected.

In **human rickets**, Seibold (1827) noted: "Die Glandula Thymus und das Mediastinum fand man meistens mit einzelnen Verhärtungen."

In 14 non-rachitic infants, du Castel ('08) found the thymus weight above 8 g. (which was considered normal) in only 1, the average being 4.50 g. But in 13 rachitic infants below 3 years of age, the thymus exceeded 8 g. in 8 cases, the maximum being 15 g. and the average 9.42 g. "On peu donc conclure que dans la majeure partie des cas le thymus rachitique est hypertrophié; l'augmentation du poids de l'organe est due à la prolifération du tissu lymphoïde; on trouve assez souvent des myélocytes en grande nombre; les corpuscles de Hassall sont également plus nombreux que dans les thymus non rachitique; enfin, le plus souvent, on n'y constate plus la sclérose, si fréquente chez ces derniers." It may be noted, however, that du Castel's thymus weights are all actually subnormal (*cf.* Fig. 79); whether the thymus is larger than would be expected in these cases, according to the general nutrition of the body, is uncertain on account of the lack of data concerning body weight, etc.

Sweet ('21) advanced the theory that rickets may be due to a deficient secretion of the thymus; but this fails to account for the apparent antagonism between rickets and starvation, which has repeatedly been noted in man and animals, in spite of the profound atrophy of the thymus during starvation.

Marfan ('22) confirms du Castel's claim that the thymus is enlarged in human rickets, accompanying a general hypertrophy of the lymphoid organs ("polyadénie").

In **experimental rickets** in rats, Shipley, Park, McCollum and Simmonds ('21) found the thymus atrophic (no weights given) in animals on diets deficient in fat soluble A, with or without deficiency also in phosphorus. A similar condition was mentioned by McCollum, Simmonds, Shipley and Park ('21) in rats on low calcium diets, with "undersized" bodies.

From a study of the weights of the thymus in an extensive series of albino rats, Jackson and Carleton ('23) found that the thymus averages slightly above Donaldson's norm in the "normal control" group, but shows a progressive decrease in weight in the test groups, reaching 70 per cent below normal in the severely rachitic group (Table 11). The weight-length ratio of the body was nearly normal, but nearly all of the test rats were subnormal in weight according to age, indicating a retardation in growth. This would tend to depress the thymus weight, irrespective of any specific effect of the rickets.

Several observations are available upon the thymus in **beriberi** (vitamin B deficiency). Andrews ('12) in 18 necropsies of infantile beriberi found only slight apparent changes in the thymus, aside from congestion.

In animal experiments, however, a profound atrophy of the thymus in beriberi or polyneuritis was found by Funk and Douglas ('14) in pigeons; by Williams and Crowell ('15) in pigeons and chickens; by Douglas ('15) in pigeons; by Drummond ('16) in chickens; by McCarrison ('19, '19a, '19b, '19c, '19e,

'20a, '21) in pigeons and monkeys; by Emmett and Allen ('20) in rats; by Cramer, Drew and Mottram ('21, '21a) in mice and rats; and by Findlay ('21) and Korenchevsky ('23a) in pigeons and fowls. Findlay found total disappearance of the thymus in the rice-fed as well as the starved animals (Table 13). Lopez-Lomba ('23) noted a transient hypertrophy in the second period (9th to 14th days), preceding the final atrophy of the thymus in adult pigeons on vitamin-free diet.

It may be noted, however, that during beriberi there is usually a general emaciation, with marked loss in body weight, which might account for the thymic atrophy, independent of any specific effect of the vitamin deficiency. Thus Williams and Crowell ('15) concluded: "The experimental evidence indicates that there is no apparent fundamental connection between beriberi and the atrophy of the thymus; when the latter occurs in birds fed on polished rice, as it frequently does, it is due to some other cause." On the other hand, the atrophy of the thymus in beriberi is in agreement with the doctrine of Cramer, Drew and Mottram ('21, '21a), according to which a deficiency of vitamin B causes a specific atrophy of lymphoid tissue throughout the body.

In **scurvy**, but few data on the thymus are available, according to Hess ('20). Jacobsthal ('00) in a case of infantile scurvy found no apparent gross or histological changes in the structure of the thymus. Bierich ('19) mentioned an apparent enlargement of the thymus in 1 out of 8 (adult) cases. Aschoff and Koch ('19) noted no abnormalities of the thymus in adult scurvy.

During **thirst** (aqueous inanition), Falck and Scheffer ('54) observed an apparent loss of 63 per cent in the thymus of a dog on dry diet, with loss of 20 per cent in body weight. In adult albino rats on acute thirst experiments, Kudo ('21) found an apparent loss of 78 per cent in the thymus weight; while in the chronic thirst series the loss averaged 90 per cent (Table 9). In similar experiments on young albino rats, held at constant body weight by a relatively dry diet, Kudo ('21a) found a loss of 68.9-91.3 per cent in the weight of the thymus in the various test groups, being relatively greater than the loss in any other organ (Table 10).

## CHAPTER XIX

### EFFECTS ON THE ALIMENTARY CANAL

The effects of inanition upon the alimentary canal are widespread and significant. A knowledge of the changes during the earlier stages of inanition is necessary to understand the normal processes of digestion and absorption. The effects during the later stages are associated with the marked disturbances of the digestive system which are characteristic, not only in total or partial inanition in the narrower sense of the term, but also in the state of malnutrition which is associated with so large a proportion of diseases in general. In both children and adults, there is often established a "vicious circle," the primary involvement of inanition causing an atrophy of the alimentary tract, which in turn serves to intensify the general state of malnutrition. The process of recuperation is also conditioned by the possibility of regeneration in the atrophied and degenerated tissues of the digestive system, a consideration of great practical importance to the physician. Following a somewhat brief summary of the effects upon the entire canal, the changes will be reviewed in detail under (1) the mouth, pharynx and esophagus, (2) the stomach, and (3) the intestines.

#### SUMMARY OF THE EFFECTS ON THE ALIMENTARY CANAL

The changes in the alimentary canal during inanition vary greatly in the different regions.

In the **mouth**, atrophic and degenerative changes have been noted in the epithelium of the oral mucosa, but mitoses persist in the deeper layers. The tongue is very resistant to loss in weight (frog), but during extreme thirst degenerative changes occur in the lingual muscle fibers (fowl). Lesions of the oral mucosa occur in pellagra, and especially in the gingival regions during scurvy.

In the **pharynx**, the size of the tonsils is greatly affected by the character of the diet as to calories, protein, carbohydrates and especially the fat content. The weight of the pharynx and **esophagus** is found reduced nearly in proportion to the body weight during inanition (pigeons and steers). The lesions in these segments are usually slight.

The **stomach** presents extremely variable changes during inanition. In human starvation, it usually appears contracted and small in adults, but frequently above normal weight in malnourished infants. In animals, the loss in weight is usually relatively less (rarely more) than in the body as a whole, and there may even be a persistent gain in gastric weight in the young (rat and human infant) during chronic underfeeding.

Structurally, the stomach during inanition presents a variable degree of atrophy, with degenerative changes in extreme cases. The mucosa may appear normal, aside from simple atrophy; but in advanced stages of inanition there is frequently congestion and often localized degenerative changes—erosion of the superficial epithelium, ulceration, hemorrhages, regressive changes in the gastric glands; and edema, leukocytic infiltration or fibrosis in the stroma of the mucosa and submucosa. The smooth muscle tissue likewise shows a variable degree of atrophy.

The localized degenerative gastric lesions in the advanced stages are probably due largely to gastritis, which appears to be more frequent during human starvation than in experimental inanition among animals. Infantile atrophy is usually secondary to gastroenteritis (or other disorders, such as syphilis or tuberculosis), which interferes with nutrition and establishes a "vicious circle." The resultant inanition causes atrophy of the alimentary canal and associated glands, which in turn intensifies the general state of malnutrition.

Changes similar to those described for inanition occur in the alimentary canal of the fasting salmon; and also (to a variable extent) in various animals during hibernation, during which a characteristic leukocytic infiltration of the stroma has been observed.

Very similar atrophic and degenerative gastric changes occur to a variable degree also in the different types of partial inanition, including protein and vitamin deficiencies, thirst (aqueous inanition), etc.

In the **intestines**, the changes during inanition in general resemble those in the stomach. There is a variable loss in weight with shortening and attenuation of the intestinal wall. In both man and animals there is a general and progressive atrophy in the earlier stages of inanition, following certain minor changes in the mucosa associated with the normal process of digestion and absorption. The epithelium (surface and glandular) contains mitochondria and lipoidal granules which are somewhat resistant to inanition. The atrophy affects all the tissues, but especially the intestinal glands and lymphoid structures. In the later stages, as in the stomach, more profound and degenerative lesions may occur, with enteritis, ulceration, hemorrhages, and disintegration of surface epithelium, glands, and even entire villi.

In the young, similar intestinal changes may occur; but the process is in some cases modified by the persistent growth impulse.

In various types of **partial inanition**, a variable degree of intestinal atrophy and, in more extreme cases, degenerative and inflammatory lesions occur, which are essentially similar to those found during total inanition. General atrophy and weakness of the intestinal walls, and especially of the tunica muscularis and associated sympathetic ganglia, may result in distension and meteorism. The lymphoid structures appear variable, perhaps because the primary atrophic effect of the inanition is sometimes opposed by the toxic or inflammatory conditions. The tendency to hemorrhages is especially marked in scurvy and thirst (aqueous inanition).

Upon **refeeding** after a period of inanition, mitosis (which is depressed during inanition) is greatly accelerated in the cells of the various atrophic intestinal

tissues (especially the lymphoid and epithelial), and the normal weight and structure may be promptly restored. If the inanition has been severe or prolonged, however, recuperation is usually slow and difficult. In adult starvation or infantile atrophy and similar conditions in experimental inanition, the degenerative lesions in extreme cases may render recovery impossible.

#### 1. MOUTH, PHARYNX AND ESOPHAGUS

The data as to the effects of inanition upon these segments of the alimentary canal are scanty. The teeth have already been discussed in Chapter VIII.

**The Mouth.**—Rabl ('85) found many mitoses in the *tongue glands* of *Salamandra atra* starved 5-7 months. Morpurgo ('88, '89) noted persistent mitoses in the epithelium of the *lingual mucosa* and *palate* in both young and adult rabbits during fasting. The mitoses occur chiefly in the deeper layer of cells. No abnormality in the chromatin was noted. Porter ('89) noted furring of the human tongue as characteristic in chronic famine, though it may become raw and denuded when diarrhea and dysentery set in. "The epithelial tissue was very oily, and a true fatty transformation seemed to affect the deeper layers of epithelium in greater or less extent, leading to an imperfect development of the growing cells and ready detachment of those already formed."

Reese ('13, '13a) found no significant change in the digestive tract (including *tongue*, *palate* and *esophagus*) of the hibernating alligator.

Ott ('24) noted that during hibernation and subsequent inanition in the frog (*Rana pipiens*), with progressive loss of body weight up to 60 per cent, the *tongue* (unlike the skeletal musculature) shows no definite change in weight (Table 6), and therefore becomes relatively much larger.

Lesions of the *oral mucosa*, with stomatitis, etc., were noted by Chittenden and Underhill ('17) in a dog with experimental pellagra, and similar effects are mentioned by Harris ('19) in human pellagra. Inflammation, hemorrhages and ulceration of the *gingival mucosa*, especially in the peridental region, are well known symptoms of human *scurvy*, as noted, for example, by Sato and Nambu ('08), Bierich ('19) and Comrie ('20). The changes are reviewed in detail by Hess ('20). Beach ('23) found pustules in the *mouth*, *pharynx* and *esophagus* of fowls on diets deficient in *vitamin A*.

Tiedemann ('36) cited observations indicating dryness of the mouth and throat during *thirst* in man and animals. Falck and Scheffer ('54), in a dog on aqueous inanition (dry diet) for 4 weeks with loss of 20 per cent in body weight, observed an apparent loss of only about 8 per cent in the *tongue* (with hyoid) and the same in the *esophagus*. In fowls on a dry diet, Pernice and Scagliosi ('95a) found the *tongue* showing marked passive hyperemia. The most superficial muscles appeared pale, with the muscle fibers cloudy and desiccated in appearance; cross-striation partly absent. The cells of the lingual cartilage appeared atrophic and shrunken, with some cells degenerated into amorphous granular masses. The *crop* (a dilation of the esophagus) likewise appeared hyperemic and hemorrhagic, with variably atrophic gland cells. Small cell infiltration occurred in the mucous, submucous and muscular tunics. The muscle cells were pale and cloudy, with poorly stained nuclei.

Marriott ('23) has recently reviewed the effects of thirst in man, including the cessation of salivary secretion, with dryness of the *mucous membranes* and shrivelling of the *tongue* and *lips*.

The **pharynx** and **esophagus** (including crop) were found by Chossat ('43) to average 34 per cent subnormal in weight in pigeons starved with loss of 40 per cent in body weight. Bourgeois ('70) from fasting experiments on various animals (mammals and birds) concluded that there are no marked changes in the mouth, pharynx or esophagus.

Nothwang ('91) noted that in pigeons dead from thirst the esophagus and interior of the crop appeared dry.

Thiercelin ('04) found congestion and sometimes small, superficial erosions in the esophagus of atreptic infants.

Moulton, Trowbridge and Haigh ('22a) in steers on various planes of nutrition, including some greatly retarded in growth, found the esophagus (gullet) nearly proportional to the body weight in all cases.

The experiments of Lefholz ('23) upon kittens indicate that the *palatine* and *pharyngeal tonsils* are greatly affected by the character of the diet. With a diet high in sugar and protein, and also in calories, these organs are nearly doubled in size; while if the excess calories are provided in the form of fats, they are nearly trebled in size.

## 2. THE STOMACH

Under this section will be included some general observations upon the gastrointestinal tract, as well as those referring to the stomach alone. The data on total inanition (or water only) will be considered first, followed by the various forms of partial inanition.

### (A) EFFECTS OF TOTAL INANITION, OR ON WATER ONLY

The effects upon the human stomach (adult and infant) will be considered first, followed by the data for the infrahuman species.

**Human Adults.**—Lucas (1826) cited an observation by Ballin of a contracted stomach with thickened walls in a case of starvation (religious dementia). From a review of the literature, Willien ('36) concluded that during inanition the walls of the digestive tract become atrophic, usually without inflammation. Tiedemann ('36) noted that in starved adults the stomach appears narrow and constricted, sometimes containing bile. Schultzen ('62, '63) likewise observed a contracted stomach in a girl 19 years old, who died from starvation. Curran ('74), on the contrary, found the stomach distended with gas in an old woman. Jewett ('75) found no gastric lesion excepting a disappearance of the mucosa in a man of 74 years who died from chronic starvation. Bright *et al.* ('77) in the Harriet Staunton case found the stomach small, with very thin walls, through which the undigested contents were clearly visible. Falck ('81) stated that the stomach in starvation is usually found contracted and nearly empty, with the mucosa markedly folded and white, sometimes reddish in places (as found by Schultzen). Voelkel ('86) noted very thin and pale walls in the stomach and intestines of a starved man.

In 459 autopsies upon victims of the Madras famine (including 226 men, 155 women and 78 children), Porter ('89) classified the stomach as "large" in about  $\frac{1}{3}$  of the men,  $\frac{1}{5}$  of the women and only 3 children; and as "small" in  $\frac{1}{2}$  of the men,  $\frac{2}{3}$  of the women, and  $\frac{5}{6}$  of the children. It was found empty in  $\frac{2}{5}$  of the adults and  $\frac{2}{3}$  of the children. The gastric mucosa appeared congested in 36 men, 14 women and 7 children, with variable pigmentation in 12 men, 1 woman and 1 child. It was usually soft, with an anemic, catarrhal appearance.

In a starved man, Stschastny ('98) noted marked gastric hyperemia. The lining epithelium was lacking, but the peptic glands were preserved and a few scattered "hyaline Kugeln" (parietal cells?) were observed.

Meyer ('17) recorded a weight of 112 g. in the stomach of a man who died from starvation. The mucosa was pale and yellow, but presented no gross lesions. The parietal cells of the gastric mucosa were better preserved than the chief cells, which were disintegrated. The post mortem changes (18 hours) could not be excluded.

According to Ivanovsky ('23), Oppel noted that during the Russian famine perforating gastric ulcers became frequent on account of the use of indigestible food.

The gastric changes have frequently been described in **atrophic infants**, which represent a variable group with mixed nutritional deficiencies, frequently complicated by infections, etc.

Parrot ('77) described two types of gastric lesions (ulcerous and "diphtheroid") as characteristic and of primary importance, in infantile athrepsia.

Baginsky ('84, '84a) claimed that there is in athreptic infants a primary atrophy of the gastrointestinal mucosa, which will be considered later, under the intestine.

Marfan ('94) found the surface gastric epithelium usually lacking in dyspeptic infants, possibly due to post mortem changes. The gastric mucosa is replaced by a fibrous layer, infiltrated with leukocytes and containing multinucleated cells, desquamated epithelium, remnants of the gastric glands, etc.

Fede ('97, '98, '01a) found chiefly atrophic changes, similar to those in other organs, in the gastric mucosa of athreptic infants. Instead of the more extensive lesions described by previous authors, he finds merely a marked thinning of the gastrointestinal wall, with occasional ecchymoses, but no ulcerations or destructions of glands or villi in uncomplicated cases, aside from post mortem changes.

Thiercelin ('04) described in athrepsia the various gastric lesions, gross and microscopic, similar to those found by Parrot and Marfan. The changes in the mucosa are variable. There are often punctiform hemorrhages, with intense capillary congestion and hemorrhagic exudate between the gastric glands. Rarely ulcerations occur, with localized lesions of interstitial and parenchymatous gastritis, and frequently sclerosis. The other tunics may also be involved, and the interstices infiltrated with leukocytes.

Schelble ('10) made careful histological study of the stomach and intestines in 37 atrophic infants, but could find no evidence to support the theory of

gastrointestinal atrophy as the cause of pedatrophy. Vigor ('11) demonstrated that the distension of the abdomen ("ectasie abdominale" of Variot) which occurs in malnourished infants is due to distension of the stomach and colon by gas (air).

Mattei ('14) found microscopic gastric lesions in about one-third of his cases of athreptic infants. The gastric glands appear "decapitated," with vacuolated nuclei and cloudy swelling of the cytoplasm. The stroma is infiltrated with leukocytes, which also distend the lymph-vessels, and occur in the submucous and muscle coats. The submucous lymphoid follicles are hypertrophied. The literature on this subject is reviewed fully by Nobécourt ('16).

In necropsies of famine-stricken children, Nicolaeff ('23) found evidence of gastritis, with punctiform extravasations of the gastric mucosa.

The data recorded in Table 3, for atrophic Minnesota infants, would indicate that in spite of decreased body weight the weight of the stomach is in all cases above normal. The exact amount of the increase is difficult to estimate, on account of the lack of an accurate norm for the postnatal growth in weight of the stomach.

Among the **animals**, the data upon the gastric effects will be reviewed in chronological order, excepting the early changes noted chiefly in studies of digestion and resorption, the phenomena in the migrating salmon, and the effects of hibernation, which will be considered separately.

Collard de Martigny (1828) and de Pommer (1828) observed that in dogs, cats and rabbits, starved without food or water, the gastrointestinal mucosa in general appeared pale, without signs of inflammation. The gastric and intestinal secretions are decreased.

Chossat ('43), in pigeons on total inanition with loss of 40 per cent in body weight, found an average loss of 33.4 per cent in the weight of the stomach as a whole. The thick gastric muscle (of the gizzard) alone lost 39.7 per cent (comparable to the loss of 42.3 per cent in the skeletal musculature); but the thickened, cornified epithelial lining actually increased in weight from 1.09-1.23 g., due to absorption of water, rendering the epithelium soft and pulpy. Schuchardt ('47) similarly obtained a loss of 34 per cent in the gastric muscle of starved pigeons.

In a cat starved 18 days with loss of 50 per cent in body weight, Bidder and Schmidt ('52) found an apparent loss (compared with a control) of 30.9 per cent in the weight of the esophagus, stomach and intestines.

In various animals, chiefly rabbits, starved with or without water, Manassein ('68, '69) found usually no gross changes in the stomach; although sometimes the mucosa appeared easily detachable, and petechial hemorrhages of varied size were occasionally observed. The average loss of gastric weight in 47 adult rabbits (body loss 39 per cent) was 34 per cent; in 8 rabbits  $3\frac{2}{3}$  months old (body loss 33 per cent), the gastric loss was 16 per cent; in 3 rabbits 23-25 days old (body loss 35 per cent), the gastric loss was 25 per cent. In 5 rabbits refed after a fasting period, the stomach still appeared 11 per cent subnormal in weight. In 2 crows, starved with loss of 36 per cent in body weight, the loss in gastric weight was 30 per cent.

Bourgeois ('70) from fasting experiments on various animals (mammals and birds) and an extensive review of the previous literature concluded that the stomach becomes markedly small and constricted; the mucosa greatly folded, pale and not inflamed, although thickened near the cardiac and pyloric ends. The average loss in gastric weight is 33 per cent.

In fasting dogs of various ages, Falck ('75) found the fundic region of the stomach containing air and some liquid; the mucosa white and greatly wrinkled. The pars pylorica was strongly contracted.

In tritons starved 8-14 days, Schmidt ('82) noted that the gastric nuclei appeared small and dark, with very few mitoses. Upon refeeding, no mitoses were found in 1½ hours; a few appeared in the fundus in 3½-6 hours; but none in the pyloric region until 7 hours after feeding.

In the stomach of frogs starved for long periods (up to 1½ years), Gaglio ('84a) found the stomach waxy white in color, with mucous contents. The serosa and subserosa appear slightly thickened. The muscle tunic in part shows atrophic changes, with loss of striation in the muscle fibers, and degenerative changes in the nuclei. The submucosa is not much affected, but the muscularis mucosae may show changes similar to those in the muscle tunic. The muscle fibers sometimes appear vacuolated, with enlarged nuclei. The greatest changes occur in the tunica mucosa, which shows pronounced atrophy of the gastric glands, with progressive replacement by connective tissue (fibrosis or cirrhosis).

Bizzozero and Vassale ('87) found no decrease in the number of mitoses of the gastric and intestinal glands in dogs fasting (up to 17 hours only).

Morpurgo ('88, '89, '89a) in fasting rabbits of various ages usually found no marked changes in the stomach. The lymphoid follicles become atrophic, and sometimes the gastric glands appeared likewise. In the glands, mitoses persist in reduced number, but rarely occurred elsewhere in the stomach. In rabbits refed after a fasting period Morpurgo ('90) observed an increased number of mitoses in the gastric gland cells, but none in the lymphoid or connective tissues. The mast cells had apparently disappeared.

Coen ('90) noted in the stomach of a rabbit starved 84 hours (without water) an exudate of the gastric and intestinal mucosa, resembling that of gastroenteritis. The exudate, composed of amorphous material and leukocytes, also infiltrated the mucosa and glands, down to the submucosa. Similar, but less marked, appearances were observed in 2 rabbits on water only, and in a kitten on total inanition.

In dogs fasting several days, Nikolaides and Savas ('95) found, in sections prepared by Altmann's chrome-osmic method, numerous black (fatty?) granules in the epithelial cells of the pyloric and Brunner's glands, but not in the mucous glands. These granules disappeared slowly upon refeeding.

Lazareff ('95), in guinea pigs starved with average losses in body weight of 10, 20, 30 and 36 per cent, found corresponding losses of only 1.9, 6.5, 6.5 and 11.8 per cent in the gastric weight (Table 5), which are relatively less than the loss in the intestines. Kusmin ('96) likewise found the loss in gastric weight relatively less than that in the intestines of fasting dogs, rabbits and guinea pigs; and Weiske ('97) obtained similar results in fasting rabbits (on water only).

Mann ('98) found the chief and parietal cells well preserved in the stomach of a rabbit after 22 days of inanition (on water only?). The connective tissue stroma appeared scanty.

Sedlmair ('99) noted but little change in the relative weight of the empty stomach and intestines in starved cats, the loss being nearly proportional to that of the whole body (50-55 per cent).

Fede ('00a) and Quattrochi ('01) by chronic underfeeding of puppies obtained atrophy in the gastrointestinal wall, but no ulcerations, hemorrhages or destruction of glands, etc., as had been described in atrophic human infants.

Swirski ('02) measured the gastric and intestinal contents in fasting rabbits and guinea pigs, and demonstrated that the feces are swallowed unless precautions are taken.

Smallwood and Rogers ('11) described thinning of the gastric wall in *Necturus* starved 4-16 months. The epithelial cells become vacuolated; the nuclei poor in chromatin.

Greene and Skaer ('13) found in the basal portion of the gastric epithelial cells in fasting kittens and puppies a certain amount of persistent fat granules (liposomes), with no relation to absorption fat.

In several dogs and a fox which had died from protracted inanition, Morgulis, Howe and Hawk ('15) found no striking changes in the stomach and intestines. The parietal cells of the gastric glands remain conspicuous. The glandular and surface epithelial cells in general stain poorly, with absence of cytoplasmic granulation: the nuclei migrate toward the basement membrane. Leukocytes often invade the mucous and submucous layers, either diffusely or in masses like solitary nodes.

In adult albino rats, underfed or subjected to acute inanition (water only), with loss of 33-36 per cent in body weight, Jackson ('15) found an average loss of 57 per cent in the weight of the stomach and intestines (with mesentery) (Table 4). In younger rats underfed for various periods, the loss in gastrointestinal weight was much less, and in those held at constant body weight by underfeeding from 3 to 10 weeks of age, there was even an *increase* of 28 per cent. Stewart ('18, '19) discovered that in albino rats underfed from birth the increase in gastrointestinal weight may be even greater, reaching a maximum of 100 per cent (Table 4). In the offspring of severely underfed pregnant female albino rats, however, Barry ('20, '21) found the stomach and intestines nearly normal in weight.

In albino rats refed after underfeeding from 3 to 12 weeks of age, Stewart ('18) found that the weight of the empty alimentary tract became nearly normal within 4 weeks. Similar results were obtained by Jackson and Stewart ('19) in rats underfed from birth for various periods and then refed to body weights of 25, 50 and 75 g. (Table 7). In another series of rats refed to adult condition, Jackson and Stewart ('20) found the alimentary canal even above normal weight, excepting the severely stunted group, in which it was practically normal (Table 8).

Sundwall ('17) in the stomach of a starved albino rat (on water only) described intense congestion of the cardiac region, with complete loss of the sur-

face epithelium and gastric glands. The persistent connective tissue stroma was covered with fibrin, and necrotic areas were noted.

Moehl ('22) observed frequent gastrointestinal disorders in underfed horses.

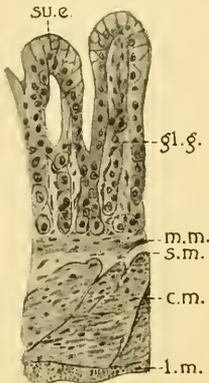


Fig. 82

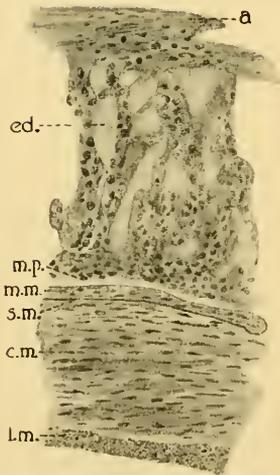


Fig. 84

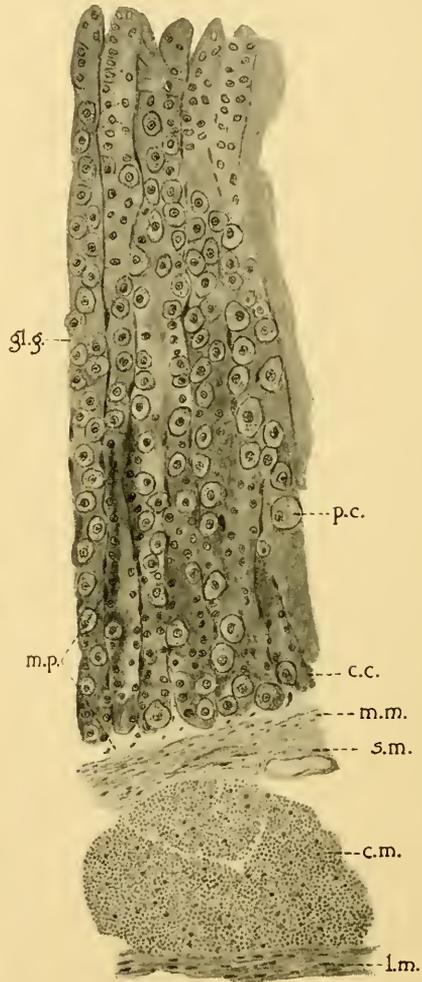


Fig. 83

FIGS. 82 to 84.—From sections through the pyloric region of albino rats. Bouin's fixation; hematoxylin-eosin stain.  $\times 50$ . *l.m.*, longitudinal muscle layer; *c.m.*, circular muscle; *s.m.*, submucosa; *m.m.*, muscularis mucosae; *m.p.*, membrana propria; *gl.g.*, gastric glands; *p.c.*, parietal cell; *su.e.*, surface epithelium; *a*, necrotic surface membrane; *ed.*, edemic spaces. (Miller '23.)

FIG. 82 shows a section of the pyloric region in a normal initial control rat 11 days old; body weight, 9.5 g; stomach weight, 0.0569 g. FIG. 83 represents the stomach structure in a final (age) control, full-fed to 37 days of age; body weight, 68 grams; stomach weight, 0.541 g. FIG. 84 shows the pyloric stomach in a rat underfed from birth to 39 days of age; body weight 9.66 g; stomach weight, 0.151 g. Note the necrotic surface membrane (*a*), the atrophic glands and edemic interglandular spaces (*ed*), and the pycnotic condition of the nuclei in the mucosa.

Moulton, Trowbridge and Haigh ('22a) found subnormal weight of the stomachs in steers on low planes of nutrition.

Miller ('22) noted that starvation must be severe to produce marked changes in the gastrointestinal epithelium of albino rats. In cells with atrophic degeneration, the mitochondria may be transformed from rod-like to spherical forms, with reduction in number or even total absence.

Miller ('23) has recently made a careful and extensive study of the gastrointestinal tract in albino rats severely underfed from birth for various periods (up to 43 days). The tract shows a marked increase in weight (in accordance with the observations of Jackson and Stewart), the increase being relatively greater in the stomach than in the intestine. Measurements also show an increase in the thickness of the mucous and muscular tunics of the stomach. Histologically, there appears a variable (usually slight) edema and regressive structural changes in the mucosa. There is atrophy and degeneration of the surface epithelial cells in restricted areas. The cells show nuclear degeneration, cytoplasmic shrinkage, vacuolation, loss of secretory granules, etc. In extreme cases, the tunica mucosa may be almost completely necrotic. The gastric tela submucosa shows no distinct changes, except occasional hemorrhages. The tunica muscularis shows a variable degree of atrophy with degeneration of the muscle fibers in certain restricted regions only. The various changes are shown by Figs. 82, 83 and 84.

Ott ('24), in the leopard frog (*Rana pipiens*) during hibernation and subsequent fasting with loss in body weight up to 60 per cent, found marked variability in the weight of the empty gastrointestinal canal. The average loss in weight, however, usually appeared relatively much less than that of the whole body, reaching a maximum of 53 per cent in the males and 30 per cent in the females (Table 6).

**Changes during Digestion and Absorption.**—Numerous studies have been made of this process, usually involving more or less incidental observations upon the changes in the early stages of inanition (a few hours up to a few days), and subsequent refeeding.

Ebstein ('70) in dogs fasting 1-4 days found the pyloric glands composed of cylindrical cells with clear (slightly granular) cytoplasm and elliptical nuclei basally placed. Changes are apparent 1 or 2 hours after refeeding, reaching their maximum in 4 or 5 hours. The gland cells become cubical in form and deeply staining; the nuclei become spherical and centrally placed. Heidenhain ('70) also described changes in the gastric gland cells (chief and parietal) in the cat and dog, up to 5 days of fasting. The changes in the herbivora (rabbit, guinea pig, sheep) were found less distinct. Similar results were obtained by Bentkowsky ('76).

Théohari ('99) studied the changes in the gastric mucosa of the cat, rabbit, guinea pig and especially the dog, in various stages up to 4 or 8 days after feeding. The parietal cells during fasting lose the vacuoles found in the early stages of digestion and the fuchsinophile granules are less numerous. Nuclear and granular changes also occur in the chief cells. Stinzing ('99) followed the changes in the chief and parietal cells of the dog, up to 11 days of inanition. At the height of digestion (4 hours after feeding) the chief cells are large, the parietal cells small. At the end of digestion (12 hours), the converse is true; the change

in nuclear size is especially striking. After 11 days of inanition, both chief and parietal cells are enlarged. The parietal cells now often are adjacent to the lumen; their nuclei are chromatin-poor and the cytoplasm vacuolated.

Paira-Mall ('00) found that in birds the gastric gland cells after fasting 2 days usually contain more secretory granules (in agreement with Langley). The lumina of the compound glands appear distended with secretion during digestion, but are smaller and collapsed in the fasting animals.

Béguin ('02) described the epithelium of the gastric and intestinal mucosa of reptiles, in relation to digestion and hunger. Kahle ('13) investigated the changes in the gastric glands of the tortoise (*Testudo graeca*) after various periods of fasting and refeeding. There are changes in the cell size, nuclear position, and cytoplasmic granules. He cited observations upon the frog by Langley and Sewall.

Jacquet and Jourdanet ('12) described the changes (especially in the ergastoplasm) of the gastric glands in the dog during fasting (2 days) and refeeding.

**Changes in the Migrating Salmon.**—These are of especial interest because the salmon apparently takes little or no food during its migration up the rivers to the breeding places. Miescher-Ruesch ('80) found the stomach and esophagus folded and contracted in fish taken at Basel, on the Rhine, in contrast with the distended condition in those taken from the sea. A slimy substance with shed epithelial cells was noted on the surface of the mucosa. Miescher ('97) described the histological changes in the salmon during this period. Stone ('97) stated that when the Quinnat salmon enters the fresh water, the appetite weakens, the throat gradually becomes narrowed and the stomach shrunken, so as to become entirely incapacitated for receiving food. Gulland ('98) and Paton ('98) described a desquamative catarrh of the gastrointestinal mucosa in the migrating salmon. Brown ('98) concluded that this was chiefly a postmortem change, but described certain other histological changes in the gastric and intestinal mucosa. Greene ('10) confirmed the observation of Rutter (Bull. U. S. Bureau of Fisheries, 1902, 22:122-) that the digestive tract of the Pacific salmon decreases markedly in size during the migratory fasting period. The whole question of fasting in the river salmon has recently been reviewed extensively by Heitz ('18).

**Changes during Hibernation.**—Valentin ('57) found an apparent loss of 14.6 per cent in the weight of the stomach in the marmot after 44 days of hibernation (body loss of 8.3 per cent); while the average loss after 166 days was 47 per cent (body loss 35.5 per cent).

In the hibernating hedgehog (*Erinaceus europaeus*), Carlier ('92) found but few changes in the *tongue*, although the tissues (as elsewhere) appeared to stain less intensely and the glands appear inactive. In the *stomach*, the cardiac gland cells appear smaller and more granular. The cells lining the ducts become swollen, apparently through accumulation of mucinogen. There is a thin layer of mucus, and epithelial débris on the surface of the gastric mucosa. Wandering cells (migrated leukocytes) in large numbers infiltrate the stroma of the mucosa and submucosa, corresponding to the decrease in blood leukocytes. These

migrated leukocytes degenerate and are removed by macrophages. Plasma cells are scarce in the canal below the esophagus.

Changes in the gastric glands during hibernation were described also by R. and A. Monti ('03) in the marmot, and by Corti ('03) in bats. Reese ('13, '13a) found no significant changes in the alimentary canal (tongue, palate, esophagus, stomach, small intestine, rectum) of the alligator after 4 or 5 months of hibernation.

#### (B) EFFECTS OF PARTIAL INANITION ON THE STOMACH

Comparatively few data are available concerning changes in the stomach during the various types of partial inanition.

McCarrison ('19, '21) has emphasized the atrophic and degenerative changes in the alimentary canal of monkeys on autoclaved rice diet (mixed deficiency of protein, vitamins, etc.). These include:

“(a) Congestive, necrotic and inflammatory changes in the mucous membrane; sometimes involving the entire tract, sometimes limited to certain areas.

“(b) Degenerative changes in the neuromuscular mechanism of the tract, tending to dilatation of the stomach, ballooning of areas of small and large bowel, and probably also to intussusception.

“(c) Degenerative changes in the secretory elements of the tract of the gastric glands, the pyloric glands, the glands of Brunner, the glands of Lieberkühn, and of the mucous glands of the colon. These changes are such as must cause grave derangement of digestive and assimilative processes.

“(d) Toxic absorption of the diseased bowel, as evidenced by the changes in the mesenteric glands.

“(e) Impairment of the protective resources of the gastrointestinal mucosa against infecting agents, due to hemorrhagic infiltration, to atrophy of the lymphoid cells, and to imperfect production of gastrointestinal juices.”

In persons malnourished through war famine (deficiency in calories and vitamins), Reiss ('21) found the stomach usually atonic with hypoacidity. (Curschmann found hyperacidity, however.) In autopsies on cases of edema disease (due chiefly to protein deficiency), Schittenhelm and Schlecht ('18) twice observed marked congestion of the blood vessels in the gastrointestinal mucosa, with numerous hemorrhages, especially in the small intestine.

Sundwall ('17) in monkeys and rats on corn-meal and similar diets (mixed deficiency of protein, etc.) found congestion of all layers in the gastrointestinal tract, atrophy of the muscle coat, hemorrhages, ulcerations and superficial erosions of the epithelium.

In **pellagra**, digestive disturbances are prominent, with the usual changes in the gastrointestinal canal (Roberts '12; Boyd '20). In **lamziekte** in cattle, Hedinger ('15) described hyperemia of the gastrointestinal mucosa, with enteritis and hemorrhages.

During **chlorine hunger** in dogs, gastric hemorrhages were observed by Cahn ('86).

In human **ricketts**, Comby ('01) and others have reported that the stomach and intestines are usually dilated. The same was found by Jackson and Carleton ('22) in albino rats with experimental ricketts. The stomach and intestines without contents were found subnormal in weight, however (Table 11).

In human **beriberi** (vitamin B deficiency), Ellis ('98) noted congestion of the stomach in 31 out of 57 autopsies; with blood clots in 4. Strong and Crowell ('12) found acute gastroduodenitis. Andrews ('12), in infantile beriberi (18 necropsies), found the gastric mucosa anemic; duodenum congested; intestines otherwise normal, or a few petechiae. In experimental polyneuritis of fowls and pigeons, Tasawa ('15) observed mild catarrhal inflammation of the crop, and distinct atrophy of the stomach (gizzard) muscle. Lumiere ('20a) concluded that pigeons on polished rice diet are subjected to starvation, with stagnation of the ingested rice in the alimentary canal due to lack of digestive secretions. Findlay ('21) noted a loss of 19 per cent in the stomach weight in rice-fed fowls, and of 23 per cent in rice-fed pigeons, with slightly larger losses during simple inanition (Table 13).

In human **scurvy**, Sato and Nambu ('08) observed that the esophageal mucosa was intact; the gastric mucosa variable, anemic or congested, with petechiae in one case. Hess ('20) stated that the scorbutic gastric lesions are usually unimportant, with occasional hemorrhages or ulcerations. In experimental scurvy in guinea pigs, Bessesen ('23) found the weight of the stomach somewhat subnormal in the early stages, but distinctly above normal in the later stages (Table 12). The intestines appeared similar in weight changes. The gastrointestinal contents, however, appeared greatly increased in the early stages of scurvy.

In a dog on **dry diet** with loss of 20 per cent in body weight, Falck and Schefler ('54) noted an apparent loss of 17.9 per cent in the weight of the stomach, and the same in the intestine.

In a similar dog, Pernice and Scagliosi ('95a) found the stomach contracted with strongly folded mucosa; pale near the cardia, reddish near the pylorus. The gastric mucosa showed numerous small, superficial, rounded erosions or ulcerations, containing brownish, hemorrhagic masses. Microscopically the stomach showed hyperemia and hemorrhagic infiltrations, with atrophy of the glands in some places. Some mitoses (normal or abnormal) were seen in the fundus glands. The superficial epithelial cells appeared reduced in size, vacuolated and poorly stained. Round cell infiltration occurred in the interglandular stroma, in the submucosa and in the muscular coat.

Kudo ('21) noted a loss of about 30 per cent in the empty stomach and intestines of albino rats on a dry diet with loss of 30-52 per cent in body weight (Table 9). In young rats held at constant body weight for various periods by dry diets, Kudo ('21a) found a progressive increase in the weight of the stomach-intestines, both empty and with contents (Table 10). This indicates a continued growth of the tract similar to that found by Jackson and Stewart in young rats during underfeeding.

### 3. THE INTESTINES

Some data concerning changes in the weight and structure of the intestine in general have already been mentioned in the foregoing pages in connection

with the stomach. These include observations by Andrews, Barry, Béguin, Bessen, Bidder and Schmidt, Bizzozero and Vassale, Boyd, Brown, Coen, Collard de Martigny, Comby, Falck and Scheffer, Fede, Gulland, Hedinger, Heitz, Jackson, Jackson and Carleton, Jackson and Stewart, Kudo, Kusmin, Lazareff, McCarrison, Miller, Morgulis, Howe and Hawk, Ott, Quattrochi, Reese, Schittenhelm and Schlecht, Sedlmaier, Stewart, Strong and Crowell, Sundwall, and Weiske. Further details concerning the changes in the intestines will now be considered under (A) effects of total inanition (or on water only), and (B) effects of partial inanition.

#### (A) EFFECTS OF TOTAL INANITION, OR ON WATER ONLY

The effects upon the human intestine (adult and infant) will be presented first, followed by the data for the infrahuman species.

**Human Adult.**—Donovan ('48) in famine victims did not find the intestinal inflammation and ulceration described by Duncan, Collard de Martigny and others. He observed: "total disappearance of the omentum, and a peculiarly thin condition of the small intestines which (in such cases) were so transparent that if the deceased had taken any food immediately before death, the contents could be seen through the coats of the bowel . . . This condition I look upon as the strongest proof of starvation." Fowler ('70), however, maintained that in acute starvation there may be no attenuation of the intestinal walls. Curran ('74) found the intestines thin and transparent, somewhat distended with gas; while Bright ('77) found them empty and collapsed, with greatly atrophic walls. In both cases, the *omentum* was atrophic and fatless. Schultzen ('62, '63) described the large intestine as contracted and nearly empty; the mucosa reddish in places.

Falck ('81) noted that in starvation the intestines are usually found contracted and nearly empty, containing a slight amount of bile. The mucosa in both large and small intestines is usually normal. Casper-Liman ('82) found the "Darmtract stellenweise verengert, ganz leer oder höchstens einzelne verhärtete Kothreste enthaltend, die Häute des Darmkanals bis zur Durchsichtigkeit verdünnt."

Porter ('89) in numerous autopsies upon victims of the Indian famine noted that the *peritoneum* usually appeared healthy, excepting a variable amount of serous effusion in nearly  $\frac{2}{3}$  of the adults and  $\frac{1}{3}$  of the children. The *mesentery* showed more or less fat in nearly half of the adults, but in only  $\frac{1}{8}$  of the children. A few cases presented edema, thickening and congestion. The *duodenum* and *jejunum* showed in general an anemic, catarrhal appearance, in some places showing loss of the surface epithelium, with congestion, atrophy and pigmentation of the stroma. In the *ileum*, the changes were more extensive; the mucosa atrophic, with indistinct villi; the epithelial layer usually absent, and the stroma markedly altered, with fatty and granular pigmentary degeneration, probably due to extravasated blood. The lymphoid tissue, including solitary glands and Peyer's patches, appeared very atrophic and absent over large areas, in children as well as in adults. The mucosa of the *large intestine* likewise usually appeared

anemic, sometimes showing inflammatory thickening or ulcerated areas. The lymph nodes were pale and inconspicuous. The changes characteristic of true dysentery rarely occur in "famine dysentery."

Meyer ('17) found the stomach and intestines only slightly filled with gas, and no ulcerations as reported by Formad and Birney ('91). The ascending and transverse colons were relaxed; the descending colon firmly contracted; the iliac and pelvic colon nearly empty. The appendices coli were completely absent and only very small masses of omental fat remained in the intervacular areas. Histologically the intestine appeared congested in places, with complete disintegration of the mucosa over extensive areas in both small and large intestines (partly due to postmortem change). Depletion of the solitary and aggregated lymph nodules, and congestion of the submucous plexuses were also noted.

Rubner ('19), Determann ('19), Ivanovsky ('23) and others have reported an increased occurrence of hernia and intussusception as a result of the malnutrition and famine during the war. The hernia may be due partly to the intestinal atrophy and partly to general weakness of the abdominal walls. Sison ('20) could sometimes see and feel the peristaltic movements of the intestines through the abdominal wall during voluntary starvation. Hehir ('22) noted severe intestinal disorders, resembling dysentery, during the chronic starvation in the siege of Kut.

In malnourished **infants**, the condition of the intestines has frequently been studied. Parrot ('77) held that athrepsia is a condition of malnutrition secondary to gastroenteritis, with "diphtheroid" or ulcerated conditions in the intestines, similar to those mentioned for the stomach. As a sign of death from inanition in the newborn, Tardieu ('80) noted: "Verdauungstractus atrophisch, durchscheinend, leer." Ohlmüller ('82) recorded an intestinal weight of 140 g. in an atrophic infant of 56 days, with body weight of 2,381 g. (previous weight not stated). In a well nourished control of the same age, the intestinal weight was 183 g., body weight 4,150 g.

Blaschko ('83) found no degeneration of the *sympathetic plexuses* of the intestinal wall in atrophic children. Baginsky ('84, '84a) described a marked distension and atrophy of the intestinal wall in athreptic infants, including partial atrophy of the muscle fibers, degeneration of the plexuses of Auerbach and Meissner, atrophy of the lymphoid follicles, and almost complete disappearance of glands and villi. Baginsky considered these atrophic changes as the primary cause of pedatrophy, a conclusion which was opposed by many subsequent investigators.

Cantalamassa ('92) claimed that in starved infants the colon shows the greatest decrease in diameter and in thickness of the walls, in comparison with other parts of the intestine.

Gerlach ('96) demonstrated that the characteristic atrophic appearance of the intestinal wall described by previous authors can be produced by simple mechanical distension with gases, etc.

Fede ('97, '98, '00, '01) likewise opposed Baginsky's doctrine of intestinal atrophy as the cause of athrepsia. He found a certain degree of thinning in the intestinal wall, with other atrophic changes in the glands, etc., but no destruc-

tion of glands or villi. Later ('01a) Fede stated that the athrepsia of Parrot is due to defective alimentation caused by gastrointestinal intoxication, while in other cases infantile atrophy with profound malnutrition is secondary to syphilis, tuberculosis, etc.

De Lange ('00) described marked atrophic intestinal changes in two cases of pedatrophly.

Heubner ('01, '01a) opposed the doctrine of a primary intestinal atrophy as the cause of infantile atrophy, ascribing the appearance to physical distension of the gut, and to postmortem changes. Nothnagel ('03) found the typical atrophic changes in the intestinal wall in 80 per cent of all autopsies, irrespective of the causes of death, and interpreted them as due to intestinal catarrh (even without clinical symptoms).

Bloch ('03, '04, '05, '06) described the usual variably atrophic changes in the intestine of atrophic infants, and agreed with the previous investigators who ascribed the changes primarily to intestinal distension or inflammatory complications. In addition, however, he noted a decreased number of Paneth cells in the intestinal glands of Lieberkühn, and thought this might be significant.

Tugendreich ('04), however, could not confirm Bloch's observation of a deficiency in the Paneth cells. After reviewing the various theories as to the cause of infantile atrophy, Tugendreich concluded that "Mit der Ablehnung der Darmatrophie ist das Wesen der Säuglingsatrophie wieder in tieferes Dunkel zurückgetaucht."

Thiercelin ('04) described the intestinal lesions at various stages of infantile atrophy. The intestine is increased in length, as found by Marfan in all infantile chronic dyspepsias. There are progressive but variable atrophic changes in the intestinal mucosa, and also in the tunica muscularis, with degenerative changes in the plexuses of Auerbach and Meissner.

Lucien ('08) found that in athrepsia the intestinal tract shows no constant changes, and does not often present gross lesions. He doubted that the athreptic condition is due to preceding gastrointestinal disorder, and ascribed it rather to lesions in the hemopoietic system, the kidney and especially the endocrine glands. Herter ('08) described a form of growth retardation due to chronic intestinal infection and imperfect absorption of food in the intestine.

Helmholz ('09), like Tugendreich (versus Bloch) found no deficiency in the Paneth cells in atrophic infants. He concluded that postmortem changes proceed more rapidly than in normal conditions.

Stickel ('10) described the changes in a malnourished infant and starved puppies: Schelble ('10) could find no structural changes in the intestine which would account for the condition of pedatrophly, and ascribed it rather to a general disturbance in the intermediary metabolism.

Lesage ('11) described an atrophy in all the elements of the alimentary canal of dystrophic infants. Eosinophile cells are said to occur in considerable quantities, and to show some peculiarities. The muscle fibers are much diminished in diameter (Variat and Ferrand). According to Lesage and Cleret ('14), in congenital spasmodic atrophy the intestines sometimes show proliferation of the submucous connective tissue, but a leukocytic infiltration predomi-

nates at this level, causing dissociation and atrophy of the glandular cul-de-sacs. Sometimes the remnants of the cul-de-sacs are surrounded by abundant lymphoid tissue.

Aschoff ('13, '21) stated: "Die Atrophie der Darmschleimhaut hat früher, besonders in der Pädiatrie, eine grosse Rolle gespielt. Seitdem Heubner nachgewiesen, dass es sich dabei um einfache postmortale Dehnungsvorgänge handelt, ist die Atrophie in den Hintergrund getreten."

Mattei ('14) found the intestinal epithelium normal in 14 cases of athrepsia. Leukocytic infiltration occurred in the villi and interglandular spaces of the mucosa and submucosa. The solitary follicles of the small intestine sometimes showed signs of hyperactivity. The literature on the intestinal changes was fully reviewed by Nobécourt ('16). In general, he concluded that the changes appear to be consequent upon chronic inflammatory processes, especially in the small intestine and colon.

Finkelstein and Meyer ('22) state: "Formerly it was believed that inanition was the cause of severe 'atrophy' and was due to interference with food absorption in consequence of a chronic inflammation and destruction of the secretory mechanism. The foundations of this teaching are today, however, overthrown; for the concurrent reports of all observers show that the intestine of the atrophic child is anatomically normal. It is clearly a question of functional disturbances, leading to a reversible metabolism, recognized by Parrot many decades ago."

In famine-stricken children of various ages, Nicolaëff ('23) found the small intestines increased in length (due to meteorism?), with hyperemia, atrophy of the mucosa, and edema of the submucosa. The large intestine showed colitis, with frequent necrotic erosions. There was complete disappearance of mesenteric and subperitoneal fat, with large amount of peritoneal fluid in some cases.

The weights of the empty intestines in atrophic Minnesota infants appear relatively large, as shown in Table 3, but the increase is uncertain on account of no adequate norm for comparison.

In **animals**, the effects of experimental inanition upon the intestine have frequently been observed. The general results of the more severe stages of inanition will be presented first, followed by a summary of the changes observed during the earlier periods following digestion and absorption. Finally a few observations during hibernation will be mentioned.

Tiedemann ('36) noted that in starved animals the entire intestinal canal is contracted and contains only a slight amount of bile and mucus. Chossat ('43) observed in starved pigeons a shortening of the intestine with loss of 42 per cent in weight, nearly proportional to the loss in body weight. Manassein ('66, '68, '69) observed that the intestines, especially the small intestine, become considerably shortened in rabbits and pigeons during starvation. He observed an average loss of 28 per cent in the intestinal weight of 47 adult rabbits (body weight loss 39 per cent), but usually less in younger rabbits. Upon refeeding, nearly normal length and weight of the intestine were restored.

Voit ('66) noted an apparent loss of 18 per cent in the empty intestines of a starved cat, with loss of 33 per cent in body weight. Bourgeois ('70) found a reduction of about one-fourth in length and also a decreased diameter in the

intestines of various starved animals. The mucosa appeared pale, otherwise normal; as likewise noted by Falck ('75) in fasting dogs.

In the fasting larvae of *Rana tigrina* and *Bufo melanostictus*, Cunningham ('80) found general intestinal atrophy, the lymphoid nuclei being replaced by masses of fatty and pigment granules. The changes begin in the upper intestinal segments. The lining epithelium degenerates first in the middle portion, and finally disappears completely.

Isaëw ('87) noted granular degeneration and vacuolation in the sympathetic ganglion cells of the alimentary canal in starved dogs. Paneth ('88) observed persistence of the goblet cells, and also the characteristic Paneth cells, in the intestine of the mouse during fasting experiments.

Hofmeister ('87) found a gradual decrease in the number of mitoses in the intestinal lymphoid cells of cats during inanition up to 17 days. Morpurgo ('89, '89a) observed no gross changes in the intestines of fasting rabbits (young and adult), aside from atrophy of the solitary and agminated lymph nodules. Mitoses were found in reduced number in the intestinal glands; also frequently in the agminated lymph follicles, especially in the periphery. Mitoses also occurred in the smooth muscle, especially in the younger animals. Morpurgo ('90) found mitoses more numerous in refed animals, and slightly larger in diameter ( $5.12\mu$ ) than in the starved rabbits ( $4.89\mu$ ).

In addition to the leukocytic infiltration found by Coen ('90) in the gastrointestinal mucosa of starved rabbits and kittens, he noted slight atrophic changes in the glands of Lieberkühn and of Brunner. He also cited changes observed by previous investigators (Osborne, Taylor, Gaglio, Hofmeister and Morpurgo).

Lazareff ('95), in 4 groups of fasting guinea pigs with losses of 10, 20, 30 and 36 per cent in body weight, noted corresponding losses of 0.5, 10.2, 10.5, and 25.8 per cent in the weights of the intestines (Table 5), which is relatively greater than the losses in stomach weight, but less than the losses in body weight.

The observations by Gulland ('98) and others upon the changes in the alimentary canal of the migrating salmon were referred to above.

Nikolaides ('99) found abundant fatty granules in the epithelium of the intestine and various glands in fasting dogs. He interpreted these granules as degenerative in character.

Yung and Fuhrmann ('99?) discovered that long continued fasting causes a shortening of the intestine of fishes, with disappearance of the associated fat, thinning of the intestinal wall and decrease in the size of its cellular elements.

Nemzer ('99) found that during starvation in white mice, with loss of 21 per cent in body weight, the loss in nuclear substance is greater in the intestines than in the liver and kidneys.

According to Morgulis ('23), Mingazzini ('00a) observed that during inanition leukocytes infiltrate the intestinal mucosa and accumulate in the lumen, where they ultimately disintegrate.

Fede ('00a) subjected young puppies to chronic underfeeding. As in atrophic infants, he found digestive disturbances with emaciation, intestinal

atrophy and decrease of cytoplasm, but never destruction of villi or glands. His results were confirmed by Quattrochi ('01) who obtained atrophy with mild inflammatory changes in the intestinal wall (small cell infiltration of mucosa and submucosa). No ulcerations were found, and occasional absence of the surface epithelium was ascribed to postmortem change. Very similar results were obtained by Alessandrello ('02), Iapichino-Paternò ('02) and Pagano ('06) in newborn or nursing puppies underfed in various degrees and for various periods.

Konstantinovitsch ('03) noted fat droplets in the intestinal epithelium of starving rabbits, near the membrana propria. Kunizki ('04) stated that starvation has no influence on the fermentative power of the intestinal juices. Opie ('04) found a decreased number of eosinophiles in the intestinal wall of guinea pigs during prolonged fasting.

Bujard ('05) claimed that the different forms of the intestinal villi found in various vertebrates are due to the type of nutrition (herbivorous, carnivorous, etc.). Babák ('06) found it possible to vary the size and form of the gut in frog larvae by variations in the diet, and concluded that the form is determined by chemical rather than mechanical influences. Eggeling ('08), however, doubted whether the structural differences in the intestine of the various teleost fishes are due primarily to the mode of nutrition.

Erdely ('05) studied the variations in the intestinal lymphoid tissue in rats fasting (on water only) for 3-5 days, also on meat, fat and potato diets. He described 5 types of cells in the mucosa, which vary in relative numbers during inanition and on the different diets. Mitoses were rare during both fasting and feeding. He confirmed Hofmeister and Heidenhain as to the general decrease in the number of lymphoid cells during fasting, yet they may remain abundant in places. The number of granular cells is also reduced by fasting, and likewise the number of lymphocytes emigrating into the surface epithelium. The lymphocytes were not found to be especially concerned with fat resorption.

Yung ('05, '05a, '12) claimed that the marked shortening of the alimentary canal in frog larvae (*Rana esculenta* and *Rana fusca*) during metamorphosis is due to inanition, which also shortens the intestine of the adult about one-eighth during hibernation. The shortening of the intestine in the tadpoles is greater if no ingestion is permitted than if filter paper is swallowed, which proves a mechanical factor (in addition to the chemical factor assumed by Babák).

Ficker ('05) found that after certain periods of inanition there is, in the rabbit, dog, cat, mouse and rat, an invasion of bacteria, apparently due to increased permeability of the lining intestinal epithelium.

Drzewina ('10) found that the eosinophile leukocytes, which are very numerous in the intestinal mucosa and submucosa of certain teleost fishes (*Labridae*), almost entirely disappear during fasting but reappear upon refeeding. In *Labrus* and *Crenilabrus* fasting 15 days to 2 months, Drzewina ('12) observed a few multinucleated giant cells among the surface epithelial cells of the villi, and apparently formed by fusion of the neighboring epithelial cells.

Morgulis ('11) made careful measurements of the surface epithelial cells of the duodenum in *Diemyctylus viridescens* during protracted inanition. There is

a very marked reduction in the size of the cells, the loss being relatively greater than that of the body as a whole. The nuclei are more resistant than the cytoplasm, and therefore become relatively larger; also more elongated in form. The normal size and proportions are soon restored upon refeeding.

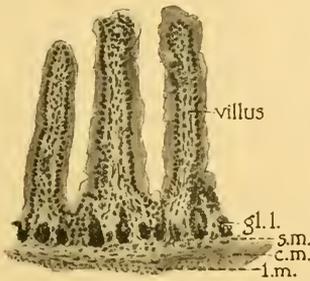


Fig. 85



Fig. 87

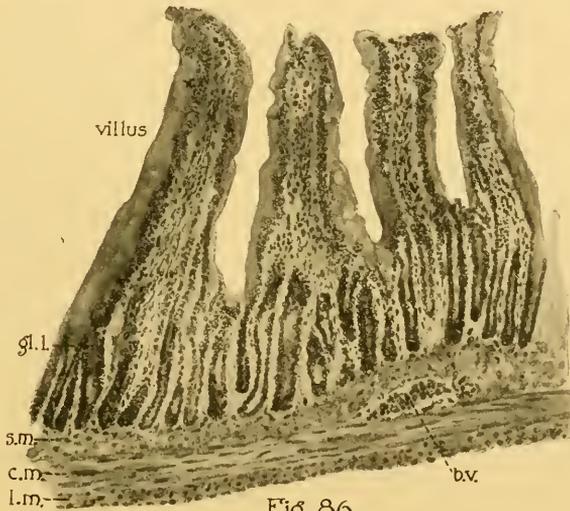


Fig. 86

FIG. 85 to 87.—From sections through the duodenum of albino rats. Bouin's fixation; hematoxylin-eosin stain.  $\times 50$ . *l.m.*, longitudinal muscle layer; *c.m.*, circular muscle; *s.m.*, submucosa; *b.v.*, blood vessel; *gl.l.*, intestinal glands (of Lieberkühn). (Miller '23.)

FIG. 85 shows the structure of the duodenum in an initial control rat; age 2 days; body weight, 6.5 g. Fig. 86 is the final (age) control; age 35 days; body weight, 48 g. Fig. 87 represents the condition in the test rat, underfed from birth to 34 days of age; body weight, 7.6 g. Note that the villi have disintegrated into an irregular mass filling the intestinal lumen. The bases of the atrophic intestinal glands (*gl.l.*) are evident.

In *Necturus maculatus* fasting 4-16 months, Smallwood and Rogers ('11) found atrophy of the intestinal mucosa, submucosa and muscularis, with degenerative changes (shrinkage and vacuolation) in the surface cells, especially over the longitudinal folds.

Brüning ('14) found a relative elongation in the intestine of young rats with retarded body growth on a one-sided carbohydrate diet.

Giannelli ('16) noted gross atrophy of the intestines in the teleost fish, *Tinca vulgaris*, after 5 months of starvation.

In steers on low planes of nutrition, Moulton, Trowbridge and Haigh ('22a) found a relative increase in the length of the intestines, while the weight appeared to remain nearly proportional to the body weight.

Ono ('20a) found that in "various animals" during inanition the mitochondria of the intestinal epithelial cells decrease in number, size and amount. On refeeding, the mitochondria increase, filamentous forms regenerating from the minute granules which resulted from starvation. Glycogen and fat droplets disappear completely during starvation, and reappear upon refeeding.

Miller ('22) studied the effects of acute inanition and of vitamin deficiency on the mitochondria of the gastrointestinal epithelium and pancreas cells of the albino rat. No changes in the mitochondria occur except in cells suffering severe degenerative atrophy, in which case there may be a transformation of mitochondria from rod-like to spherical forms and a reduction in the number, or even complete disappearance of the mitochondria. Miller ('23) also found that in young albino rats severely underfed for long periods the intestinal villi appear variably atrophic, and in extreme cases even completely degenerated and disintegrated. The surface epithelial cells in both small and large intestines also present variable atrophic changes, such as nuclear pycnosis, cytoplasmic degeneration with apparent decrease in the characteristic granules and mitochondria. The glands of Lieberkühn also show atrophic and degenerative changes with slight edema in the interstitial stroma. Atrophy of the tunica muscularis appeared less marked than in the stomach. The changes are shown in Figs. 85, 86 and 87.

**Early Changes Associated with Digestion and Resorption.**—The intestinal changes previously reviewed have concerned chiefly the later stages of acute or chronic inanition. We have now to consider certain observations upon the earlier stages, which have been studied chiefly in connection with the process of digestion and absorption. It is impossible to review these changes in detail, but the more important phenomena will be mentioned briefly.

Brettauer and Steinach ('57) claimed that the striated (rodded) border of the epithelium on the villi is distinct during fasting, but becomes homogeneous during absorption (especially of fat). Eimer ('67) studied the cycle of fat absorption in the intestinal epithelium, finding the fat droplets appearing first in the outer portion, later throughout the cell body; some droplets may persist through several days of fasting.

Hofmeister ('81, '87) found the number of lymphoid cells in the intestinal mucosa of the cat greatly reduced during fasting and increased upon refeeding. This was confirmed by Heidenhain ('88), in fasting dogs. He also disproved the claim of Brettauer and Steinach that the striated border of the intestinal epithelium is characteristic of starvation. Heidenhain noted an increased migration of leukocytes (lymphocytes) into the epithelium, sometimes forming subepithelial masses in the tips of the villi in guinea pigs starved 3 or 4 days. There is also a reduction in the number of granular cells during fasting, but no variation according to the type of diet.

Grünhagen and Krohn ('89) noted that during hibernation the intestinal epithelium of frogs may serve as a storehouse of fat, which occurs in groups of cells between the villi. Nicolas ('90) and Krehl ('90) described in detail the changes in the intestinal epithelium during fat absorption.

Mingazzini ('00, '00a) claimed that in fasting fowls the surface epithelial cells of the villi, which are  $40\mu$  high during digestion and absorption of food, are soon reduced to half this height by the disintegration and resorption of the basal ends of the cells, giving rise to subepithelial spaces. This phenomenon was considered a part of the normal process of digestion and resorption. This theory was confirmed to a certain extent by Reuter ('03) for the rat and mouse and by Pugliese ('05) in dogs; but it was opposed by Béguin ('04) for *Lacerta* and *Bufo*; by Bezzola ('04) for fowls and other animals; by Luca ('05) for the chick, cat, rat, guinea pig and bat; by Arcangeli for *Box salpa*; by Corti ('06) for the hibernating hedgehog (*Erinaceus europaeus*); by Biscossi ('08) for the sparrow; and by Demjanenko ('09) in numerous species. The spaces of Mingazzini have usually been interpreted by subsequent investigators as artefacts due to shrinkage or imperfect fixation.

Luca ('05a) described in the fowl's intestine a subepithelial layer of mast cells, which become atrophic during starvation 3-8 days, with deeply staining granules obscuring the poorly stained nuclei.

Asher ('08) by Altmann's method found the granules in the epithelial cells of the villi larger and more numerous in rats starved 2 days (water only) than in those normally fed. In the glands of Lieberkühn, however, the granules appeared smaller and indistinct during inanition. Champy ('09) described the mitochondria in the intestinal epithelium of fasting animals (triton, turtle, axolotl, frog, lizard, snake, rat, Myoxus, and guinea pig), and claimed that they are transformed from filaments into granules during digestion and absorption. The changes especially in the granules and mitochondria of the epithelial cells during digestion, absorption and the early stages of fasting have also been described by Demjanenko ('09) in fishes, amphibia, pigeon, rat, guinea pig, cat and dog; and by Zillenbergs-Paul ('09) and Holthusen ('10) in various species; by Policard ('10) in the frog (*Rana temporaria*); by Stickel ('10) in the human newborn, also starved puppies; by Corti ('12) in fishes, *Lacerta*, *Gallus*, *Mus decumanus*, *Vesperugo*, and in *Erinaceus* and *Vesperugo* during hibernation. The literature on the question of the significance of the various granules in the intestinal epithelium and their changes during digestion, absorption and the early stages of inanition has been reviewed fully by Arnold ('14).

McIntosh ('18) noted fat droplets in the epithelium of the mucosa and associated glands in the stomach and intestine of cats fasting 24-48 hours. He concluded that these lipoidal granules are probably normally present, independent of fat absorption. Tang ('22) used varied technique in studying the Paneth cells in several mammals during fasting, including the squirrel (to 110 hours), guinea pig (to 170 hours) and the pig (starved 10 days). There is apparently at first a shrinkage in size of the Paneth cells, with a variable increase later. The cell structures show certain changes, but the secretory granules are retained and there is no indication of degeneration.

During **hibernation**, certain observations upon the shortening of the intestine of the frog by Yung, and changes in the intestinal epithelium of the frog by Grünhagen and Krohn ('89) and of the hedgehog and bat by Corti ('06, '12) were mentioned above. Carlier ('92) in the hibernating hedgehog (*Erinaceus europaeus*) found an emigration of leukocytes into the mucosal stroma, as described above for the stomach. Otherwise the intestine appears quiescent, with but slight changes. Monti ('03) followed the changes in the intestine of the hibernating marmot, and likewise found numerous leukocytes in the epithelium and stroma. The mucosa in general appears quiescent, with no mitoses. Luca ('05a) mentioned some observations by Ballowitz ('91) and others on the mast cells during hibernation.

#### (B) EFFECTS OF PARTIAL INANITION ON THE INTESTINES

These will include the effects of deficiencies in protein (including pellagra), fats, salts (including rickets), vitamins and water.

Lefholz ('23) found that in kittens the lymphoid tissue of the alimentary canal, including the agminated glands, solitary glands, tonsils, etc., is regulated to some extent by the calories and the protein content of the diet, but especially by the specific **fat** content.

Rosenheim ('91) found catarrhal inflammation of the intestines in a dog on protein-poor diet. Hoare ('15) likewise noted a chronic intestinal catarrh in an edemic disorder of cattle on protein-poor diet. Chittenden and Underhill ('17) observed a severe stomatitis with intestinal congestion, ulceration, etc. in dogs on a protein-poor diet producing a condition somewhat resembling **pellagra**.

In human pellagra, varied intestinal disorders, with acute or chronic enteritis, congestion and ulceration of the mucosa, atrophy of the muscular coat, etc., have been noted by Fraenkel ('69-'70), Tuzcek ('93), Marie ('08, '10), Kozowsky ('12), Raubitschek ('15) and Harris ('19). Lynch ('17), in chronic cases, described the intestinal mucosa as pale, mucus-covered and atrophic, with thinning of the tunica muscularis.

Wohlauer ('11) held that intestinal disorder is an important element in human **rickets**. The abdomen is distended through intestinal meteorism, due to enteritis, with either constipation or diarrhea. He states that Monti and Vierordt ascribed an etiological significance to the intestinal disorder in rickets (causing lessened absorption of calcium salts). Heubner ascribed the distension to atony of the intestinal musculature.

As previously mentioned, McCarrison ('19, '21) laid great emphasis upon the intestinal lesions and disorders produced by variously defective diets, as mentioned above, in connection with the stomach.

**Vitamins.**—Emmett and Allen ('20) found that in the rat no special effect was produced by lack of vitamin A, but portions of the intestine appeared congested on diets deficient in vitamin B. In kittens, Mackay ('21) noted abdominal distension, diarrhea and intestinal atrophy on diets deficient in vitamin A. Cramer, Drew and Mottram ('21) claimed that deficiency of

vitamins (especially of vitamin B) produces in mice and rats a specific atrophy of lymphoid tissue in general, including the agminated glands (Peyer's patches), etc., in the intestine. Mottram, Cramer and Drew ('22) held that the functional activity of the intestinal epithelium is profoundly affected by the presence of vitamins A and B, especially the latter. There is, however, no delay in the passage of food in the absence of vitamins. Lymphocytes also play an important rôle in the absorption of food. These results support the theory that marasmus from dietary deficiency of vitamin B is due to impaired absorption and assimilation of food from the intestine.

Voegtlin and Lake ('19) in experimental polyneuritis of cats, dogs and rats on diets deficient in vitamin B found degenerative changes in the intestines. Lumière ('20) and others have noted diarrhea and intestinal disorder in polyneuritic pigeons on polished rice diet.

In human **scurvy**, Sato and Nambu ('08) observed punctate hemorrhages in the intestinal mucosa; also ulceration, especially in the large intestine. Aschoff and Koch ('19) mentioned scorbutic enteritis. Hart ('12) observed hemorrhages in the intestinal mucosa during infantile scurvy. Hess ('20) has reviewed fully the literature concerning the changes in the intestine during scurvy. The mucosa is frequently congested, and the solitary and agminated follicles enlarged, sometimes hemorrhagic. These changes may progress to necrosis and extensive ulceration, dysentery, etc. Hemorrhages may occur in any layer. The intestinal epithelium appears edematous, often showing an increased number of cells.

In pigeons on a **dry diet**, Schuchardt ('47) found an average apparent loss of 56 per cent in the intestine weight, in comparison with only 34 per cent in the gizzard. Pernice and Scagliosi ('95a) in a dog on dry diet found in the duodenum changes similar to those before mentioned in the stomach. Hemorrhages were more prevalent, especially in the submucous and muscular coats; also in many lymph-nodules. The glands showed cystic changes. Mitoses were numerous, especially in the glands of Lieberkühn. The various lesions become less frequent in passing toward the large intestine.

## CHAPTER XX

### EFFECTS ON THE LIVER

The effects of inanition upon the liver are of interest, since this gland forms an important part of the digestive system. As will be shown, there are marked hepatic changes associated with inanition and malnutrition of various types. After a brief summary, these changes in the liver will be considered under (*A*) total inanition, and (*B*) partial inanition.

#### SUMMARY OF THE EFFECTS ON THE LIVER

In interpreting the data on loss of weight in the liver during the various forms of total and partial inanition, it must be remembered that even under normal conditions the liver is exceedingly variable in weight (ranking close to the spleen in this respect), so that unless the observations are very numerous the results may be influenced by chance variations. This will doubtless account for a part of the apparently discordant results, which are also due to differences in species, age and other conditions, as well as in the type and degree of inanition.

On the whole, however, it is clear that in general the liver during inanition suffers a marked **loss in weight**, usually relatively greater than that in the body as a whole. This applies to total inanition (complete or incomplete), especially in adult man and animals. In the young, the loss of weight in the liver is often less marked, and under some conditions (in the young rat and during adult compensatory hypertrophy) the persistent growth impulse of the liver may even overbalance the tendency to atrophy, resulting in a gain. In experimental inanition, it has been shown that the loss in weight of the liver is relatively heavier in the early stages, probably due to the rapid loss of hepatic glycogen and a part of the fat.

During the various types of partial inanition the changes in the weight of the liver are more variable, with a tendency to atrophy in malnutritional edema, pellagra, beriberi and aqueous inanition (thirst). In rickets, the liver is frequently enlarged, while in scurvy and other types the results are more variable.

**Changes in Structure.**—The loss in the weight of the liver is invariably found to be due to atrophy of the parenchyma, although this may be masked to some extent by the frequent passive hyperemia and more rarely by fibrosis (cirrhosis). The atrophy of the gland-cells concerns chiefly the cytoplasm, the nuclei being more resistant.

The changes in the hepatic gland-cell are usually complex, on account of its varying content of glycogen, protein, fat, secretory granules, mitochondria, etc. The changes in the fat content have been much disputed, partly because of variation in different species. Apparently the incoming blood-fat (derived

through intestinal absorption or from fat in other cells of the body) is deposited in the liver-cells partly as fat of the ordinary "wandering" type, which is quickly mobilized during inanition; and partly as fat of the lipoidal "sessile" type which, as in other cells, is very resistant to inanition. The general question of fatty degeneration versus fatty infiltration has been the subject of much controversy, especially in the liver-cells.

During the more advanced stages of inanition, a progressively increasing number of liver-cells undergo degeneration in various forms, including cloudy swelling, vacuolar, granular or fatty degeneration, pigmentation (of hemato-genous origin), and finally in some cases karyolysis, pycnosis or karyorrhesis, with complete disintegration and removal of the cell. These degenerative changes occur likewise variably in the different forms of partial inanition. They are obviously not characteristic of inanition only, however, since they occur in many other abnormal conditions of the liver.

Upon adequate **refeeding** after a period of inanition, the liver as a rule promptly regains its normal weight, partly by hypertrophy of the atrophic gland-cells, and partly by hyperplasia. In young animals, the mitoses, which are greatly decreased in number during inanition, become very numerous upon refeeding.

#### (A) EFFECTS OF TOTAL INANITION, OR ON WATER ONLY

The effects upon man (adult and infant) will be discussed first; later those among the animals.

**Human Adult.**—Tiedemann ('36) noted that after death from starvation the gall-bladder appears distended with bile, an observation which was confirmed by Donovan ('48) and others. Willien ('36) also noted that the liver becomes dense and anemic. Schultzen ('62, '63) observed gross atrophy with fatty and granular degeneration in the liver of a 19 year old girl who died from starvation on account of an esophageal stricture. Macroscopic changes in the liver during inanition were noted by Frerichs ('66).

Curran ('74) in an old native woman who died from starvation found the liver very small (15 ounces or 428 g.), anemic and brownish in color. Bright ('77) in a female 35 years old, with weight reduced by starvation from 121 to 74 pounds, found the liver weight  $34\frac{3}{4}$  ounces. Casper-Liman ('82) stated that in starvation the liver appears pale, anemic, and hardened; the gall-bladder distended with dark-colored bile. Popow ('85) observed hemorrhages in the liver in a case of death from esophageal stricture. Voelkel ('86) noted a fatty liver in a man who died from voluntary starvation.

In victims of the Madras famine, Porter ('89) found the average weight of the liver 32 ounces in the men and 28 ounces in the women. The ratio to body weight averaged 1:36, which is not far from the normal, indicating that the liver had lost in weight relatively to the same degree as the entire body. The liver appeared congested in 58 men (about  $\frac{1}{4}$  of all cases), in 16 women ( $\frac{1}{8}$ ), and in 16 children ( $\frac{1}{4}$ ); and anemic in 16 men, 31 women and 12 children. In some cases the liver presented nearly normal gross and microscopic appearances. "Fatty degeneration" appeared in 113 men (65 per cent), 103 women (83

per cent) and 50 children (78 per cent). There was a "nutmeg" appearance in 39 men, 44 women and 4 children; cirrhosis, with "hobnail" appearance in 5 men and 6 women; pigmentation in 17 men, 6 women and 1 child. The gall-bladder varied from distension to emptiness; and the bile also varied much in color and consistency.

In the cases with the most extreme general atrophy of the body (4 men, averaging 77 pounds; 4 women,  $66\frac{3}{4}$  pounds; and 4 children) the liver was always small, averaging about 24 ounces in the adults. It also appeared nearly always anemic and fatty, yellowish in color. A similar appearance was noted by Formad and Birney ('91) in the liver of a woman 60 years old, who died of starvation.

Stschastny ('98) in the liver of a starved man found stasis of blood, atrophy of the cell-columns, pigmentation, deeply staining nuclei (sometimes vacuolated) and hyalin degeneration of the connective tissue. Dünschmann ('00) mentioned atrophy of the liver as characteristic at death from starvation. Helly ('11) described various types of hepatic steatosis, which he considered an expression of the fatty metabolism of the cell and dependent upon its vitality and the circulatory relations, affected by inanition and other factors. Sternberg ('13, '21) described in cachexias, inanition and senile marasmus a general atrophy of the hepatic parenchyma. The gland cells become reduced in size, some entirely destroyed; often (especially in senility) containing pigment (lipochrome) masses. Vacuolation, steatosis and other degenerative changes may occur. There is a relative increase in the connective tissue stroma.

Meyer ('17) in a man who died from starvation found the liver pale and soft, weighing 914 g. (body weight decreased from about 135 to 80 pounds). Microscopically the liver appeared very atrophic, with disintegration of the cell-cords, especially near the central vein of the lobule. "Many of the hepatic cells are reduced to one-fourth or even to one-fifth their normal size. Others are represented by a small amount of protoplasm surrounding a nucleus, while still others are mere shadows of cells. A good deal of golden pigment is found intracellularly and in considerable masses also extracellularly."

Bean and Baker ('19), in a large series of adult autopsy weights, found the average weight of the liver greatly affected by the general nutrition of the body. In 771 white males, the average increased from 1,342 g. in the "extremely emaciated" group to 1,909 g. for the "obese;" and in 523 white females from 1,150 g. in the extremely emaciated to 1,790 g. in the obese. Similar increases were noted for the negroes.

Rubner ('19) mentioned atrophy of the liver as one of the results of under-feeding in Germany during the war. This was also noted by Roessle ('19), excepting cases where the atrophy is masked by fatty or amyloid degeneration.

In a few cases of voluntary starvation (complete or incomplete) Sison ('20) found on living patients a distinct decrease in the hepatic area of dulness on percussion. He ascribed this partly to an actual atrophy of the liver, and partly to increased tympany of the overlapping lung margin.

Krieger ('20) found the apparent loss in liver weight greater in general cachexias than in infections, probably because the atrophy in the latter is

masked by cloudy swelling and fatty degeneration. Her results are shown in the accompanying table, all cases being males, excepting group I (6 males, 4 females). Data for loss in body weight were lacking.

AVERAGE WEIGHT OF THE LIVER IN VARIOUS CONDITIONS OF INANITION (KRIEGER '20)

Group	Number of cases	Normal weight (2.69 per cent of body wt.), grams	Observed weight, grams	Estimated loss in weight, per cent
I. Emaciated insane.....	10	1,592	921	42.1
II. Chronic diarrhea.....	6	1,754	991	43.5
III. Malignant growths.....	21	1,786	1,198	32.8
IV. Chronic infections.....	15	1,786	1,284	28.0
V. Tuberculosis.....	29	1,754	1,269	27.7
VI. Aged.....	17	{ 1,786 1,498 <sup>1</sup>	{ 1,097 1,097	{ 38.0 26.0 <sup>1</sup>

<sup>1</sup> Making allowance for normal age decrease.

Weber ('21) found an apparent decrease of about 10 per cent in the weight of the liver (excluding pathological organs) at Kiel, comparing data from the

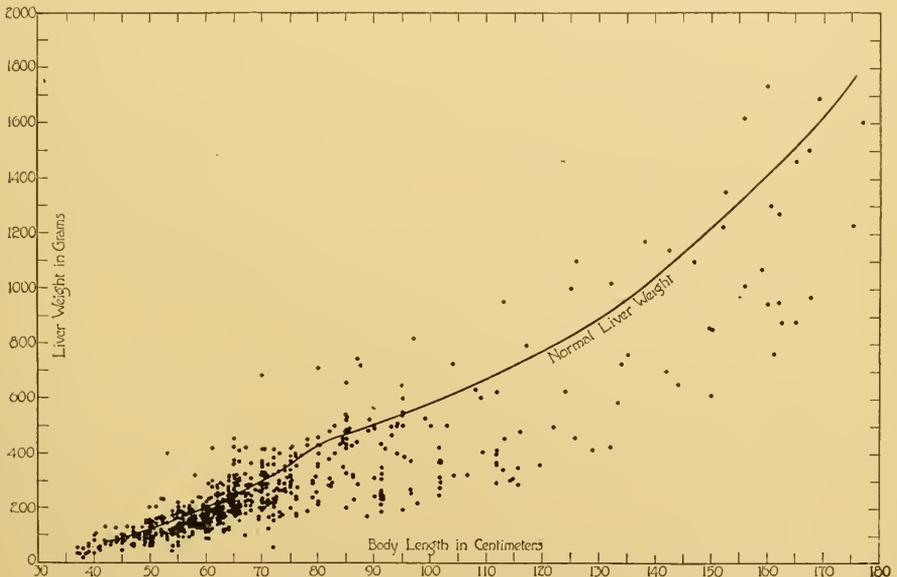


FIG. 88.—Graph showing the individual weights of the human liver, according to body length, in atrophic or emaciated cases, up to 20 years of age. Data from various sources. Curve of normal liver weight from data compiled by Prof. R. E. Scammon. The liver appears below the normal weight in most cases.

period of subnutrition (1916-1918) with an earlier period of good nutrition (1914-1915). Data for body weight were lacking, however. From 50 necropsies in cases of starvation (age 1-63 years), Stefko ('23) concludes that the liver loses in both relative and absolute weight.

Figure 88 is a field graph showing the liver weight plotted against body length in a large number of atrophic cases up to 20 years of age, from various sources. Most of the cases clearly lie below the curve for normal average liver weight.

The data for **atrophic infants** will now be considered.

Parrot ('68, '74, '77), the pioneer in the study of infantile athrepsia, suspected that disorder of the liver plays an important rôle in this condition, although he could find no marked changes in this organ. He found the hepatic parenchyma congested and dark reddish or violet. Although he considered visceral steatosis characteristic in athrepsia, he was unable to demonstrate any large amount of fat in the liver cells, especially in extreme marasmus. The gall-cyst appeared distended with bile.

Ohlmüller ('82) noted a weight of 104.2 g. in the liver of an atrophic infant 56 days old; body weight 2,381 g. (previous weight not given). In a "normal" control of the same age, the liver weighed 144.6 g., body weight 4,150 g.

Cantalamassa ('92) found the gall-bladder distended with thick bile in infantile starvation. Thiercelin ('04) stated that the liver in athreptic infants is usually hypertrophied. Inflammatory lesions have been described (Gaston). The hepatic cells contain a large nucleus and some pigment granules, but no fat.

Bovaird and Nicoll ('06) presented data from 571 autopsies on children, and concluded that the weight of the liver is largely dependent upon the state of general nutrition, and is very low in the emaciated.

Lucien ('08) mentioned the liver in athreptic infants as dark violet in color and of firm consistence. Histologically no marked or characteristic lesions are found. A more detailed description was given by Lucien ('08d). In weight, the liver is nearly normal, averaging 141 g. (8c-210 g.) in infants of 2-10 months. Intense congestion is found, but otherwise no constant or characteristic structural change. Lucien therefore concluded that gastroenteritis and intestinal infections are not of primary importance in athrepsia.

Helmholz ('09) likewise found inconstant changes in the liver of atrophic infants. Of 22 cases, however, only 2 failed to show pigmentation (with iron-reaction;); 8 others showed only the normal amount; 12 showed much pigmentation and 6 excessive amounts. In the latter, "Die Leberzellen sind leicht geschwollen, was bei den Alkoholpräparaten durch die zurückbleibende Membran zu erkennen ist, trotz der Schrumpfung der Zellen; das Protoplasma ist leicht gekörnt, keine fettige Degeneration. In den Leberzellen ist gröberes und feines, dunkelbraunes und goldgelbes Pigment, das sich meistens um die Kerne gruppiert. Besonders fällt aber in diesen Präparaten auf die starke Pigmentation der Endothelzellen der Leber, die mit olivengrünem Pigment z. T. in grossen Schollen gefüllt sind."

Triboulet, Ribadeau-Dumas and Harvier ('10) noted that the liver in athreptic infants appears small, firm, and violet colored, with congestion and periportal fibrosis (insular cirrhosis). The gross atrophy of the liver is due to atrophy of the cords of liver-cells, which appear narrow, between the dilated

capillaries. The liver-cells are decreased in size, with finely granular cytoplasm (no steatosis), and pycnotic nuclei. The iron-reaction is constant, though variable in intensity, but is not characteristic of athrepsia.

Schelble ('10) made a careful histological study of the liver in 35 cases of pedatrophny (with early fixation in 16), but could find no constant, marked or characteristic lesions.

Lesage ('11, '14) noted a weight of only 109 g. in the liver of an atrophic infant, the normal being 300 g. The hepatic cells may become atrophic, and fail to secrete the bile necessary for digestion. Lesage and Cleret ('14) found in congenital spasmodic atrophy a marked sclerosis of the liver and other organs. Maillet ('13) noted lesions in the liver of athreptic infants.

Hayashi ('14) made a special study (with review of the literature) of the liver fat in atrophic infants, using optical and microchemical methods. In 8 cases, 5 showed neither fats nor lipoids; 1 showed partial and 2 marked fatty degeneration. Hayashi concluded that the hepatic fat in athrepsia differs from that found in experimental inanition.

Mattei ('14) usually found in athreptic infants but little change in the liver structure, which appeared normal in 5 out of 15 cases. In some zones the columns of liver-cells appeared slightly compressed between the dilated blood capillaries. The hepatic cells are sometimes swollen by vacuoles (fat droplets) of variable size, which may occur around either the central vein or portal vessels. Some cells contain pigment (probably siderosis of hematic origin). Atrophic cells with karyolytic nuclei may occur throughout the gland. Sometimes the cells appear more deeply stained in the periphery of the lobule, and clearer toward the center (not due to difference in glycogen content). There may be periportal sclerosis.

Nobécourt ('16) reviewed the literature and concluded that in atrophic infants the liver may be either normal or diminished in size. Congestion is characteristic and a variable degree of fibrosis, steatosis or siderosis may be found.

Marfan ('21) held that the hepatic siderosis in athreptic infants is related to the hemolysis and anemia found in these cases. Huebschmann ('21) claimed that in acute nutritional disorders (intoxications, "Mehlnährschaden") there is a toxic disturbance of the general cell metabolism resulting in a characteristic steatosis of the liver and a related disappearance of suprarenal lipoids. Stephani ('23) likewise noted severe fatty degeneration in acute cases, but not in chronic malnutrition, in which hepatic hemosiderosis occurred.

In famine-stricken children of various ages, Nicolaeff ('23) found the liver weight always over 20 (sometimes 45-55) per cent subnormal for age, being smallest in edematous subjects. The histologic structure appears variable. In non-edematous cases, there is frequent venous and capillary hyperemia; atrophy of the hepatic cell-cords, especially near the center of the lobule; and complete absence of fat and glycogen. In edematous subjects, there is venous hyperemia, and adipose infiltration in the periphery of the lobule. Stefko ('23) observed the reestablishment of normoblasts in the liver of children who died from starvation.

I have estimated the loss of the liver weight in atrophic infants upon several bases, taking all available data, including some original observations upon Minnesota cases (Table 2). Thus in comparison with the normal for final body weight, the liver averaged 6.3 per cent subnormal (or 11.2 per cent for the Minnesota data alone). Compared with the normal for the maximum body weight during life, the liver averaged 33 per cent subnormal, which is relatively more than the loss in body weight (20.9 per cent). Compared with the normal for body length, however, the liver averaged only 23.2 (or 26.3) per cent subnormal; and for age it averaged 27.1 (30.3) per cent below the norm.

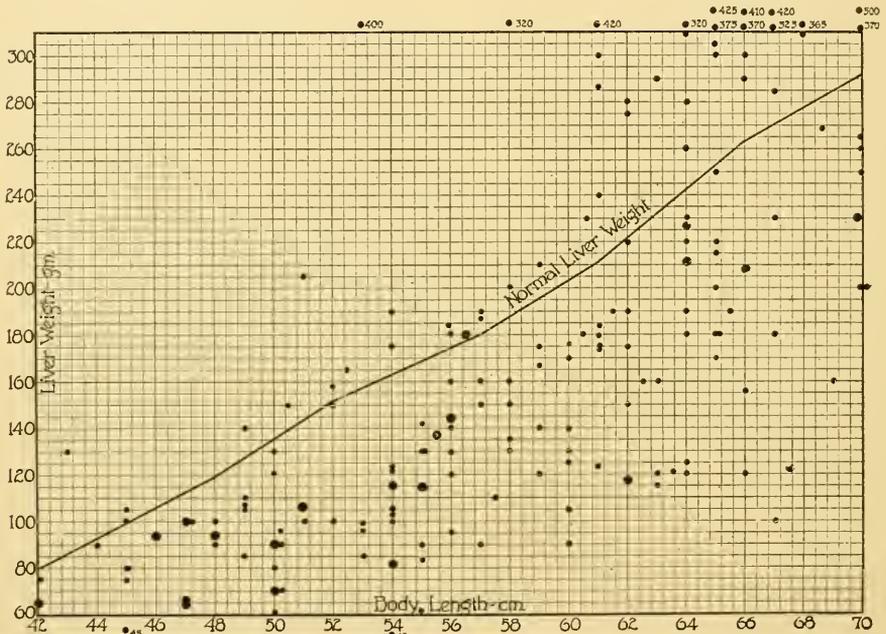


FIG. 89.—Graph showing the individual weights of the liver, according to body length, in 170 atrophic infants. The larger dots represent original Minnesota cases; others from various sources. The curve of normal liver weight is from data compiled by Prof. R. E. Scammon. Although there is much individual variation, the average liver weight is markedly subnormal, especially in the (younger) cases on the left half of the chart.

The individual weights of the liver for some of the Minnesota cases are included in Table 3. It will be noted that in most cases the liver weight (as likewise the body weight) is considerably below the normal for birth. A better idea of the relative weight of the liver in atrophic infants is obtained from Figs. 88 and 89. It is evident that there is a marked variation in the weight of the liver (which is known to occur even under normal conditions); but most cases are considerably below the norm, in accordance with the averages noted in Table 2.

In the **animals**, observations on the effects of inanition upon the liver are very numerous, and will be considered in chronological order, excepting some data on seasonal changes and hibernation, which are placed last.

Lucas (1826) reported that in mammals (guinea pig) the liver may appear normal, even after long fasting. Collard de Martigny (1828) in starved dogs and rabbits found the liver small and anemic, and the gall-bladder distended with bile. Tiedemann ('36) cited numerous earlier investigators who observed an abundance of bile in the bile-passages of starved animals.

Chossat ('43) found that in pigeons on total inanition with average loss of about 40 per cent in body weight the liver lost 52 per cent.

Heumann ('50) was apparently the first to study the microscopic changes in the liver of the pigeon during inanition, finding the cells decreased in size and containing smaller granules. Statkewitsch ('94) says Heumann noted a fatty and granular degeneration. Jones ('56) and Beale ('60) are said to have observed fatty degeneration of the liver cells in fasting animals; and Rindfleisch ('68) figured the changes in the cell structure.

Bidder and Schmidt ('52) found an apparent loss of 59.6 per cent in the liver of a cat starved with loss of about 50 per cent in body weight. Voit ('66) also found that in the cat during starvation the liver loses in weight relatively more than the body as a whole.

Manassein ('68, '69) observed that during starvation the liver appears atrophic and variably hyperemic; the gall-bladder distended. In 47 adult rabbits with average loss of 39 per cent in body weight, the loss in liver weight averaged 66 per cent. In 8 rabbits  $3\frac{2}{3}$  months old, with loss of 33 per cent in body weight, the liver lost 53 per cent; in 3 rabbits 23-25 days old, with loss of 35 per cent in body weight, the liver lost 59 per cent. In 5 adult rabbits amply refed after a period of starvation, the liver appeared 42 per cent above normal weight. The average loss in liver weight in 2 starved cats was 69 per cent; and in 2 crows, 46 per cent.

Manassein also measured the diameters of the rabbit liver-cells, finding the normal average 0.0223 mm. (range 0.015-0.033); in starvation, 0.0089 (0.006-0.018) mm.; and on refeeding, 0.0252 (0.015-0.0345) mm. During starvation the liver-cells not only decrease in size, but apparently degenerate, with various degrees of granulation and nuclear disappearance, and (in extreme cases) final complete cell disintegration, the fat collecting in large free droplets.

Bourgeois ('70) in numerous starved mammals (guinea pig, rabbit, cat, dog) with average loss of about 40 per cent in body weight, found a loss of 52 per cent in the liver. The liver appeared anemic and reddish-yellow in color, with distended gall-bladder. Lépine ('74) described a fatty degeneration of the liver-cells during inanition. Carville and Bochefontaine ('74, '75) in a dog starved 27 days found no fatty degeneration, but a finely granular degeneration in the liver-cells. Falck ('75) found considerable fat content in the liver-cells of fasting dogs, but not more than in normal animals. Falck ('81) cited data from Stackman indicating that in fasting cats the liver loses relatively more than the entire body.

Kayser ('79) studied in Heidenhain's laboratory the liver-cells of mammals during digestion and fasting. With alcoholic fixation and carmine or hematoxylin stains, the cells during inanition appeared reduced in size, with poorly staining nuclei which are obscured by the cloudy, granular cytoplasm. The

observations were confirmed and extended by Heidenhain ('80, '83) who noted the disappearance of the glycogen (by iodine tests). In fasting larvae of the frog (*Rana tigrina*) and toad (*Bufo melanostictus*), Cunningham ('80) observed a full gall-bladder and a mass of yellowish-brown or reddish granules in the liver-cells. The liver was greatly decreased in size.

Mankowski ('82) noted atrophy of the liver in fasting rabbits, and Luciani and Bufalini ('82) atrophy and apparently fatty degeneration in the liver of a fasting dog.

In a puppy starved 23 days, Ohlmüller ('82) cites Voit's observation of a liver weight of 313 g., while in a full-fed litter-mate control the weight was only 335 g. This is also stated by Voit ('94) and would indicate a relative resistance to inanition in the liver of the young animal.

Langley ('82, '86) described the changes in the liver-cells of the frog and mammals in digestion and fasting. The cytoplasm of the vertebrate liver-cells shows a honey-comb structure, enclosing granules (probably protein) and fat droplets, together with a homogeneous substance probably containing protein and glycogen. During fasting, the cytoplasmic network becomes more distinct, with a reduction in the hyalin substance but definite granulation. The seasonal changes in the frog's liver will be mentioned later.

Afanassiew ('83) studied the changes in the liver-cells of dogs fasting 3 or 4 days and then killed or refed in various ways. In comparison with the condition during digestion after full feeding, the liver-cells in fasting appear reduced about one-half in average diameter, showing distinct granulation, but usually no glycogen or fat droplets.

Skoritschenko ('83) noted an average loss of 41.62 per cent in the weight of the liver in 6 fasting rabbits (with or without water), with loss of 43.7 per cent in the body weight.

Gaglio ('84a) in frogs fasting 4 months to 1 year, found progressive decrease in size with granular and fatty degeneration of the liver-cells. There appeared also a cirrhosis, with increase of the perivascular and interlobular connective tissue; also hyperemia, increased pigmentation, and apparent new formation of bile-ducts. Barfurth ('85) found that in the summer frog 3-6 weeks of complete inanition are required for the removal of the hepatic glycogen.

Ranvier ('85) noted that, in the meshes of the cytoplasmic reticulum in the hepatic cells of the rat, glycogen disappears after 48 hours of fasting, but granules of other materials are persistent.

Popov ('85, '85a) observed atrophic granular, pigmentary and fatty degeneration in the liver-cells of starved rabbits and mice; on the other hand, some regenerative phenomena were evident, such as increased number of nuclei and proliferation of connective tissue.

Ochotin ('85, '86) studied the progressive changes in the liver-cells of fasting rabbits, finding cloudy swelling, granular and fatty degeneration. These changes are scarcely apparent until the loss in body weight exceeds 13 per cent, and are exceedingly variable in different cells, only a few showing the more extreme changes.

In the fasting frog, Kux ('86) found a loss of 68 per cent in the volume of the liver-cells; also the appearance of lipochrome droplets and increased granulation (fatty degeneration?).

Lahousse ('87) described the changes in the liver-cells of the frog, pigeon and rabbit during digestion and early fasting stages. Stolnikow ('87) also included observations on the changes in the hepatic cells of the frog during starvation. The changes in hepatic fat and water content of dogs, fowls and rabbits were studied by Pfeiffer ('87). Isaëw ('87) noted atrophy, fatty and "albuminous" degeneration in the liver-cells of starved dogs.

Moszeik ('88) observed that in starvation the cytoplasm of the liver-cells in the frog is reduced to a greater extent than the nucleus, with loss of glycogen. The changes are described on refeeding with various diets. Aldehoff ('89) gave weights of the liver in the frog, pigeon and fowl after various periods of inanition. Glycogen may persist in the liver for considerable periods of inanition, but is less resistant than that in the muscles.

Morpurgo ('88, '89, '89a) found that in starved rabbits of various ages the hepatic cells were reduced (in a rabbit 15 days old, after 5 days fasting) from  $27.5\mu$  to  $17.8\mu$  in average diameter. The cell boundaries become indistinct and the cytoplasmic granulation obscures the nucleus. The capillaries may be distended between the atrophic cell-cords. Mitoses are greatly reduced in number in the young rabbit, but are found even abnormally numerous upon ample refeeding.

In starved pigeons, Morpurgo ('89b) found the hepatic cells reduced to about 36 per cent of the normal volume (from  $11.34 \times 8.54\mu$  to  $8.73 \times 6.74\mu$ ). The nuclei, however, are but slightly reduced in absolute size, therefore greatly increased in relative size. In young rabbits refed 5 or 6 days after starvation for 6-10 days, Morpurgo ('90) found the liver nearly normal in appearance in structure. The average diameter of the liver-cells in normal controls was  $21.0\mu$ ; in starvation,  $15.7\mu$ ; and in the refed,  $20.4\mu$ . Thus the cells appeared normal in size, although the normal weight of the liver had not yet been recovered. The nuclear diameter averaged  $7.42\mu$  in the normal controls;  $6.45\mu$  in the starved; and  $7.88\mu$  in the refed rabbits. Mitoses occurred in variable number throughout the liver in the refed animals, though extremely rare in the controls. They seemed more frequent in the vicinity of richly pigmented cells (glandular or connective tissue cells).

Aducco ('89) studied the effect of light upon the hepatic glycogen in fasting pigeons. Tonninga ('93) noted the changes in nitrogenous substances of the liver and other organs in fasting rats and rabbits.

Lukianow ('88, '89) investigated the water content of the liver and other organs in fasting pigeons. Lukianow ('92) found that in (total) fasting guinea pigs the liver in the early stages of inanition losses most heavily in weight, decreasing relatively from 3.38 per cent to 3.03 per cent of the body, at an average body loss of 5.53 per cent in weight. Thereafter the loss is relatively less in the liver, which regains a relative weight of 3.36 per cent of the body, at a body loss of 16.18 per cent. At a body loss of 25.17 per cent, the liver forms 3.25 per cent of the body; and at body loss of 34.46 per cent it forms 3.54 per cent,

indicating that the liver loses relatively less than the entire body in the later stages of inanition. The water content and bile secretion were also noted.

Altmann ('90) studied the structural changes in the liver during inanition, especially in the frog. Grossly the liver in starvation appears small and dark colored, in contrast with its large size and yellowish color after ample feeding. Microscopically the liver-cells when well nourished appear large, containing fuchsinophile threads and granules, also osmic staining globules. In starvation, the cells are markedly reduced in size and filled uniformly with fuchsinophile granules.

Coen ('90) in the starved rabbit and kitten found the liver cell-cords separated by distended blood capillaries, with occasional hemorrhagic foci or pigment masses of hematogenous origin. Some slight leukocytic infiltration indicated early inflammatory stages. The liver-cells appeared reduced in size, with scanty, finely granular cytoplasm. The nuclei sometimes were small and poorly staining.

Böhm and Davidoff ('94) state that the mammalian liver-cell during fasting presents an inner denser granular cytoplasmic zone and an outer less granular zone containing glycogen and minute droplets of bile secretion.

Statkewitch ('94) studied the changes in the liver-cells of fasting cats, dogs, rabbits, guinea pig, pigeons, etc., with or without water. In the early stages of inanition there is cloudy swelling, with loss of glycogen. After loss of 10-15 per cent in body weight, granular degeneration occurs, and fat droplets may appear in the cells around the central part of the lobule. The fatty degeneration becomes much greater and spreads toward the periphery of the lobule in more advanced stages of inanition (loss of 20-25 per cent in body weight), finally involving nearly all the cells. The fatty degeneration is well marked in the guinea pig, dog and cat, less marked in the rabbit and least in the pigeon. The rounded nuclei become ellipsoidal or irregular, with final chromatolysis or karyorrhexis. The epithelium of the bile-passages may show similar, but less marked, degenerative changes. Desquamation of cells may occur, sometimes forming a ring in the lumen of the bile-duct.

Von Bechterew ('95) gave data showing the loss in weight of the liver in fasting newborn kittens and puppies.

Lazareff ('95), like Lukianow ('92), found that the liver in guinea pigs loses most heavily in the early stage of inanition. With body loss of 10 per cent, the loss in liver weight averaged nearly 18 per cent. At later stages, the loss in the liver appeared more nearly proportional to that in the body as a whole (Table 5).

Kusmin ('96) mentioned hyperemia and extravasations in the liver of hyperthermic rabbits and guinea pigs. Zanier ('96) found no diminution in the granular "bioblasts" of Altmann in the liver and kidney of the fasting frog and rat. Habas (Chabas) ('97) claimed that during fasting the normal fat disappears quickly from the hepatic gland cells, but is retained in the endothelial and stellate Kupffer cells in birds (fowls and geese) until the loss in body weight has reached 40 or 50 per cent. In extreme inanition, the liver-cells undergo atrophic and granular degeneration, with vacuolation. Upon refeeding after

inanution, the fat reappears first in the Kupffer cells in pigs, and in the vascular endothelium of birds, being deposited later in the hepatic parenchyma.

Weiske's ('97) data indicate a loss of over 50 per cent in the liver of fasting rabbits with loss of 35-41 per cent in body weight.

Lukianow ('97, '97a) made some extensive measurements on the hepatic nuclei of mice fasting and on various diets, with loss of about 30 per cent in body weight. On total (complete) inanition, the decrease in nuclear diameters indicated an average decrease of 44.4 per cent in nuclear volume. The nuclear decrease was less marked on the diets, averaging 39 per cent for peptone, 26.3 per cent for sugar, 21.8 per cent for egg-albumin and only 6.3 per cent for fat. It may be remarked that such extensive shrinkage of the nuclei (without degeneration) during inanition is contrary to the results of other investigators, who (excepting Beeli) have found that the nuclei of the liver (like those in other organs), lose but slightly in volume. Nemzer ('99), however, found that in fasting white mice the decrease in nucleins in the liver was greater than in the kidney, but less than in the intestines.

Gulland ('98) noted that the liver-cells in the salmon taken at the river mouth contained much fat in the form of droplets, while there was little fat in those after fasting during the ascent of the river. In both cases the gall-bladder showed a "desquamative catarrh."

Nikolaides ('99) observed the appearance of lipoidal granules in the liver and other organs of dogs fasting 2-30 days, but they disappear before death from starvation. He upheld the doctrine of metamorphosis of cell proteins into fat. Lindemann ('99) and others supported the theory of fatty infiltration rather than degeneration of the liver-cells during inanition. Elbe ('99) claimed an increase in the hepatic fat of rabbits during the first two days of fasting, with a decrease later. Schmaus and Albrecht ('99) described the liver-cell structure in inanition and various diets.

Sedlmair ('99) found that in starved rabbits the liver loses in weight relatively more than the whole body.

Arapow ('98, '01) claimed that in starvation the number of binucleated hepatic cells in white mice is but slightly increased; but a larger number appears on fat or sugar diet, and relatively most on albumin or peptone.

Sjöbring ('00) noted that in the liver-cells of rabbits fasting 24-48 hours the mitochondria (chondriosomes), which normally appear as short rods, have changed into large, round forms.

Quattrochi ('01) found the liver small in nursing puppies placed on insufficient or improper diet, with loss of about one-fourth in body weight. Cruet ('02) noted a loss of weight in the liver of starved guinea pigs nearly proportional to the loss in body weight.

Holmgren ('02) found that in the fasting hedgehog the "Saftkanälchen" of the liver-cells become scarce or absent; but the "trophospongium" is persistent. Certain changes on a carbohydrate diet were noted.

Konstantinovitch ('03) described a process of fatty infiltration (rather than degeneration) which in the liver of various animals (lizard, frog, rabbit, guinea

pig, mouse, hedgehog) appears in general to decrease during inanition. An atrophy of the cells and nuclei was also found.

Traina ('04) investigated the fat content in the liver-cells and other organs of man and the rabbit during inanition. He distinguished two types of fat (1) "wandering" or "usable" fat, the ordinary fat of the adipose tissue, etc., which is greatly reduced by starvation; (2) the "sessile" or "permanent" in the form of granules (resembling the lipochromes) which appear to constitute a constant and integral part of the cytoplasm in most gland cells. This epithelial fat in general appears very resistant to inanition, except in the liver, which shows a marked decrease.

Koiransky ('04) described in the amphibian liver-cells some peculiar chromatic-bodies, which he thought might have a secretory or nutritive significance. Pugliese ('c4, '05) found that the liver in fasting dogs loses relatively less than the body as a whole. On refeeding, the liver gains in weight with extraordinary rapidity, due chiefly to increase in glycogen content. The morphological changes in the liver-cells were found similar to those described by Mörpurgo.

Carrier ('05) in white rats during short fasting periods described changes in the liver-cells which were interpreted as of functional significance.

Jomier ('05) found that the liver-cells in most fasting dogs show no glycogen after  $8\frac{1}{2}$  days; the amount varies normally according to diet. Ingested fat appears in the liver of the dog in 5-7 hours, or 7-9 hours in the rabbit. It disappears slowly, and is still present after  $5-8\frac{1}{2}$  days; but the amount is not proportional to the length of the fast. The maximum amount is found in 10 hours (Deflandre). The glycogen granules likewise persist in variable amount for several days, especially in the dog. An increase of hepatic fat during short fasts (up to  $8\frac{1}{2}$  days) was also noted by Gilbert and Jomier ('04) in the dog, and to a less extent in the rabbit. They thought this might be correlated with the increase in blood-fat noted by Schulz, Daddi and others. Gilbert and Jomier ('05, '05a) found that in fasting rabbits the hepatic glycogen practically disappears in 2-4 days, though sometimes it persists longer. In dogs, it was similarly variable.

Gilbert and Jomier ('06, '07, '08, '09) described in the liver of dogs and rabbits, after Flemming's fixation, two types of gland cells (1) large and clear, (2) small and dark, which appear to behave differently during inanition, but show no characteristic differences on various diets. Bernard and Loederich ('08) claimed that the "clear" cells are due to their glycogen content, which was disputed by Gilbert and Jomier, and by Ramond ('08) and Rathery ('09).

Mosse ('06) found that the cytoplasm of the liver-cells in dogs nephrectomized or starved 65-67 hours is more basophilic, which he ascribed to acidosis.

Gerhartz ('06) found the liver of *Rana esculenta* apparently reduced from 0.87 g. to 0.62 g. in 3 months of starvation, and to 0.45 g. in  $4\frac{1}{2}$  months. Roger ('07) studied the changes in water content of the liver and other organs in fasting and refed rabbits.

In starved cats Beeli ('08) found the liver soft and greatly diminished in size; the hepatic gland cells variably atrophic, many (also occasionally the endothelial cells) with pycnotic nuclei. In some cases fat globules appeared

in the gland cells, rarely in the endothelium, but these also occurred in normal cats. Beeli estimated that the (endothelial?) nuclei showed an average loss of 50 per cent in volume, and gave a table showing the statistical distribution of nuclear diameters at various stages of inanition.

Mottram ('07, '09, '09a) found in short fasting periods, usually 1-2 days, a marked increase of microscopically visible hepatic fat in 17 rabbits and 15 guinea pigs; and a very doubtful increase in 3 hedgehogs, 2 pigeons and 18 rats. In several normal controls, only one showed a large amount of fat. Chemical evidence confirms the microscopic appearance, and the increased fat is considered due to infiltration of mobilized depot-fat. The hepatic glycogen (rabbit) is almost entirely removed in one day of fasting.

Boehm ('08) described the liver-cell changes in white rats on various diets and fasting on water only (time not stated) and also measured the diameters of cells and nuclei, obtaining the averages (in micra) shown in the accompanying table.

AVERAGE DIMENSIONS (MICRA) OF THE LIVER-CELLS IN WHITE RATS ON VARIOUS DIETS  
(BOEHM '08)

Diet	Cell length	Cell breadth	Nuclear diameter
Albumose.....	31.5	22.9	9.0
Fat.....	24.3	20.6	8.2
Albumin.....	24.5	18.8	7.9
Asparagin.....	24.2	19.0	7.0
Alanin.....	21.9	17.5	6.8
Starvation.....	17.7	15.2	7.2

It is evident that in Boehm's experiments the total hepatic cell volume was least in starvation, but not the nuclear volume.

Cesa-Bianchi ('09) discovered that in the atrophic liver (and kidney) of the fasting white mouse, the cell changes in the earlier stages correspond to those produced by hypotonic or hypertonic salt solutions; while the later changes correspond to those produced by aseptic autolysis. The nuclear changes come late, when all the available food material has been consumed, and true cell-hunger supervenes. The changes progress from hyperchromatosis to either pycnosis or karyorrhexis. (See further details in Chapter XXIII.) When the loss in body weight is 40 per cent, the liver has lost 50 per cent, and the liver-cells 50 per cent, but the nuclei only 15-20 per cent.

Rathery ('09, '09a) by appropriate fixatives showed that the "clear" cells of the liver in fasting rabbits still contain fuchsinophile granules.

Policard ('09, '09a) applied mitochondrial methods to the study of the liver-cells of the frog and dog during fasting and refeeding. Siderophile filaments and granules undergo changes which are interpreted as secretion phases of the liver-cells. Mayer, Rathery and Schaeffer ('10) studied these mitochondria and granules in the liver-cells of geese and rabbits in various conditions

of nutrition, and found them unchanged during starvation of 5 or 6 days (rabbit).

Rabe ('10) gave some data on glycogen changes in the liver of rabbits. Stickel ('10) found the liver in starved puppies hyperemic; fat droplets in the liver-cells are rare, but the Altmann granules usually more numerous. Fiesinger ('11) reviewed in detail the liver-cell changes, including those during inanition. He concluded that all recent studies agree that the hepatic cells are much more granular during fasting than when well nourished, especially on a carbohydrate diet.

Morgulis ('11) measured the hepatic cells and nuclei in the starved salamander (*Diemictylus viridescens*), and found that the total cell volume decreases relatively more than the body weight. The nuclei change in form, but decrease much less than the cytoplasm. Similar observations were made on the liver-cells in young albino rats stunted by underfeeding.

Rathery and Terroine ('13) found that in dogs fasting 26-28 days the filamentous mitochondria of the liver-cells are replaced by irregular fuchsinophile granules. Fat granules are normally scarce, except after a rich, fatty diet; but in a dog starved 68 days a marked increase in fat droplets of various size was noted. Smirnow ('13) found a decided increase in fatty infiltration of the liver in rabbits fasting 4 days or more without water; and to a lesser extent after 10 days or more with water. Wegelin ('13) also made observations on the liver-fat in white rats fasting 2-8 days.

Arnold ('14) reviewed the structural changes (especially in the granules and mitochondria) in the liver during digestion, absorption and early inanition.

Berg ('12) studied the liver-cells in Triton, mouse, rabbit and man during fasting and various diets. He found after casein feeding certain characteristic droplets interpreted as "gespeichertes Eiweiss," which disappear during fasting. Berg ('13, '14) investigated further the changes in the liver-cells of the rabbit, salamander, etc., with special reference to the changes in glycogen, fat and protein content of the cells. "Es finden sich in den Leberzellen gut genährter Tiere in reichlicher Menge Tropfen, die bei Hungertieren vollkommen fehlen, und durch Eiweissfütterung, nicht aber durch Kohlenhydrat oder Fettfütterung hervorzurufen sind." The conditions in the liver of the salamander during fasting and refeeding were shown in further detail by Berg ('20, '22).

Morgulis, Howe and Hawk ('15) noted vacuolar degeneration and a tendency to formation of syncytia in the liver-cells of fasting dogs with loss of body weight up to 50 per cent. Rothschild ('15) found an increase in the cholesterin content of the liver, suprarenals and blood of rabbits starved 2-9 days.

The changes observed by Jackson and coworkers in the weight of the liver in the albino rat during various degrees of inanition are shown in Table 4. In acute inanition of adults (on water only), Jackson ('15) observed a loss of 58 per cent in liver weight, with loss of 33 per cent in body weight. In chronic inanition, with loss of 36 per cent in body weight, the average loss in liver weight, was only 43 per cent. In young rats underfed from 3 weeks of age, Jackson ('15a) found a slight increase (10 per cent) in liver weight, but a loss of 39 per cent in those underfed for longer periods beginning at 10 weeks of age. In

underfeeding experiments beginning on newborn albino rats, Stewart ('18) found an increase of from 17 to 64 per cent in liver weight, but ('19) a loss of 23 per cent in rats held at birth weight by severe underfeeding for 16 days. Barry ('20, '21) noted that the liver appeared 45 per cent subnormal in weight

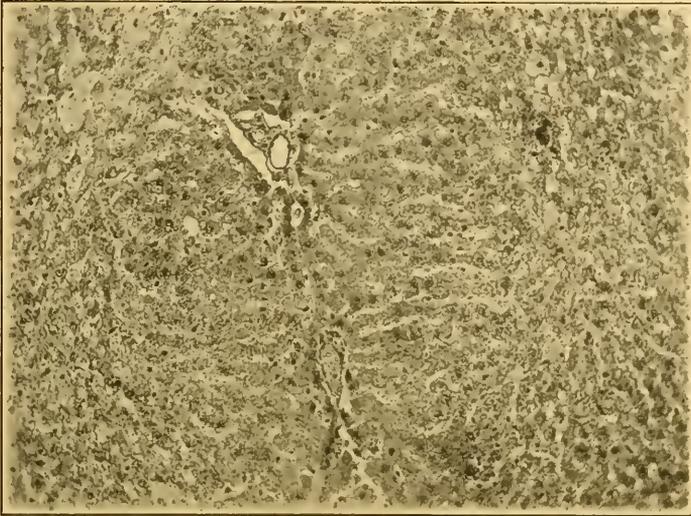


FIG. 90.—Photograph of a section of the liver in a normal adult albino rat (No. S. 14). Zenker fixation; hematoxylin-eosin stain.  $\times 135$ .

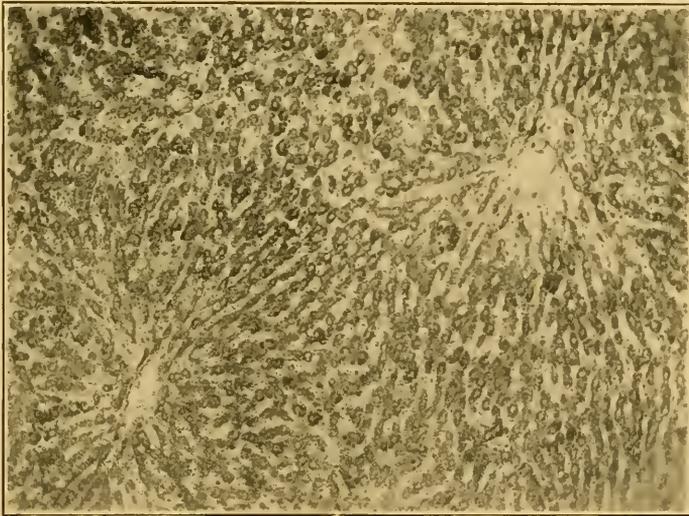


FIG. 91.—Photograph of a section of the liver in an adult albino rat (No. O. 4) after 6 days of inanition on water only with loss of about 25 per cent in body weight. Estimated loss of about 58 per cent in weight of the liver. Compare with Fig. 90, noting the capillary congestion and the atrophy of the hepatic cell-cords, especially near the central veins. Nuclei poorly stained. Zenker fixation; alum-hematoxylin stain.  $\times 135$ .

in the offspring of underfed pregnant albino rats. Thus there is apparently an age period in young albino rats when the growth impulse of the liver during

(incomplete) inanition appears much stronger than at either earlier or later periods of life.

The atrophic changes in the liver of the albino rat during inanition are shown by Figs. 90 and 91.

In young albino rats refed after being held at constant body weight by underfeeding from 3 to 12 weeks of age, Stewart ('16) found the liver weight restored to normal (and in some cases apparently above normal) within 4 weeks. Jackson and Stewart ('19) likewise found the liver nearly normal (or above) in rats underfed from birth to 3, 6, or 10 weeks, and then refed to 25, 50 or 75 g. in body weight (Table 7). In rats permanently stunted in growth by prolonged underfeeding, Jackson and Stewart ('20) found that the liver appeared slightly above normal weight (Table 8).

Giannelli ('16) incidentally noted a marked decrease in the size of the liver, with distended bile-vessels, in the teleost, *Tinca vulgaris*, after 5 months of inanition.

Sundwall ('17) described extreme congestion, cloudy swelling, fatty degeneration and partial to total atrophy of the liver-cells in white rats on inanition (complete or incomplete) 8-17 days with loss of about 50 per cent in body weight.

Trowbridge, Moulton and Haigh ('18), Moulton ('20) and Moulton, Trowbridge, and Haigh ('22a) studied the liver among other organs in steers kept on various planes of nutrition. The liver appeared markedly subnormal in weight in the animals retarded in growth by underfeeding.

Asada ('19) noted congestion, cloudy swelling, hemosiderosis, vacuolation and variable atrophy, but no fatty degeneration in the liver-cells of rabbits fasting 10-20 days, with loss of 27-52 per cent in body weight.

Davis, Hall and Whipple ('19) found that hepatic areas of necrosis produced in dogs by chloroform anesthesia show a certain amount of regenerative repair, even during fasting, or on a fat diet; but the regeneration is more rapid and complete on a carbohydrate diet, and best of all on a bread and milk diet.

McCarrison ('21) found a marked decrease in relative as well as absolute weight in the liver of starved pigeons (Fig. 35).

Terroine ('20) from a biochemical study concluded that the fat content of the liver is not materially affected by inanition in the rabbit and pigeons and is sometimes lowered in dogs. While fat may be greatly increased by overfeeding in the liver of young pigeons and geese, the liver in general apparently does not act as a storehouse for fats. Salvioli and Sachetto ('21) studied the so-called fatty degeneration in the hepatic cells of animals during inanition and phosphorus poisoning. Okuneff ('22) found that in starved rabbits there is a deposition of fat (apparently cholesterin esters) in the Kupffer cells and the epithelium of the smaller bile-ducts. Sometimes the hepatic gland cells contained lipoidal granules, staining differently from neutral fat.

Noel ('23) recently made a historical review and an investigation of the changes in the liver-cells of the white mouse during a fasting period of 24 hours. The cells are slightly reduced in size, and present a variable content of glycogen and fat. The siderophile filaments and granules are also variable. In fasting

rabbits, Okuneff ('23) describes simple atrophy of the liver-cells, with later degenerative changes in the mitochondria (chondriosomes). As shown by a modified Altmann technique, these "ihre Form, Grösse und Färbbarkeit verändern und sich in voluminöse, runde, stark tingierte Gebilde resp. Tropfen umwandeln, die sich weiter zu Bläschen umgestalten können." Jolly ('24) found a loss of 10 per cent in the nuclear area of underfed rabbits and guinea pigs.

Rous and McMaster ('24) noted, in accordance with previous observers, that in adult albino rats on water only there is a marked atrophy of the liver. The atrophy of the cell cords increases toward the center of the lobules, with correspondingly greater distension of the blood capillaries near the central veins. "In rats fasted after the removal of about seven-tenths of the liver the remaining fragment undergoes ordinarily a marked simple hypertrophy and attains the weight reached through a process of simple atrophy by the entire liver of fasting controls. Under circumstances of exceptionally severe inanition, the hypertrophy may not occur, the fragment remaining unchanged or even undergoing a slight atrophy. But since in comparable controls the hepatic atrophy is extreme, the duplication in liver weights still manifests itself." These results (which are in agreement with those of Davis, Hall and Whipple above mentioned) are interpreted as indicating an adjustment of the liver to meet the functional requirement of the fasting organism.

Ott ('24) found that in frogs during hibernation and subsequent inanition with losses in body weight from 10 to 60 per cent, the liver weight varied somewhat in the two sexes, but was always relatively greater than the loss in body weight (Table 6).

During **hibernation**, some of the changes in the liver-cells have already been mentioned incidentally. Further data are contained in the works of Langley ('82, '86) for the frog, toad and snake; also Langendorff ('86), Leonard ('87), Moszeik ('88) and Altmann ('90) for the frog; Carlier ('92) for the hedgehog (*Erinaceus europaeus*); Gaule ('01) and Athanasiu and Dragoin ('08) for the frog; Berg ('14a, '22) for the salamander; and Ott ('24) for the frog. There are marked seasonal changes in the liver of hibernating animals, fat and glycogen being gradually deposited in the feeding period during the summer, and slowly consumed during hibernation, accompanied by variable atrophy and histological changes in the liver.

#### (B) EFFECTS OF PARTIAL INANITION

The effects of partial inanition will be considered under deficiencies of protein (including pellagra and malnutritional edema), salts (including rickets), vitamins (including beriberi and scurvy) and water (thirst).

Under **protein** deficiency, though involving also salts, vitamins, etc., we may classify the experiments of Brüning ('14), who noted fatty degeneration of the liver-cells in young rats whose growth in body weight was prevented by a one-sided carbohydrate diet. McCarrison's experiments (to be mentioned later under vitamins) also involved protein deficiencies. Rosenheim ('91) found hepatic enlargement and fatty metamorphosis in a dog on protein-poor diet.

For reasons stated in Chapter V, the **malnutritional edema** frequently observed during war famine and similar conditions has also been classified as

a protein deficiency, although it is admittedly a partial inanition of mixed and variable type. Atrophy of the liver in association with this disorder was noted by Budzynski and Chelchowski ('16), Hülse ('17), Schittenhelm and Schlecht ('18), Enright ('20), Maase and Zondek ('20) and Prince ('21). Paltauf ('17) reported the weight of the liver as low as 980 g. (usually 1,000-1,200 g.), while Oberndorfer ('18) found it as low as 950 g. On the other hand, Richet and Mignard ('19) found hypertrophy of the liver common in ex-prisoners suffering from chronic inanition, but without edema.

As to the histological changes in the liver during human malnutritional edema, Paltauf ('17) and Oberndorfer ('18) mentioned capillary congestion and cell atrophy, with absence of glycogen and fat droplets. Paltauf also observed pericapillary edema. Nuclear vacuoles (noted by Oberndorfer) were thought to be related to the inclusion of erythrocytic fragments, as first observed by Branz. Maase and Zondek ('20) likewise found little hepatic glycogen. Schittenhelm and Schlecht ('19) observed hepatic hyperemia, but only slight fatty metamorphosis; while Enright ('20) noted almost constantly fatty degenerative changes in the liver-cells. Mann, Helm and Brown ('20) found the liver usually slightly cirrhotic in 200 necropsies. Fracassi ('22) reported hepatic capillary hemorrhages and slight increase of connective tissue.

In human **pellagra**, Morelli ('55) found the liver affected more frequently than any other organ (in 31 out of 37 autopsies), usually enlarged, soft and friable, yellowish in color and anemic. Fraenkel ('69-'70), however, reported the liver diminished in size in 28 out of 30 cases. Lombroso ('92) found hepatic lesions frequently, with decreased size of the liver in 18 out of 39 cases, and "brown atrophy" in 8. Tuzcek ('93) and Carraroli ('02) observed hepatic atrophy and fatty degeneration, and De Giovanni ('96) found the liver "small and undeveloped," according to Harris ('19).

Nicholls ('12) reported an average liver weight of 37½ ounces in African pellagrins, the normal being 52 ounces. Kozowsky ('12) found hepatic congestion and fibrosis; parenchyma atrophic, with degeneration, brown pigment and fatty infiltration of the gland-cells. Similar observations were made by Nicholls ('12, '13). Raubitschek ('15) reviewed the changes in the liver, which is sometimes enlarged, but usually decreased in size, with frequent brown atrophy and fatty degeneration. Similar changes were described by Marie ('08, '10), Lynch ('17), and Harris ('19).

Degenerative changes were found by Rondoni and Montagnani ('15) in the liver of guinea pigs on maize diet, and by Sundwall ('17) in various animals on protein-poor diet. Rondoni ('19) found the liver slightly above normal weight in guinea pigs on maize diet.

**Mineral Deficiencies.**—Von Hösslin ('82) observed fatty infiltration of the liver in young dogs on iron-poor diet.

In human **ricketts**, Whistler (1645), Seibold ('27), Comby ('01) and Pfaundler ('22) noted that the liver and spleen are often distinctly enlarged, although Stoeltzner ('03) and others failed to find any significant change in size. According to Vincent ('04) and Cheadle and Poynton ('07), the liver is sometimes enlarged, but usually normal in size.

In experimental rickets in puppies on calcium-poor diet, Voit ('80) found the liver slightly enlarged, while Dibbelt ('09) found it apparently atrophic. In rats with experimental rickets on various diets, Jackson and Carleton ('23) found the liver averaging above normal weight in the earlier stages, but becoming subnormal in severe rickets (Table 11).

**Vitamin Deficiencies.**—These include the effects of dietary deficiency in the vitamins A, B, and C.

**Vitamin A.**—Deficiency in this vitamin in rats caused no appreciable change in the liver, according to Emmett and Allen ('20) and Davis and Outhouse ('21). Tsuji ('20) and Meyerstein ('22) made a few observations on the liver in young white rats on diets deficient in vitamins A and B.

**Vitamin B.**—In adult human beriberi, Duerck ('08) recorded in 10 cases the weights of the liver, which varied from 557 to 1,480 g., showing congestion (venous stasis) and atrophic changes. Strong and Crowell ('12) reported hepatic ecchymoses, with acute congestion and degenerative changes. In infantile beriberi, Andrews ('12) in 18 necropsies found the liver often slightly enlarged, with congestion, and slight albuminous or fatty degeneration. Nagayo ('23) states that passive congestion and necrosis of the liver distinguish human beriberi from experimental polyneuritis.

In **experimental beriberi**, Funk and Douglas ('14) reported degenerative changes in the liver-cells of pigeons. Schnyder ('14), in white mice, cats, dogs, pigeons and fowls, found no definite lesion in the liver, aside from marked congestion (especially of the central veins). The liver-cells showed (glycogen?) vacuoles, but no fat. Tasawa ('15) in 200 fowls and 150 pigeons found the liver sometimes anemic; the weight usually slightly subnormal and the parenchyma cloudy. Douglas ('15) reported atrophy of the liver in pigeons, and McCarrison ('19, '21) found the same in deficiently fed pigeons, guinea pigs and monkeys. Brucco ('20) found in dogs no atrophy of the liver-cells (as occurs in starvation), but marked fatty degeneration. Findlay ('21) in fowls and pigeons observed marked congestion and fatty degeneration, with the nuclei often pale and vesicular, never in mitosis. Souba and Dutcher ('22) and Souba ('23) obtained significant losses in the weight of the liver in young chickens. Lopez-Lomba ('23) found slight, irregular losses in the liver of adult pigeons on vitamin-free diet, excepting a marked atrophy in the final period.

**Vitamin C.**—In human adult scurvy, Sato and Nambu ('08) found in general but little change in the liver, which was usually anemic or normal in blood content. No hemorrhages were observed, and the gall-bladder was filled with bile. Scherer ('13) noted hepatic fibrosis. Aschoff and Koch ('19) found variable changes, chiefly lobular fatty metamorphosis, either central or peripheral; sometimes fatty changes in the arterial endothelium. No hemorrhages were found; the usual amount of pigment occurred, and cirrhosis was noted once. Erdheim ('18) found congestion of the liver in 9 out of 31 necropsies of infantile scurvy. Hess ('20) reviewed the hepatic changes in scurvy, which frequently include congestion and occasionally cloudy or fatty degeneration, or cirrhosis. LaMer and Campbell ('20) found no change of weight in the liver of scorbutic guinea pigs. Bessesen ('23), however, found an apparent loss in the liver

weight during the earlier stages of scurvy, but a return to normal weight in advanced stages (Table 12).

Höjer ('24) describes in the liver of scorbutic guinea pigs variable atrophic cell changes, combined with (fatty) degeneration and necrosis with calcification.

**Aqueous Inanition.**—Schuchardt ('47) in pigeons on a dry barley diet with loss of 44 per cent in body weight found a loss of 41 per cent in the weight of the liver. Falck and Scheffer ('54) in a dog on dry biscuit with loss of 20 per cent in body weight observed an apparent loss of 25 per cent in the liver. Skoritschenko ('83) gave data on the change in water content of the liver, etc., in rabbits on dry diet.

Pernice and Scagliosi ('95a) in a dog on dry bread diet with loss of 24 per cent in body weight, found the liver at autopsy hyperemic, with slight thickening of the capsule. The gall-bladder contained a little thick fluid. Histologically there was an increase of interlobular stroma, sometimes showing slight round cell infiltration. All the veins appeared hyperemic, with thickened walls; in the portal vessels, the intima formed a deeply staining layer, rich in nuclei. The bile-ducts appeared widened, with lining cells sometimes hypertrophied. The parenchyma was normal in arrangement, but the cells appeared atrophic, notably around the central vein, where they also showed granular and fatty degeneration, staining poorly with alum carmine. A few mitoses were found. In 3 young chickens similarly subjected to dry diet, the liver showed marked passive hyperemia, especially in the region of the central lobular veins. The liver-cell cords appeared atrophic (from pressure atrophy), with poorly stained nuclei. Around the large veins, the cells were compressed, forming a yellowish layer. The interlobular connective tissue appeared thickened in places, with occasional infiltration of Glisson's capsule by small round cells, especially near hemorrhages. The bile-capillaries appeared unchanged, and mitoses were rare in the liver-cells.

Durig ('01) noted that in frogs during desiccation the loss in liver weight is nearly parallel to that in the body weight. In adult albino rats on a dry diet, Kudo ('21) found in the acute thirst series a loss of 37 per cent in the liver weight (with loss of 36 per cent in body weight), and in the chronic thirst series a loss of 55 per cent in liver weight (loss of 52 per cent in body weight) (Table 9). In young rats held at constant body weight from about 1 month of age by dry diets for various periods, Kudo ('21a) found the liver averaging above normal weight in all groups (Table 10), which recalls the persistent growth of the liver during the simple underfeeding experiments previously mentioned.

## CHAPTER XXI

### EFFECTS ON THE PANCREAS AND SALIVARY GLANDS

#### 1. THE PANCREAS

The marked effects of inanition upon the pancreas are of importance in relation to the general disturbance of the digestive system in various conditions of malnutrition. The possible metamorphosis of the pancreatic acini into islets of Langerhans during starvation is of especial interest in connection with the treatment of diabetes mellitus. After a brief summary, the effects of inanition upon the pancreas will be considered under (A) total inanition and (B) partial inanition.

#### SUMMARY OF THE EFFECTS ON THE PANCREAS

The pancreas during **total inanition** (or on water only) typically undergoes a marked atrophy. In adult man, the loss in weight usually appears roughly proportional to that of the whole body; but in atrophic infants the degree of atrophy is more variable, usually less than that of the whole body, and often showing an apparent increase in weight (sometimes due to syphilitic infection). In adult animals during inanition, the pancreatic atrophy is extreme, being as a rule relatively greater than that of the entire body. This applies to the advanced stages, however; the pancreatic loss in the early stages of inanition being relatively slight (guinea pig). In the young animals, the pancreas (like the other viscera) appears in general more resistant to loss in weight.

The gross atrophy of the pancreas during inanition is shown microscopically to be due chiefly to atrophy of the secretory acini. The gland cells undergo marked shrinkage. In the earlier stages of fasting the zymogenic granules increase at the expense of the outer (basal) zone (with uncertain changes in the mitochondria), but in later stages of inanition the gland cells become less granular and more homogeneous in appearance, and may undergo characteristic degenerative changes. The loss in the cytoplasm is much greater than that in the more resistant nucleus, following the general rule.

Lewaschew and Statkewitsch noted that the degenerating acini may fuse into syncytial masses, which may resemble the pancreatic islets in appearance. On account of the importance of the islets as endocrine organs, much interest has been taken in the question as to the possible metamorphosis of the exocrine acini into endocrine islets and *vice versa*, which has been claimed especially during inanition (and refeeding.) Laguesse has been the foremost proponent of this theory, supported by Dale, Vincent and Thompson, Fischer and Retterer. On the other hand, this doctrine has been vigorously opposed by Jarotzky, Rennie, Bensley, and Giannelli (with his coworkers Bergamini and Lampronti).

Bensley's evidence appears especially strong and Giannelli's measurements indicate that the apparent increase in islet tissue during inanition is merely relative, due to a much greater shrinkage in the secretory acini.

Upon refeeding after inanition, the pancreas recuperates rapidly and is soon restored to normal size and structure. The mitoses, which in young rabbits are suppressed or greatly reduced in number during inanition, become very numerous in the pancreas during the reconstruction period.

During the various forms of **partial inanition**, the changes in the pancreas have been much less extensively and thoroughly studied. In protein deficiencies, and in rickets and scurvy, no characteristic changes have been observed. In beriberi (deficiency of vitamin B), gross atrophy and microscopic degeneration have been noted. In thirst (aqueous inanition), the gross and microscopic changes (in animals) apparently resemble those found during total inanition, or on water alone, although no special study of the changes in the islets has been made.

#### (A) EFFECTS OF TOTAL INANITION ON THE PANCREAS

The effects upon the pancreas of man (adult and infant) will be reviewed first; followed by the effects in the lower animals.

**Human Adult.**—Lucas (1826) cited a case of starvation from Gerlach, and another from Ballin, in which the pancreas appeared normal. Willien ('36) stated that the pancreas becomes small and firm during inanition.

Bright ('77) in the case of starvation of Harriet Staunton, found the pancreas, like the other viscera, small and shrunken, but otherwise apparently normal.

Porter ('89) in the victims of the Madras famine, found the average pancreas weight in 9 plump men 3.85 ounces; in 181 emaciated men 2.2 ounces; in 4 extremely emaciated men 1.5 ounces. In 8 plump women, the pancreas averaged 2.3 ounces; in 121 emaciated women 1.8 ounces; in 4 extremely emaciated women 1 $\frac{3}{8}$  ounces. The greater weight in the well nourished was ascribed partly to interlobular fat. Microscopically no abnormality was noted. Gross atrophy of the pancreas in starvation was likewise observed by Formad and Birney ('91).

In starved adult man, Stschastny ('98) observed some necrotic areas in the pancreas, with distension of the ducts by secretion, and a few mast cells between the lobules.

Laguesse ('09a) confirmed in a man with gastric cancer Jarotzky's observation (on the mouse) that in starvation the pancreatic acini adjacent to the islets have an unusually high zymogen granule content. These "peri-insular zones" were observed by Gellé in the adult human pancreas under conditions of inanition.

Sternberg ('13, '21) concluded that "Atrophie des Pankreas, wie sie als Teilerscheinung eines allgemeinen Marasmus (im höheren Alter, bei kakechtischen Zuständen u.s.w.) sich entwickeln kann, äussert sich in einer oft sehr beträchtlichen Verkleinerung der Drüse, die dann meist eine walzenförmige Gestalt, ziemlich derbe Konsistenz und oft eine dunklere, bräunliche Farbe aufweist. Mikroskopisch findet sich eine Verkleinerung der Acini und ebenso

auch eine Verkleinerung der Drüsenzellen, welche keine besondere Pigmentierung zeigen."

Sobotta ('14) supported Laguesse's theory that the pancreatic acini may by inanition be temporarily transformed into islets.

Meyer ('17) found a weight of 65 g. in the pancreas of a man dead from starvation. Histologically the parenchyma seemed quite well preserved, except the pancreatic islets, which appeared small and shrunken away from the surrounding tissue. Some of the islets formed merely a fused mass of degenerated cells; but others were somewhat better preserved. Meyer remarks that glycosuria was not observed in this case, in spite of the degenerated condition of many islets.

Roessle ('19) from organ weights at 700 necropsies on soldiers concluded that in emaciating diseases (chronic fevers, etc.) the pancreas appears variable in the degree of its loss in weight.

In cases with emaciation, Krieger ('20) found the average weights for the pancreas as shown in the accompanying table, assuming Vierordt's normal (0.15 per cent of the body weight).

EFFECTS OF MALNUTRITION UPON THE WEIGHT OF THE HUMAN PANCREAS (KRIEGER '20)

Cause of malnutrition	No. of cases	Normal weight, grams	Observed weight, grams	Percentage decrease, per cent
Chronic diarrhea.....	5	97.8	54.0	44.8
Malignant growths.....	6	99.6	66.0	33.0
Chronic general infections.....	26	99.6	69.2	30.5
Tuberculosis.....	17	97.8	69.8	28.6

The decrease in weight appeared roughly proportional to the loss in body weight, but was relatively greater in the chronic diarrheas. In individual cases, the loss may reach 60 per cent. Macroscopically "Derbheit und Blutarmut" were characteristic; brownish pigmentation appeared in 1 case, with previous malaria. (Krieger says Prym sometimes noted a brownish color in general atrophy of the pancreas.)

In **atrophic infants**, De Tommasi ('94) noted a diminutive pancreas. Bloch ('05, '06) found the pancreas normal in some cases, but in others the gland cells showed marked general deficiency of zymogen granules. Some of the cells showed pycnotic nuclei with hyalin, degenerated cytoplasm and indistinct cell-boundaries. The islets of Langerhans appeared poorly differentiated. Bloch thought the deficiency in the pancreatic gland cells, and in the Paneth cells of the intestinal glands, might be of significance as a cause of pedatrophy.

Helmholz ('09), however, found the histological structure of the pancreas apparently normal in 10 cases of pedatrophy. Similarly Schelble ('10) in 32 cases, and DeVilla ('11) in 5 cases, could not find the pancreatic lesions described by Bloch.

Mattei ('14) found the pancreas usually rather low in weight (1.5-4.0 g.) and pale or reddish in color in 8 cases of atrophic infants with body weights of 2,200-3,100 g. The secretory acini appeared normal in structure, but there was a thickening of the fibrous capsule and stroma, with marked sclerosis in one case. The outer coat of the ducts and blood vessels also appeared somewhat sclerotic. The pancreatic islets always appeared increased in number and showed changes as follows:

“Les formations langerhansiennes présentent, en dehors de leur abondance, deux ordres d'altération appréciables: l'état vacuolaire ou pycnotique des noyaux cellulaires et la perte complète des limites des cellules langerhansiennes. Il y a ainsi dans de nombreux cas, comme un tassement de l'îlot qui n'en conserve pas moins un volume notable. La sclérose intrainsulaire est rare; nous l'avons vue dans deux cas, les traînées fibreuses, très fines, relient la coque péri-insulaire au centre de l'îlot affectant ainsi une disposition plus ou moins régulièrement rayonnante.”

Mattei concluded from this evidence that the pancreatic islets (like the hypophysis) show signs of functional hyperactivity in atrophic infants. Nobécourt ('16) stated that there is an increased number of islets and numerous transition forms to the secretory acini. Marfan ('21) also reviewed the pancreatic lesions in infantile atrophy.

In famine-stricken children of various ages, Nicolaeff ('23) found the pancreatic weight only 10-20 per cent subnormal for age. The microscopic structure is well preserved, but the cells appear small. The islets of Langerhans are very distinct, and even appear hypertrophied.

In my data from Minnesota atrophic infants (Table 3) the pancreas appears variable in weight. In some cases it appears very low, in others above normal. In some cases the high weight of the pancreas may be due to (unrecorded) syphilitic infection.

Among the **animals**, observations on the pancreas are more numerous. Lucas (1826) found no marked change in the gross appearance of the pancreas in starved animals of various species. Collard de Martigny (1828) in starved dogs and rabbits found the pancreas very small, firm, pale and anemic. Tiedemann ('36) reviewed the earlier observations upon the gross atrophy of the pancreas during inanition. Chossat ('43) found an average loss of 64.1 per cent in the pancreas of starved pigeons with a loss of about 40 per cent in body weight.

According to Traina ('04), Heumann ('50) noted a diminution in the size of the pancreas cells in starved pigeons.

Bidder and Schmidt ('52) found an apparent loss of about 85 per cent in the pancreas of a starved cat, with loss of about 50 per cent in body weight. Bourgeois ('70) reported the pancreas in starved animals (guinea pigs, rabbits, cats, dogs, etc.) as extremely atrophic and anemic, with average loss of 64 per cent in weight.

Heidenhain ('75) made a careful study of the pancreatic cell structure in dogs starved 30-48 hours and then fully refed with meat. He distinguished a first digestive period of 10 hours, a second digestive period of 10 hours (20

hours in all to complete digestion), and a subsequent fasting period. The tissue was fixed by alcohol and stained with carmine or hematoxylin. Two cell zones were described: an inner, poorly staining, granular one (next to the lumen); and an outer, more deeply staining, homogeneous zone, with the nucleus between the two zones. The granular inner zone is depleted in the first digestive period, causing actual decrease in cell volume; but during the second digestive period the granular zone is regenerated at the expense of the homogeneous zone, and the entire cell increases in volume. During fasting also the granular inner zone predominates; but in prolonged inanition the entire cell may diminish in volume, with a relative increase in the outer zone. The nucleus also undergoes certain changes in form and structure, being round during active digestion, but becoming often oval with irregular borders during inanition.

Ohlmüller ('82) and Voit ('94) recorded a weight of 37.7 g. in the pancreas of a well-nourished control puppy, while in a starved litter mate (with loss of about one-third in body weight) the pancreas weighed 26.6 g. In an adult dog starved on water only, Luciani and Bufalini ('82) found the pancreas atrophic and firm.

Lewaschew ('86) described in the pancreas certain cell-groups which appear intermediate between the islets and the secretory tubules. These intermediate groups rarely appear during total inanition (in dogs and especially cats), but are abundant in the well-fed, and apparently represent modified secretory acini. Lukianow ('88, '89) studied the changes in weight and water content of the pancreas and other organs in fasting pigeons.

Morpurgo ('88, '89, '89a) found mitoses in the pancreas of normal rabbits during a considerable part of their postnatal life. During starvation, however, the mitoses disappeared from all except one rabbit 20 days old, in which they were rare. On refeeding after inanition, the mitoses became abundant in the pancreas, 4 or more being visible in a single field. In starved pigeons, Morpurgo ('89b) found the pancreas cells reduced from an average of  $11.34 \times 8.54\mu$  to  $8.73 \times 6.74\mu$ , which would correspond to a loss of 52 per cent in volume. The decrease was chiefly at the expense of the inner granular zone of the cytoplasm, the nucleus being practically unchanged in size (average diameter of  $3.91\mu$  in the normal, and  $3.90\mu$  in the starved pigeons).

Nicolaides ('89) obtained in fasting dogs changes in the pancreas cells differing from Ogata's results on cold-blooded animals. Certain intranuclear eosinophilic plasmosomes persist during 24 hours of fasting, while other extranuclear red or violet (hematoxylin) stained bodies disappear during this period.

In fasting *Salamandra maculata*, Müller ('90) found a numerical increase in the pancreatic paranuclei, and certain changes in the filamentous and granular cytoplasmic zones; but no change in the nucleus, aside from an increase in chromatin.

Statkewitsch ('94) studied the structural changes in the pancreas and other organs in various animals (cat, dog, rabbit, guinea pig, pigeon, lizard, turtle, frog) fasting for various periods, with or without water. Flemming's fluid, mercuric chloride, Müller's fluid or alcohol were used as fixatives, with various stains. He concluded: "Das Endresultat der Veränderungen von Seiten der

Epithelialzellen des Pankreas bildet die Umwandlung derselben in helle, durchsichtige, glänzende, sich nicht färbende, polygonale Zellen, die ganze Anhäufungen bilden und denen von Professor Podwyssozky die Bezeichnung 'Pseudofollikeln' beigelegt worden ist. Dank meinen Untersuchungen und denen des Professor Lewaschew ist es erforderlich, gegenwärtig jene irrige Meinung vollkommen zu lassen, dass nämlich jede Zellhäufungen lymphatische Gebilde darstellen; und zwar erwiesen sie sich als nichts Anderes als das Resultat einer intensiven Veränderungen der Drüsenzelle."

Statkewitsch found in the pancreas cells during fasting an early increase in the outer homogeneous zone at the expense of the inner, granular zymogenic zone. The latter finally disappears, and the outer zone may stain more deeply. The acinar cells become smaller and more irregular in form, and may coalesce into syncytial masses with pycnotic nuclei. (Similar masses, "points folliculaires" were considered as lymph follicles by Renaut, and as "pseudofollicles" by Podwyssozky '82). While these masses resemble the islets of Langerhans, Statkewitsch agrees with Lewaschew ('86) that they are merely modified glandular epithelium. Such groups occur oftener in the fasting dog and cat, less often in the rabbit, guinea pig and pigeon. Intermediate forms also occur. The cylindrical cells lining the larger pancreatic ducts show cloudy swelling in the earlier stages of inanition; later there is granular degeneration, occasionally fatty degeneration and desquamation. No difference appears with or without water. The nuclei of the pancreas (as elsewhere) in general are less affected than the cytoplasm. They may become irregular in form, especially in the duct; and the nuclei in pycnosis may be reduced one-half in diameter. Vesicular nuclei are rare.

In guinea pigs on total inanition with average losses of 10, 20, 30 and 36 per cent in body weight, Lazareff ('95) found corresponding losses of 3.33, 5.33, 24.67 and 39.33 per cent in the pancreas (Table 5). The pancreas therefore apparently loses relatively little in the earlier stages of inanition, but undergoes marked atrophy later. Cell measurements indicated that at body loss of 20 per cent the pancreas cells had lost only 7 per cent in volume; but at body loss of 36 per cent the pancreas cells lost 42 per cent. The nuclear loss was very slight.

Carlier ('96) found the pancreas gland cells apparently active and rich in zymogen granules in the hedgehog at the end of hibernation. The islets of Langerhans appear small but numerous, with many large cells containing eosinophile granules.

Gulland ('98) in fasting salmon reported that "The pancreas was not often present in the portions of salmon from the rivers received for examination, but where it was to be seen the cells were generally shrunken and shrivelled, and contained no granules."

Brunner (unpublished work under Lukianow) in fasting rabbits with loss of 35 per cent in body weight found in the pancreas cells an average decrease of 10.11 per cent in length and 13.25 per cent in breadth; in the nuclei, the length decreased 3.09 per cent and the breadth 6.9 per cent.

Jarotzky ('98, '99) made extensive measurements on the diameters of the pancreas cells and nuclei in 5 series of white mice on total inanition and three

diets, with controls. There was a loss of about 30 per cent in body weight in each of the 4 test groups, with changes in cell measurements (compared with controls) as shown in the accompanying table. A distribution table was also

EFFECTS OF VARIOUS DIETS UPON THE DIMENSIONS OF THE CELLS IN THE PANCREAS OF WHITE MICE (JAROTZKY)

Diet	Days	Average percentage change in				
		Cell diameter		Nuclear diameter		Nuclear volume
		Long	Short	Long	Short	
Starch.....	10.0	-18.30%	-15.78%	+ 1.55%	+ 2.69%	+ 6.4%
Tallow.....	10.6	-17.69	-17.11	-11.05	- 7.50	-25.6
Inanition.....	3.7	-22.62	-15.72	-11.05	- 5.19	-23.1
Sugar.....	11.0	-39.02	-40.04	-21.07	-18.27	-48.3

given, grouped according to nuclear dimensions. The zymogen granules were markedly reduced in number during inanition and sugar diets, with certain changes on starch and tallow diets. The islets of Langerhans appeared as independent organs (not modified acini). "Sie betheiligen sich an deren secretorischen Thätigkeit, soweit man nach der Hypertrophie der anliegenden Lobuli und dem Reichtum derselben an Zymogen-Körnelungen beurtheilen kann, welche unter gewissen Verhältnissen (hauptsächlich bei totaler Inanition, ferner bei ausschliesslicher Talgdiät, sowie mitunter an normalen Thieren) beobachtet werden."

Nikolaides ('99) found in the cells of the pancreas and other glands of fasting dogs abundant fat granules, which he assumed to be derived by metamorphosis of the cell-proteins.

Sedlmair ('99) found in 2 starved cats, with losses of 51 and 55 per cent in body weight, a relatively slightly greater loss in the weight of the pancreas.

Laguesse ('99) maintained that the islets of Langerhans are not permanent structures, but capable of transformation into exocrine tissue, especially in certain favorable places, such as the tail of the pancreas in certain snakes (adder). Here the islets appear to be reduced to a minimum in number and volume in a few days of fasting, but after a longer inanition period (at least 6 weeks) they increase to a maximum in size and abundance. Laguesse ('09) likewise claimed to produce in the pigeon an experimental transformation of pancreatic acini into islets, and *vice versa*. In controls and refed animals he found 1.45-5.27 islets per cu. mm., while after fasting 8 days the number was increased, ranging from 2.69 to 8.42. Laguesse ('09a) reviewed more fully his "balance" theory of the islet metamorphosis in man.

Ssobolew ('02) found granules in the islet cells of transplanted pancreas (dog), most numerous during fasting and decreased on feeding carbohydrates. Konstantinowitsch ('03) in starving rabbits described the pancreatic cells as decreased in size and indistinct in contour. Fat droplets were found in a few of

the cells of the alveoli. In the fasting guinea pig, the fat droplets were more numerous, and very fine droplets occurred in the cells of the islets of Langerhans.

Braitmaier ('04) in the pigeon noted that granules are scarce in the pancreas cells 6 hours after feeding, but become abundant after 48 hours of fasting. The islets of Langerhans appear unchanged. Dale ('04), however, claimed both numerical and volumetric increase in the pancreatic islets of the toad during prolonged inanition. Numerous transitional stages between islets and acini were also observed. This conclusion was confirmed by Dale ('05) in the pancreas of an emaciated cat.

Pugliese ('05, '05a) studied the pancreas in 5 dogs, normal, fasting (time not stated) and refed 1-4 days. He confirmed the observations of Morpurgo and Statkewitsch as to the reduced size of the acini and cells, with indistinct outlines, during fasting. The cytoplasm appeared very scanty and sparsely granular. No confluent masses were noted. On refeeding, the pancreas made rapid recovery. Even after the second meal the alveoli appeared larger, the cells taller, and the nuclei rounded, with distinct nucleoli; and in many cells the inner granular zone had become distinct. On the fourth day of refeeding, the structure appeared normal.

Vincent and Thompson ('07) obtained data for the dog, cat, pigeon and frog, supporting the doctrine that the effect of inanition is to increase the "leptochrome" (islet) tissue at the expense of the zymogenic epithelium. Rennie ('09), however, found great variation in the islets in different parts of the pancreas, and was unable to produce them experimentally by starvation in *Tropidonotus natrix* in parts of the gland normally free from them. He therefore (like Jarotzky) concluded that the islets are independent structures.

Strong evidence against the theory of the transformation of acini into islets by inanition was given by Bensley ('11), who perfected an ingenious technique (by injection of neutral red), which stained the islets differentially and made it possible to count the total number of the entire gland. In 6 guinea pigs fasting (with water) 5-8 days, together with a larger number of normal controls, he found much individual variation, but no evidence of a change in the number of the islets by inanition. He also confirmed this by similar experiments on dogs.

Morgulis ('11) found that in the salamander, *Diemyctylus viridescens*, the pancreatic cells and nuclei resemble those of the liver and duodenum in their reactions to inanition. "During inanition the whole pancreas suffers great reduction in size, so that after 3 months it is scarcely more than a mere shred attached to the intestine, and a microscopic examination shows that it has become very poor in cells." After 2 months of inanition (with loss of 21 per cent in body weight) the pancreatic cell volume has decreased 55.6 per cent, and the nucleus 37.2 per cent. After 3 months (with loss of 36 per cent in body weight) the cell volume has decreased 71 per cent, and the nucleus 35.2 per cent. The nucleus also becomes more oval in form during inanition. On refeeding, the pancreas rapidly regains its normal size and structure. Even in 4 days, the reduced cell volume has increased 94.3 per cent and the nucleus 27.4 per cent. In 8 days the cell volume has increased 135 per cent and the nucleus 33.1 per cent. In young albino rats stunted by underfeeding, the pancreas

cells appear much smaller in volume than in full-fed controls. The nuclei (as in *Diemyctylus*) were less affected than the cytoplasm, but showed no change in form.

Fischer ('12) studied the pancreas in frogs and tritons fasting up to 4 months. His results confirmed the transformation theory, indicating an increase in the number of islets with marked reduction in the exocrine tissue and pancreas as a whole. Intermediate forms were observed in both normal and fasting conditions. Upon refeeding after a period of inanition, the islets were found to undergo an involution, first disappearing almost entirely, later returning to normal number, some islet cells being retransformed into acini. Changes in the acinar gland cells during inanition were also described.

Retterer ('13) claimed that during inanition in the guinea pig, not only are the exocrine gland cells transformed into islet cells, but the islet cells may form erythrocytes!

Giannelli, Bergamini and Lampronti ('14), on the other hand, found no change in the number, size or structure of the pancreatic islets in the turtle dove, rabbit and rat (?) during inanition. This result was confirmed and extended by Giannelli and Bergamini ('14, '14a) for the fasting lizard (*Lacerta muralis*) and frog (*Rana esculenta*). In both of these forms, measurements of the areas in cross section showed a *relative* (not absolute) increase in the islets, which undergo but slight shrinkage in comparison with the marked atrophy of the pancreatic tubules during inanition. Thus in the frog the islets present an increase of about one-third in relative area, and in the lizard they appear nearly doubled; although actually slightly decreased in absolute size.

Giannelli ('16) likewise found that in the teleost fish, *Tinca vulgaris*, the pancreas is greatly atrophied by inanition. Measurements from serial sections showed 25 islets per sq. mm., as compared with 23 per sq. mm. in normal controls. They likewise showed little change in structure, size or distribution of the islets. The cells of the secretory tubules appeared greatly decreased in size and homogeneous in structure, the granular zone having disappeared.

Mann ('16) found that in the hibernating gopher (*Spermophilus tridecemlineatus*) the pancreatic islets undergo but very slight changes in structure.

Barry ('20, '21) noted practically normal weight of the pancreas in the stunted offspring of pregnant albino rats subjected to severe underfeeding.

McCarrison ('21) found great atrophy of the pancreas in starved pigeons, the loss in pancreatic weight appearing relatively nearly twice as great as that in the body as a whole (Fig. 35).

Miller ('22) studied the effect of acute inanition and vitamin deficiency upon the mitochondria of the epithelium in the pancreas and intestine of the albino rat. No marked changes were observed except in advanced stages with marked cell degeneration, which involved a transformation of the rod-like mitochondria to granular forms, with a reduction in their number, or sometimes total disappearance.

Trowbridge, Moulton and Haigh ('18) and Moulton, Trowbridge, and Haigh ('22a) noted that in steers on various planes of nutrition the relative weight of the pancreas is not much affected.

Okuneff ('22) found that in fasting rabbits with loss of 30-40 per cent in body weight there is no apparent change in the lipoidal fat in the cells of the pancreas. He ('23) claims that the rod-like mitochondria of the gland cells fail to undergo the normal transformation into secretory granules, but instead form an increased number of granular chondriosomes.

#### (B) EFFECTS OF PARTIAL INANITION ON THE PANCREAS

A few observations upon changes in the pancreas during the various forms of partial inanition have been recorded.

In **malnutritional edema** (chiefly due to protein deficiency), Schittenhelm and Schlecht ('18) observed no gross change in the human pancreas. In young rats on a diet deficient in tryptophan, Cramer ('23) noted thyroid lesions, cutaneous myxedema, and a marked edema of the pancreas.

In human **pellagra**, according to Raubitschek ('15), the pancreas usually shows no characteristic changes.

Seibold ('27) stated that in human **rickets**, the pancreas is "meistens sehr verhärtet," but this does not seem to have been confirmed by later observers.

McCarrison ('21) found that autoclaved rice and similar diets (deficient in protein, salts, vitamins, etc.) cause marked atrophy of the pancreas in pigeons and monkeys. Histologically the shrunken cells show decreased granulation and sometimes a considerable amount of necrobiosis, with congestion, hemorrhages, etc. Occasionally round cell infiltration and increased fibrous stroma were noted, especially in the periphery of the pancreas in pigeons. "No marked changes were found in the islets of Langerhans, although in a few cases in monkeys these structures appeared to form a higher proportion of the sections than in health."

Rondoni ('22) in guinea pigs on maize diet (mixed deficiency of protein, etc.) reported a hyperplasia of the pancreatic islets of Langerhans.

With diets deficient in **vitamin A**, Emmett and Allen ('20) found more or less passive congestion in the pancreas of rats, while Davis and Outhouse reported the pancreas normal in histologic structure in most cases. In young rats on vitamin-free (polished rice) diets, Tsuji ('20) noted atrophy of the pancreatic alveoli in severe cases only.

In pigeons with **beriberi** (due to deficiency in vitamin B), Funk and Douglas ('14) noted signs of degeneration in the pancreas and other organs. In an extensive study of experimental polyneuritis in chicks and pigeons, Tasawa ('15) found atrophy of the pancreas. McCarrison ('19a, '21) concluded that in pigeons a dietary deficiency in vitamin B has results similar to a complete vitaminic starvation, causing marked atrophy of the pancreas. Findlay ('21) in beriberi of fowls and pigeons found the loss in pancreas weight roughly proportional to the loss in body weight (Table 13). The alveolar cells showed cloudy swelling, with pale, vesicular nuclei; but no degenerative changes were noted in the islets. Souba ('23) found the pancreas somewhat subnormal in weight in young chicks on diets deficient in vitamin B. In adult pigeons on a vitamin-free diet, Lopez-Lomba ('23) noted a preliminary increase in pancreatic weight, followed by a progressive decrease.

In **scurvy** (deficiency of vitamin C), Sato and Nambu ('08) found pancreatic hemorrhages in but one out of 13 necropsies. Aschoff and Koch ('19) observed no characteristic changes in the human pancreas. Hess ('20) found no other reference to pancreatic lesions in scurvy. Bessesen ('23) found the weight of the pancreas variable in scorbutic guinea pigs, but with no evident tendency to atrophy.

In **thirst** (aqueous inanition), Schuchardt ('47) found that in pigeons on dry barley diet, with loss of 34 per cent in body weight, the pancreas apparently lost 56 per cent. Similarly, Falck and Scheffer ('54) in a dog on dry diet, with loss of 20 per cent in body weight, noted an apparent loss of 36 per cent in the pancreas.

Pernice and Scagliosi ('95a) studied the pancreas in a dog subjected to dry diet, with loss of 24 per cent in body weight. The pancreas appeared grossly atrophic. Microscopically there was hyperemia and gland cell atrophy, the lighter zone being relatively increased and the granular zone sometimes indistinct. The connective tissue stroma was slightly increased.

In adult albino rats on a dry diet, Kudo ('21) found that in the acute thirst series (with body loss of 36 per cent) the average loss in the weight of the pancreas was 53 per cent, and about the same in the chronic thirst series (with body loss of 52 per cent) (Table 9). In a rat on complete total inanition, with body loss of 47 per cent, the pancreas lost 59 per cent. In a series of young albino rats held at constant body weight by a relatively dry diet from age of 4 weeks for various periods, Kudo ('21a) found a progressive increase in the weight of the pancreas from 16 to 46 per cent in the different groups (Table 10). This indicates that during inanition in young rats the pancreas shows the same persistent growth tendency as found in the other viscera.

## 2. THE SALIVARY GLANDS

Observations upon the changes in the salivary glands during inanition are scarce. The few available data will be summarized briefly, and then reviewed in detail under (A) total inanition, and (B) partial inanition.

### SUMMARY OF THE EFFECTS ON THE SALIVARY GLANDS

During **total inanition** (or on water only) the salivary glands of adults undergo a marked atrophy, the loss of weight in these glands (at least during experimental inanition in animals) being relatively greater than that of the entire body. In the young, the salivary glands appear more resistant to inanition and in atrophic infants they may even increase in weight.

Microscopically, the atrophy of the salivary glands during inanition is found to be due to decrease in the parenchyma, the parotid gland cells presenting the typical picture of atrophic degeneration. The loss is chiefly in the cytoplasm, which loses its characteristic granulation, undergoes cloudy swelling, and later may present vacuolar or fatty degeneration. Traina claims that the salivary epithelium (rabbit) contains normally a variably lipoidal content, which, as in other glands, is unaffected by inanition. The nuclei are (as elsewhere) relatively resistant, but may undergo pycnotic degeneration.

In the submaxillary gland, the crescents (demilunes) become smaller and may undergo degenerative changes, but the mucous cells appear in general somewhat more resistant.

The salivary duct epithelium is somewhat more resistant than the glandular epithelium, but in the later stages of inanition it may likewise undergo the characteristic degenerative changes, and desquamation.

Upon **refeeding** after a period of inanition, the salivary glands promptly recuperate and apparently regain their normal size and structure within a few days. There is a reappearance of mitosis, which is suppressed during inanition.

During **partial inanition**, data upon changes in the salivary glands are very scarce, but the typical atrophy apparently occurs upon diets deficient in protein, vitamins, etc. A very marked atrophy has been shown to occur during thirst (aqueous inanition), which probably exhausts the salivary glands in an effort to prevent dryness of the mouth.

#### (A) EFFECTS OF TOTAL INANITION ON THE SALIVARY GLANDS

**Human Adult.**—Lucas (1826) cited from Ballin's "Erfahrungen" a case of starvation during religious dementia in which the parotid, submaxillary and sublingual glands appeared "regelwidrig klein." Aside from this, the only reference found concerning the salivary glands in adult human inanition was that of Meyer ('17) in a case of voluntary starvation. He found that in the parotid gland "Many of the peripheral acini look shrunken and the connective tissue framework surrounding them is too large. Some of the degenerate-looking acini take an acidophile stain. Other acini have almost completely disappeared, although these changes have affected only relatively small portions of the gland. The remaining protoplasm is often toothed or cogged as in macerated specimens, and the nuclei are collected near the center of the cell. Vacuoles are common and large. The mucous cells seem better preserved. Accumulations of lymphocytes are found about some of the ducts . . . The submaxillary and sublingual glands show somewhat less marked though similar changes."

No reference to changes in the salivary glands in **atrophic infants** were found in the literature. The weights observed by me for the parotid, submaxillary and sublingual glands in 3 cases (Table 3) would appear to indicate an increased weight for these organs in most cases, but the conclusions are uncertain on account of the lack of adequate norms for comparison.

Among the effects of starvation on **animals**, Tiedemann ('36) mentioned that the salivary glands, like the other glands, incurred a marked loss in substance.

Bidder and Schmidt ('52) in a starved cat with loss of about 50 per cent in body weight, found an apparent loss of 65 per cent in the weight of the salivary glands.

Valentin ('57) noted apparent losses of 13 and 15 per cent, respectively, in the salivary glands of hibernating marmots with losses of 8 and 35 per cent in body weight.

In Chapter XIII were mentioned the observations of Manassein ('69) on the "*Harderian gland*," which may possibly refer to the infraorbital salivary gland, in the fasting rabbit.

Ohlmüller ('82) and Voit ('94) observed a loss of about 39 per cent in the weight of the salivary glands in a fasting young dog, with loss of 32 per cent in body weight.

Morpurgo ('88, '89, '89a) found no mitoses in the parenchyma of the parotid and submaxillary glands in fasting rabbits of various ages, although mitoses appeared both in normal controls and in rabbits amply refed after a period of inanition. In a subsequent study, Morpurgo ('90), refed 4 rabbits, 6-18 months old, for 4 or 5 days after total inanition 6-10 days. Mitoses were found in variable numbers in the submaxillary glands (though not in the controls). None were found in the parotid gland.

Seidenmann ('93) incidentally noted relatively few crescent cells in the orbital and submaxillary glands of dogs in a fasting condition (time not stated).

Statkewitsch ('94) studied the changes in the salivary glands of various animals, especially the cat, dog, rabbit and guinea pig, fasting for various periods (up to death), either with or without water. The **parotid** gland showed marked changes, the diameter of the lobules being reduced one-fourth to one-half by atrophy of the epithelial cells. The nuclei decrease but slightly in size. In the earliest periods, the cells appear to swell slightly, with cloudy cytoplasm and obscure granulation. With progressive inanition the granules become more distinct. In later stages the cells appear in various stages of degeneration, with coarse albuminous granules. Occasionally fatty degeneration was observed in a few lobules, with osmic-staining droplets of various sizes. The fatty degeneration appeared most frequent in the guinea pig and cat (especially those on total inanition), more rarely in the dog, and not at all in the rabbit. In the cat, some lobules appeared to undergo mucous degeneration, intermingled in later stages with fatty degeneration. The nuclei of the parotid cells in general become more irregular in outline, and may become pycnotic (sometimes vacuolated) in the degenerated cells. The epithelium of the parotid ducts likewise undergoes atrophic degeneration, and occasionally desquamation. The peripheral rodDED cytoplasm becomes granular, later frequently showing fatty degeneration.

In the **submaxillary** gland, Statkewitsch similarly found decreased size of the lobules due to atrophy of the gland cells, which appeared alike in those fasting with or without water. The crescents of Gianuzzi decrease progressively in size and number, becoming rare toward the end of inanition. The crescent and serous cells may show granular, but never fatty, degeneration. In the mucous cells, in the second half of inanition, fatty granules and droplets appear and increase in size and number. They may represent a metamorphosis of mucinogen granules into fat, but fat droplets are rare in the saliva. The nuclear changes occur as in the parotid, especially in the mucous cells. The submaxillary duct epithelium shows cloudy swelling in the earlier stages; later the rodDED cytoplasm shows granular, but rarely fatty, degeneration.

Nikolaides ('99), in opposition to Statkewitsch, observed that in dogs fasting 2-30 days numerous fatty granules appear in the cells of the demilunes of Gianuzzi in the submaxillary glands, although only vacuoles were found in the cell of dogs dying from inanition. Since these fat granules occurred only in the demilune cells, Nikolaides thought they represent a metamorphosis of the protein granules *in loco*, rather than a fatty infiltration from other sources.

Noll ('02, '02a) found the crescent (demilune) cells of Gianuzzi in dogs fasting 11 days or more, on water only, but the normal granular structure of the cells appears replaced by vacuoles which he interpreted as secretion droplets.

Traina ('04) made a careful study of the fat in the various tissues, using scarlet red and other fat stains. He found that a variable number of lipoidal granules appears normally in the epithelium of the salivary glands of the rabbit. These granules are not affected by starvation, although the ordinary connective tissue fat disappears. The atrophy of the gland cells during inanition affects chiefly the cytoplasm, the nucleus remaining nearly unchanged.

Pugliese ('05, '05a) in fasting dogs (time not stated) found the **parotid** gland tubules very small, with indistinct cell boundaries, and the cytoplasm reduced to a thin layer. No fatty degeneration was found (versus Statkewitsch). The nucleus usually remained rounded, with a distinct nucleolus. After 1 day of refeeding, the cells appeared larger, with more definite outlines; and in 4 days nearly normal size and structure had been regained. In the **submaxillary** gland during inanition the gland cells showed similar atrophy (no fatty degeneration). The nucleus, however, here, as normally, is usually flattened and peripherally placed. The crescents (demilunes) of Gianuzzi appeared smaller and less numerous. Recuperative changes were apparent after 1 day of refeeding, and by 4 days apparently normal conditions were restored.

In the submaxillary gland of starved dogs, Morgulis, Howe and Hawk ('15) found the cytoplasm "thin" and generally unstained. Many cells appeared without nuclei. The crescent (demilune) cells stained darkly. The general appearance was that of a resting gland.

Some of the atrophic changes produced in the submaxillary gland of the adult albino rat by acute inanition (water only) are evident by a comparison of Figs. 92 and 93. The ducts appear to undergo relatively less atrophy than the acini, and therefore become relatively more prominent.

**Hibernation.**—Calabresi ('19) studied the *parotid*, *submaxillary* and *retro-lingual* glands of the hibernating hedgehog, with special reference to the mitochondria and related structures. He found that the mitochondria, which are filamentous in the active gland, become during hibernation curved, irregular and sometimes fragmented. They also undergo certain changes in position. No evidence was found to support the theory of a transformation of the mitochondria into secretory granules. There is, however, during hibernation an accumulation in the inner cell zone of granular material probably representing early stages of secretory granules.

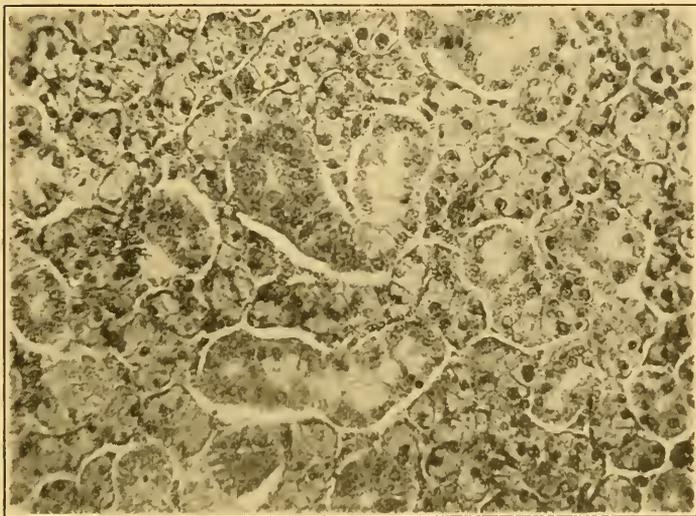


FIG. 92.—Photograph of a section of the submaxillary gland in a normal adult albino rat. The acini are chiefly serous; a few of the larger acini contain mucous cells (light). Zenker fixation; alum-hematoxylin stain.  $\times 250$ .

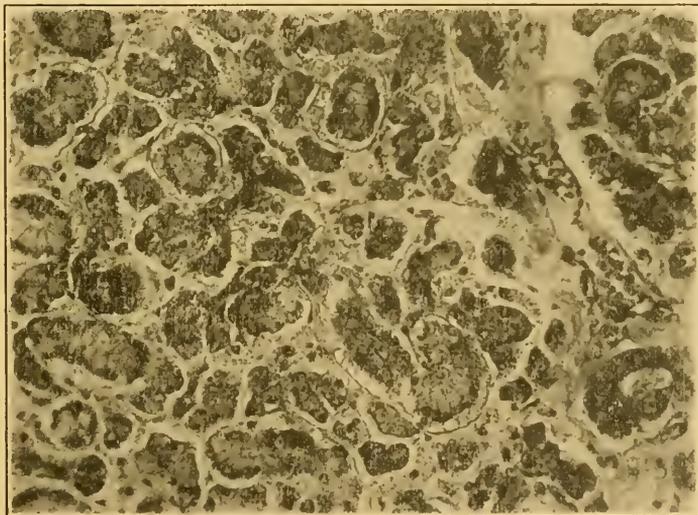


FIG. 93.—Photograph of a section of the submaxillary gland in an adult albino rat after 12 days of inanition (on water only) with loss of 32 per cent in body weight. Compare with Fig. 92, noting the marked atrophy of the secretory acini, with relative increase in the amount of the stroma. Zenker fixation; alum-hematoxylin-eosin stain.  $\times 250$ .

## (B) EFFECTS OF PARTIAL INANITION ON THE SALIVARY GLANDS

Only a few data are available as to the effects of partial inanition upon the salivary glands. In malnutritional edema and similar disorders (ascribed chiefly to protein deficiency, for reasons given in Chapter V), Lubarsch ('21) mentioned hemosiderin deposits in the epithelial cells of the salivary and other glands.

In young rats on **vitamin-free** (polished rice) diets, Tsuji ('20) found atrophy of the parotid alveoli in severe cases only. In the submaxillary gland, the serous portion showed degenerative atrophy of the ducts and alveoli, while the mucous portion was unaffected.

McCarrison ('21) in deficiently fed monkeys noted a marked loss (20-30 per cent) in the weight of the submaxillary glands, which occurred in animals becoming emaciated on diets variously deficient in protein, vitamins, etc. McCarrison remarks that probably this atrophy involves some impairment of function, and cites the observation by Sullivan and Jones (Publ. Health Rep., 1919, 34:1068) that the saliva of pellagrins has a peculiarropy consistency.

Höjer ('24) finds in guinea pig **scurvy** an early atrophy of the salivary glands (confirming Toverud). Both mucous and serous alveoli are affected.

During **thirst**, the salivary glands are subjected to an unusual strain, in order to secrete sufficient saliva to prevent drying of the oral mucosa. In a dog on dry food with loss of 20.7 per cent in body weight, Falck and Scheffer ('54) observed an apparent loss of 33.7 per cent in the weight of the salivary glands.

In adult albino rats on a dry diet, Kudo ('21) found in the acute thirst series (with loss of 36.1 per cent in body weight) a loss of 57.6 per cent in the parotid glands, and of 47.1 per cent in the submaxillary glands. In the chronic thirst series (with loss of 52.4 per cent in body weight), the parotid glands showed a loss of 69.7 per cent, and the submaxillary glands a loss of 64.5 per cent. In a rat on total inanition (with loss of 47.2 per cent in body weight), the parotid glands showed an apparent loss of 67.6 per cent, and the submaxillary glands a loss of 63.3 per cent (Table 9).

In a series of young albino rats held at constant body weight by relatively dry diet for various periods, beginning at about 4 weeks of age, Kudo ('21a) noted that the parotid glands within 1-2 weeks showed an average decrease of 47.6 per cent. For longer periods the loss remained about the same. In the submaxillary glands, a similar loss was apparent, excepting the first group, where it was somewhat less (Table 10). It would therefore appear that during aqueous inanition the salivary glands do not show the persistent growth tendency found in the liver, pancreas and various other organs.

## CHAPTER XXII

### EFFECTS ON THE RESPIRATORY TRACT. LUNGS, TRACHEA AND LARYNX

Terminal bronchopneumonia appears to be unusually frequent in conditions of inanition and malnutrition, including most of the deficiency diseases. Following a brief summary, the effects of inanition upon the lungs will be considered under (*A*) total inanition and (*B*) partial inanition. A few data for the larynx, trachea, etc. are also included.

#### SUMMARY OF THE EFFECTS ON THE RESPIRATORY TRACT

The lungs appear exceedingly variable in weight during inanition, partly on account of the variable degree of congestion present, and especially through the frequency of secondary infections, notably terminal bronchopneumonia, which may increase the weight of the lungs in the late stages. In uncomplicated cases of **total inanition**, or on water only, the lungs are usually normal in appearance. The loss in weight of the lungs in such cases is usually relatively less than that in the body as a whole, though sometimes equal to, or even relatively greater than, that of the entire body. In the young, the lungs usually appear more resistant to loss in weight. There is also a moderate loss in the weight of the larynx and trachea, relatively about half that in the body as a whole.

The **structural changes** may include a general atrophy of the alveolar walls. There is frequently localized atelectasis in some regions and emphysema in others. The lining epithelium may undergo fatty degeneration, and the frequent terminal infections are associated with the usual leukocytic infiltration and hemorrhagic exudation into the alveolar lumina, etc. The mucosa of the trachea and bronchi likewise shows atrophy with frequent degenerative and inflammatory changes in the later stages of inanition. The pleura usually appears normal, excepting cases of secondary infections.

On **refeeding** after a period of inanition the lungs, as a rule, promptly regain their normal weight and structure.

In the various forms of **partial inanition**, the lungs show even greater variability in weight and structure. In malnutritional *edema* and *pellagra* they seem to undergo in general the same atrophic changes as during total inanition. In *ricketts* and *scurvy*, the thoracic deformity may impede respiration and result in pulmonary disorders with increased liability to infection. Congestion and edema of the lungs are very frequent in human *beriberi*, though not in experimental beriberi of animals. In *thirst* (aqueous inanition) the lungs usually show pronounced atrophy, with degenerative changes, including pigmentation, round cell infiltration and some fibrosis.

## (A) EFFECTS OF TOTAL INANITION OR ON WATER ONLY

The data for the human species, adult and infant, will be presented first, followed by the observations upon the lower animals.

**Human Adults.**—Donovan ('48) noted a normal appearance of the lungs in victims of the Irish famine. Cyr ('69) found pulmonary gangrene very frequent during starvation in the insane, as noted first by Guislain in 1836. Bright ('77) observed in the case of Harriet Staunton a small tubercular lesion in the apex of the left lung, which probably had no relation to the starvation. In a man who died from voluntary starvation, Voelkel ('86) found the lungs full of air throughout, and dry upon sectioning.

Porter ('89) in the victims of the Madras famine found the lungs in general wasted, aside from cases with pulmonary complications. In 22 men in whom both lungs appeared free from disease, the ratio of lung weight to body weight averaged 1:84.4; and in 23 women, 1:78.9. The normal for Hindus is not known, but for Europeans Quain's norm of 1:37 for men and 1:43 for women was cited.

In a starved man, Meyer ('17) noted a brick-red color and slight pneumokoniosis in the lungs. The left lung weighed 324 g., and was nearly normal; the right lung weighed 385 g., with complete adhesion of the pleura. Meyer estimated that this represented a loss of 28.6 per cent in the weight of the lungs, with a loss of about 40 per cent in body weight.

Sison ('20) by percussion found hyperresonance of the lungs in adults during short periods of voluntary total inanition. He thought this hyperresonance probably due to marked loss of water in the lung tissue.

Beitzke ('21) stated that atrophy of the entire lung is found in old age and in various cachectic conditions.

In atrophic infants, Parrot ('68, '77) observed steatosis in the lungs and other viscera. Granular masses and oily drops were found in the alveoli. The fat content may rise to 17 or 18 per cent of the total dry weight of the lung; the normal being 6 per cent. Tardieu ('80) stated that in starvation the lungs of infants are very pneumatic and bright red in color.

Ohlmüller ('82) found the lungs weighing 85 g. in an atrophic infant of 8 weeks (body weight 2,381 g.) while in a well-nourished control of the same age the lungs weighed 106.4 g. (body weight 4,150 g.).

In two infants dead from inanition, Cantalamassa ('92) found the lungs at necropsy somewhat collapsed and slightly crepitant. DeTommasi ('94) mentioned pulmonary atelectasis in infantile atrophy.

Thiercelin ('04) stated that in athreptic infants the pulmonary lesions (aside from complications, such as bronchopneumonia) are steatosis, alveolar emphysema and softening of the lung. Steatosis is more marked in the periphery of the lung, especially in the postero-superior region. Sometimes this lesion presents merely fatty granules in the alveolar epithelium; or there may be accumulations in the alveolar lumina. Alveolar emphysema always accompanies the steatosis, and is associated with athreptic dyspnea. Softening

of the lung is rare, and results from thrombosis in the pulmonary arteries or branches.

Lucien ('08) concluded that in athreptic infants the respiratory tract shows no changes beyond the usual lesions from terminal pulmonary infections, basal congestion of the lungs and catarrhal bronchopneumonia. Lesage ('11) likewise held that in uncomplicated cases the lungs are usually intact and the respiration normal. Lesage ('14) recorded a weight of 26 g. in the lungs of an atrophic infant of 4 months (normal 35 g.). In congenital spasmodic atrophy, however, Lesage and Cleret ('14) claimed that the fundamental lesion, sclerosis, occurs in the lungs as well as in the other viscera. Nobécourt ('16) concluded that the lungs show no characteristic changes in cachectic infants.

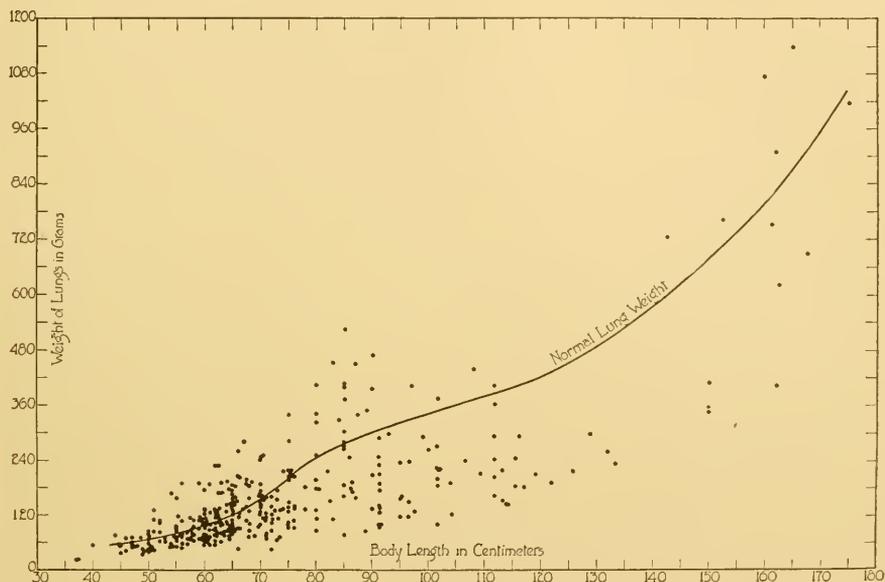


FIG. 94.—Graph showing the individual weights of the human lungs in atrophic cases, up to adult. Data from various sources. The normal curve is from data compiled by Prof. R. E. Scammon. In most of the cases the lungs appear subnormal, although the weight is frequently increased by terminal bronchopneumonia.

In famine-stricken children of various ages, Nicolaeff ('23) found the lungs often edematous, but frequently 40–50 per cent subnormal in weight according to age.

In Fig. 94, the weights of the lungs are plotted against the body length, in all available data in atrophic cases up to 20 years of age. It will be noted that while in most cases the lungs appear subnormal in weight, they are quite variable, and some even above normal. Many of the latter doubtless represent cases with terminal bronchopneumonia, which is very common. The same applies to Fig. 95, representing the lung weight in atrophic infants only.

In Table 2, the average weight of the lungs (excluding pneumonia cases) in atrophic infants is given, in comparison with the normal from different stand-

points. Compared with the norm for the final body weight, the lungs averaged 24.5 per cent above normal (or 12.8 per cent in the Minnesota cases alone). Compared with the normal for the maximum body weight observed during life, the lungs appeared 4.5 per cent below normal; for body length (height) they appeared 20.6 per cent below normal; while for age they appeared 21.2 (16.7) per cent below normal. Some data for individual cases are given in Table 3. These weights indicate that the lungs in atrophic infants have suffered relatively less in weight than has the body as a whole. The lungs are markedly affected in weight by congestion, however, so conclusions are somewhat uncertain.

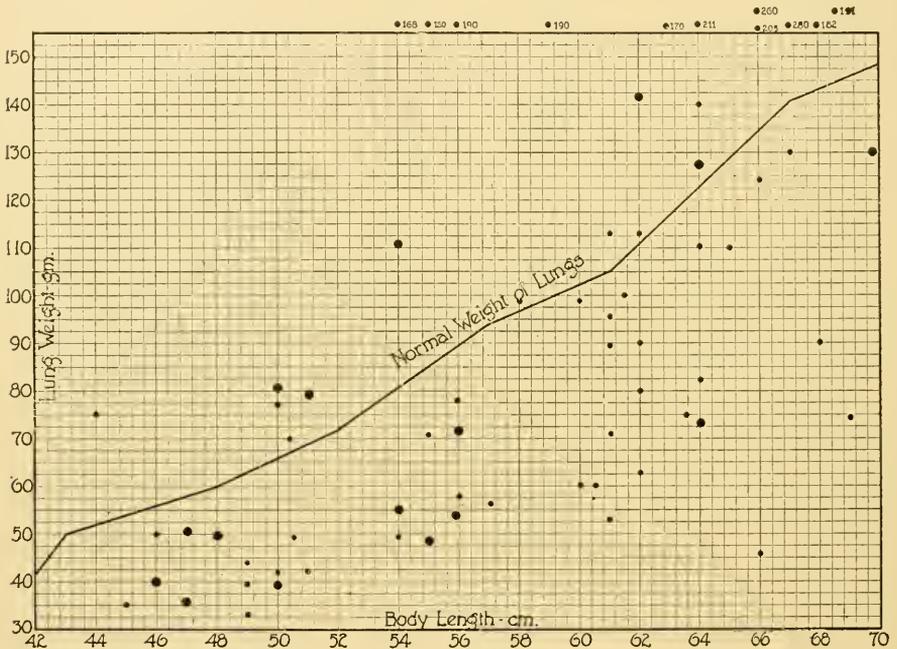


FIG. 95.—Graph showing the individual weights of the lungs, according to body length, in atrophic infants. The larger dots represent original Minnesota cases; the others are from various sources. The curve of normal weight of the lungs is from data compiled by Prof. R. E. Scammon. The *e* is marked individual variation, though the weight is subnormal in most cases.

In **animals**, Lucas (1826) found no abnormality in the appearance of the lungs after death from starvation. In starved dogs and rabbits, Collard de Martigny (1828) observed that the lungs were pink, crepitant and bloodless; the tracheal mucosa pale. This was confirmed by Bourgeois ('70).

Chossat ('43) in pigeons on total inanition, with average loss of about 40 per cent in body weight, found a loss of 22.4 per cent in the weight of the lungs and of 21.4 per cent in the trachea and larynx.

In a starved cat with loss of about 50 per cent in body weight, Bidder and Schmidt ('52) noted an apparent loss of 25.9 per cent in the lungs, and of 26.2 per cent in the larynx and trachea. In a cat losing 33 per cent in body weight, Voit ('66) observed an apparent loss of 17.7 per cent in the weight of the lungs.

In *hibernating* marmots with loss of 8.3 per cent in body weight, Valentin ('57) found an apparent loss of 4.14 per cent in the lungs with larynx, etc.; with body loss of 35.5 per cent, the lungs, etc. lost 44.6 per cent.

In 47 adult starved rabbits with average loss of about 39 per cent in body weight, Manassein ('68, '69) found an average loss of 40 per cent in the weight of the lungs. In 8 rabbits  $3\frac{2}{3}$  months old, with loss of 33 per cent in body weight, the lungs lost 30 per cent; and in 3 rabbits 23-25 days old, with loss of 35 per cent in body weight, the lungs lost 25 per cent. In 2 starved cats, the lungs apparently lost 29 per cent in weight; and in 2 starved crows the lungs lost 45 per cent. In 5 rabbits amply refed after a period of inanition, the lungs appeared 22 per cent above normal weight.

In dogs of various ages starved for various periods, Falck ('75) noted that pleura and trachea appeared moist and glistening. The lungs were emphysematous, and variably reddish in color.

In 6 fasting rabbits (with or without water) with loss of 43.7 per cent in body weight, Skoritschenko ('83) found an average loss of 21.75 per cent in the weight of the lungs.

In 3 rabbits and 1 kitten starved to death with or without water, Coen ('90) found the pleura normal but the lungs atelectatic in some regions. In some of the alveoli and around the bronchi in places there appeared accumulations of red blood cells and especially leukocytes, indicating small foci of inflammation. The bronchial mucosa and walls appeared normal, but the large bronchi contained some mucus with leukocytes.

Tonninga ('93) noted changes in the nitrogen content of the lungs and other viscera in fasting rats and rabbits. Lukianow ('88, '89) investigated the changes in water content of the lungs and other organs in pigeons during inanition.

Voit ('94) found the weight of the lungs practically the same in a dog fasting 22 days with loss of 32 per cent in body weight and in a normal control of the same litter.

Bich ('95) observed normal appearance in the pleura and lungs (anemic) in starved dogs. Bechterew ('95) found that in fasting newborn kittens and puppies the lungs lose relatively less than the body as a whole, and hence gain in relative weight.

In fasting guinea pigs with average losses of 10, 20, 30 and 36 per cent in body weight, Lazareff ('95) found corresponding losses of 0.93, 0.31, 0.62 and 4.97 per cent in the weight of the lungs (Table 5).

In hyperthermic animals (dog, rabbit, guinea pig), with or without water, Kusmin ('96) noted that the lungs and heart may increase in weight (probably in association with their increased functional activity), even during loss in the body weight. Bloody pleural exudates were also observed.

In 3 fasting rabbits (on water only), Weiske ('97) found the apparent loss of weight in the lungs over 50 per cent, with loss of 35-41 per cent in body weight. Sedlmaier ('99), on the other hand, found a slight increase in the weight of the lungs in 1 starved cat (body weight loss 50.6 per cent), and a loss of about one-third in another (body weight loss 54.6 per cent).

Konstantinowitsch ('03) found the lungs congested and unchanged in weight in starving rabbits. No fat was found in the alveolar epithelium of starved rabbits and guinea pigs. Opie ('04) found a decreased number of eosinophile cells in the lung of guinea pigs during prolonged fasting. Roger ('07) noted the water content of the lungs and other organs in a fasting rat. Beeli ('08) in cats killed at various stages of inanition found the lungs collapsed and nearly normal in appearance, with but slight apparent loss in weight in the earlier stages, but proportional to the loss in body weight in the extreme stage.

In guinea pigs on acute inanition (water only), Rondoni and Montagnani ('15) found the lungs normal in appearance; in chronic inanition (underfeeding), the lungs appeared slightly hyperemic, and irregularly atelectatic; some of the bronchi showed slight hemorrhagic suffusion.

Sundwall ('17) in starved albino rats found the lungs extremely congested, the alveolar walls thickened and the alveoli often filled with blood.

In adult albino rats on acute inanition (water only) with loss of 33 per cent in body weight, Jackson ('15) found a loss of 31 per cent in the weight of the lungs; and in chronic inanition, with body loss of 36 per cent, a loss of 40 per cent in the lungs (Table 4). In rats held at constant body weight by underfeeding from 3 to 10 weeks of age the lungs lost only 15 per cent. Stewart ('18) observed a loss of 26 per cent in the lungs of rats underfed from birth to 3 or 10 weeks of age; but a slight increase (3 per cent) in the lungs of those held at birth weight for 16 days (Stewart '19). Barry ('20, '21) found the lungs 39 per cent below normal weight in the stunted offspring of albino rats severely underfed during pregnancy (Table 4).

In young albino rats amply refed after underfeeding (maintenance) from 3 to 12 weeks of age, Stewart ('16) found the lungs still somewhat below normal weight in 1 week, but somewhat above thereafter. Jackson and Stewart ('19) found the lungs practically normal or above in weight upon refeeding to 25, 50 and 75 g. in body weight after underfeeding from birth for various periods (Table 7). In rats underfed by Jackson and Stewart ('20) from birth to 3, 10 and 20 weeks, and then refed to adult size, the lungs appeared slightly subnormal (12-15 per cent) in weight, but 31 per cent above normal in those refed after underfeeding nearly 1 year (Table 8).

Asada ('19) noted intense congestion of the capillaries and small arteries of the lung and other organs in rabbits fasting 11-20 days, with loss of 28-52 per cent in body weight. Trowbridge, Moulton and Haigh ('18, '19) and Moulton, Trowbridge and Haigh ('22a) in steers on various planes of nutrition found the lungs nearly proportional to the body weight. Terroine ('20) noted the changes in the fat content of the lungs and other organs of fasting animals.

Ott ('24) found the weight of the lungs in fasting frogs so variable as to render conclusions uncertain. There appears to be a marked increase in lung weight (not due merely to water absorption) in the earlier stages; this persists throughout in the female, but in the male the lungs show a decrease in the later stages (Table 6).

## (B) EFFECTS OF PARTIAL INANITION

The effects of partial inanition include deficiencies of protein (malnutritional edema, pellagra, etc.), of salts (rickets), of vitamins (A, B and C) and of water.

In "**cachexia aquosa**" of sheep, Fröhner and Zwick ('15) mentioned the lungs as puffed and whitish.

In human **malnutritional edema**, Hülse ('17) found the lungs at autopsy "häufig klein, stark retrahirt, anämisch, schlaff, an den Rändern vielfach atelektatisch." Schittenhelm and Schlecht ('18) observed in the lungs "meist Oedem, Bronchitis and bronchopneumonische Herde." Enright ('20) noted marked reduction in the size and weight of the lungs and other organs.

In **pellagra**, Tuczek ('93) noted atrophy and fatty degeneration of the lungs and other organs. Marie ('08, '10) found atrophy of the lungs and other organs (especially those supplied by the vagus). Nicholls ('12) found an average lung weight of  $9\frac{1}{3}$  ounces (the normal being  $13\frac{1}{2}$  ounces) in 8 African pellagrins. Raubitschek ('15) stated that the pulmonary lesions in pellagra frequently include edema, hyperemia, emphysema, and chronic adhesive pleurisy. Harris ('19) reviewed the pathology of pellagra, including marked alterations in the lungs.

In human **rickets**, Seibold (1827) found the lungs adherent to the pleura, or collapsed, often purulent. Cheadle and Poynton ('07) mentioned the lungs among the organs affected by rickets. Wohlaer ('11) pointed out that respiration may be greatly impeded by the thoracic deformity in rickets, resulting in dyspnea, bronchitis and catarrhal pneumonia.

Jackson and Carleton ('22, '23) found no regular or important changes in weight of the lungs in albino rats at various stages of experimental rickets (Table 11).

Daniels, Armstrong and Hutton ('23) observed that in rats diets deficient in **vitamin A** weaken the immunity of the organism, with resultant infection of the respiratory tract, involving "snuffles" and (in young rats) pus formation in the paranasal sinuses and mastoid cells. Similarly Beach ('23) found a nasal discharge, as well as pustules in the mouth, pharynx and esophagus, in chicks with ophthalmia on diets deficient in vitamin A.

In human **beriberi**, Ellis ('98) observed edema (usually slight) of the lungs 78 times in 125 cases. Duerck ('08) gave data showing exceedingly variable weight of the lungs in 11 cases of beriberi and ('08a) stated that the lungs are usually edematous. Strong and Crowell ('12) noted congestion and edema of the lungs in a case of adult beriberi. Andrews ('12) likewise found extensive hypostatic congestion and a variable amount of edema at 18 necropsies in cases of infantile beriberi. McCarrison ('21) cites various observations indicating that pulmonary edema is very frequent in human beriberi, whereas it appears rare in experimental beriberi of birds. Similarly, Nagayo ('23) mentions the enlargement and general passive congestion of the lungs as a feature distinguishing human beriberi from experimental polyneuritis.

In experimental beriberi (polyneuritis) in 200 fowls and 150 pigeons on polished rice diet, Tasawa ('15) found no noteworthy changes in the gross appearance of the lungs.

Voegtlin and Lake ('19) found degenerative changes in the lungs of cats, dogs and rats with polyneuritis on diets deficient in vitamin B. Emmet and Allen ('20) found passive congestion of the lungs and other organs in rats on diets deficient in vitamin B, but no appreciable change on diets deficient in vitamin A.

McCarrison ('21) noted that an autoclaved rice diet (mixed deficiency of protein, vitamins, etc.) apparently resulted in a loss in weight of the lungs in monkeys, but an increased weight of the lungs in guinea pigs and pigeons.

In infantile **scurvy**, Erdheim ('18) reported pulmonary complications in 24 out of 31 cases; bronchitis occurred in 11, and bronchopneumonia in 13. The thoracic deformity may explain the respiratory disorders. Hart ('12) found pulmonary hemorrhages in scorbutic monkeys. Hess ('20) reviewed the pathology of scurvy, concluding that pulmonary congestion is nearly always present. Aside from terminal pneumonia and edema, however, the lungs appear remarkably free from abnormality. Pulmonary hemorrhages are less common than might be expected. Subpleural hemorrhages and terminal pneumonia are found in experimental scurvy in guinea pigs.

Bessesen ('23) in guinea pigs dying from scurvy found a marked increase in the weight of the lungs, which he thought might be due to terminal pneumonia (Table 12).

In **thirst** (aqueous inanition), the lungs might be expected to be particularly affected by the dessication. In 5 pigeons on dry diet, with loss of about 44 per cent in body weight, Schuchardt ('47) noted an apparent loss of only 13 per cent in the lungs. Falck and Scheffer ('54), in a dog losing about 20 per cent in body weight on a dry diet, found an apparent loss of 26.9 per cent in the weight of the lungs, trachea and larynx. Bowin ('80) found that in dogs on dry diet the lungs and other organs lost in weight much as during total inanition, and that there was no marked change in water content of the lungs.

Pernice and Scagliosi ('95a) observed that in a dog which died after 11 days on dry diet, the pleura was apparently normal and the lungs pale and anemic. Histologically, the pulmonary vessels appeared congested, and some of the alveolar lumina contained blood. There was a general connective tissue sclerosis, and in many places small round cell infiltration. Some of the alveolar walls appeared atrophic. The medium-sized and small bronchi were affected, the mucosa showing small cell infiltration. The epithelium was poorly stainable, with some desquamation. There was an exudate with red blood corpuscles and leukocytes containing black pigment granules. In 3 young chicks similarly subjected to dry diet, the lungs showed general congestion. The interlobular connective tissue and most of the alveoli contained red blood corpuscles. The bronchi appeared inflamed, and the bronchial walls and interlobular connective tissue contained much black pigment.

In adult albino rats on a dry diet, Kudo ('21) found in the acute thirst series (body loss of 36 per cent) a loss of 44 per cent in the weight of the lungs; in the

chronic thirst series (body loss 52 per cent), a loss of 51.5 per cent in the lungs, and in a rat on total inanition (body loss 47 per cent), a loss of 52.7 per cent in the lungs (Table 9). In young albino rats held at constant body weight on a relatively dry diet from age of 3 weeks for various periods, Kudo ('21a) found no significant change in the weight of the lungs (Table 10).

## CHAPTER XXIII

### EFFECTS ON THE URINARY TRACT. KIDNEYS AND BLADDER

Although not so marked as in many other organs, the effects of inanition upon the urinary tract are sufficient to justify more attention by the urologists. The changes are extensive in advanced stages of malnutrition, and especially in certain types of partial inanition, such as pellagra and thirst. Following a brief summary, the effects of inanition upon the urinary tract will be considered under (*A*) total inanition, and (*B*) partial inanition. The available data refer chiefly to the kidney, with a few observations upon the urinary bladder, ureters and urethra.

#### SUMMARY OF EFFECTS ON THE URINARY TRACT

During both total and partial inanition in the adult organism, the **kidneys** undergo atrophy and loss of **weight** to a variable degree, but usually relatively much less than the loss in the body as a whole. In the young, the kidney is still more resistant to loss in weight, and may even increase considerably while the growth in body weight is suppressed by chronic inanition.

In **structure**, the kidney usually appears nearly normal in the earlier stages of inanition, during which the cell-atrophy is much less conspicuous than in many other organs. In later stages, there may be congestion and progressive degenerative changes, which appear exceedingly variable according to the species, age, individual, region of the kidney, length and type of inanition, etc.

In general the change first observed (aside from congestion) is cloudy swelling in the epithelium of some of the convoluted tubules and Henle's loops. Changes occur also in the mitochondria and related structures, rods, brush border, etc., which have an uncertain relation to the decrease in urinary function. Later the cytoplasm may undergo granulo-fatty or vacuolar degeneration. Nuclear atrophy is less marked, but especially in later stages there is a progressive shrinkage of the nuclei, with a variable degree of pycnosis, and finally karyorrhexis or karyolysis. Casts of various types frequently occur in the tubules, and in extreme cases there may be total degeneration of glomeruli and tubules. Hemorrhages and interstitial sclerosis, pigmentation, etc., are somewhat rare and usually slight in extent.

The atrophy and parenchymatous degeneration of the kidney are not specific for total inanition, but occur likewise during the various types of partial inanition (as well as in many other abnormal conditions). The changes are particularly severe in certain forms of inanition, such as pellagra; and especially during aqueous inanition (thirst), which apparently causes an intense renal irritation, with round cell infiltration in addition to the above mentioned

degenerative changes. In general, the renal changes during inanition in many respects resemble those of a parenchymatous (tubal) nephritis.

Upon adequate **refeeding** after a period of inanition, the kidney usually soon regains its normal size and structure; but in case of severe lesions, traces may persist for a considerable time.

In the **urinary bladder**, the atrophy and loss of weight during inanition appear in general somewhat greater than in the kidney, although relatively less than in the body as a whole. During various forms of total or partial inanition, the bladder sometimes shows a marked increase (instead of a loss) in weight, caused perhaps by infection in the condition of lowered resistance. No marked lesions of the bladder have been described, however, excepting in scurvy (guinea pig). The few observations upon the **ureters** and **urethra** during the various forms of inanition have revealed no significant changes.

#### (A) EFFECTS OF TOTAL INANITION, OR ON WATER ONLY

The effects upon man (adult and infant) will be reviewed first, followed by the data for the lower animals.

**Human Adult.**—Lucas (1826) cited from Ballin's "Erfahrungen" a case of starvation (in religious dementia) in which the kidneys and ureters appeared normal; the bladder small and thick-walled. Willien ('36) concluded that during inanition the kidneys are small and firm; the bladder normal, with pale mucosa. In a girl of 19 years who died from starvation due to an esophageal stricture, Schultzen ('62, '63) found a slight granulo-fatty degeneration of the kidneys, which appeared somewhat small and hyperemic, with increased stroma. Curran ('74) noted that in an old native woman, greatly emaciated from starvation, the kidneys appeared relatively large and the surface granular. On incision, the kidney substance was tough, and bloody serum exuded from the cut surface. In the case of starvation of Harriet Staunton, aged 35, with loss of 40 per cent in body weight (final weight 74 pounds), Bright ('77) found the kidneys small but normal in appearance. The right kidney weighed  $3\frac{3}{4}$  ounces, and the left 4 ounces, which would indicate that they had lost relatively little in weight.

Popow ('85, '85a) in a case of inanition from esophageal stricture observed albuminuria, with decreased amount of urine. The kidneys showed hemorrhages, round cell infiltration, and atrophic degeneration (cloudy swelling, granulation) in the epithelium of the renal tubules. In a large man of 64 years who died from voluntary starvation, Voelkel ('86) reported the urinary bladder empty and the kidneys "normal, nur etwas schlaff."

Porter ('89) in autopsies on victims of the Madras famine (226 men, 155 women and 78 children) found in the men an average weight of 2.87 ounces (range  $1\frac{1}{2}$ – $6\frac{1}{8}$  oz.) in the right kidney and 3 ounces ( $1$ – $10\frac{1}{4}$ ) in the left kidney. In the women (excluding 1 horseshoe kidney weighing  $5\frac{1}{4}$  ounces), the right kidney averaged 2.64 ounces ( $1\frac{3}{8}$ – $4\frac{3}{4}$  oz.), and the left kidney 2.7 ounces ( $\frac{7}{8}$ – $5\frac{3}{8}$  oz.). The ratio of kidney weight to body weight in the men was 1:214; in the women, 1:192. Porter concluded that although these weights of the

kidney are low, on account of general emaciation, the ratio to body weight is higher than the European normal (1:240, according to Quain). Superficial pigmentation of parts of the cortex appeared in 5 men, 5 women and 1 child. The kidneys appeared anemic in 31 men (18 per cent), 36 women (29 per cent) and 14 children (22 per cent); and were more or less fatty in 73 men (42 per cent), 82 women (66.6 per cent) and 31 children (48.4 per cent). In about  $\frac{1}{3}$  of the women and  $\frac{1}{2}$  of the men and children the microscopic appearance of the kidney was nearly normal, excepting congestion and desquamation of cells in 21 men, 2 women and 3 children. In 4 extremely emaciated men, average age about 42 years, without apparent disease, the right kidney averaged  $2\frac{5}{8}$  ounces; the left  $2\frac{3}{4}$  ounces. Similarly in 4 markedly emaciated women (age 55 years), the right kidney averaged 2 ounces, the left  $2\frac{1}{2}$  ounces. The renal substance appeared anemic and fatty in all of these women and 3 of the men. Porter concluded that in general the kidneys in these men wasted relatively somewhat more than the body as a whole; but in the women somewhat less.

In a man who died after 35 days of starvation, Stschastny ('98) found various stages of "albuminous and granular" degeneration in the renal epithelium; also hyperemia, especially in the glomeruli.

In a man starved 60 days (on water only), with estimated loss of about 40 per cent in body weight, Meyer ('17) found a weight of 115 g. in the left kidney and 101 g. in the right (loss estimated at 49.16 per cent). The renal cortex was thin, but otherwise the gross appearance was normal. In stained sections, multiple small hemorrhagic areas were visible, with pronounced atrophy and degeneration of the renal parenchyma. Some of the glomeruli were completely destroyed, only blood corpuscles being left, while others appeared very much shrunken.

Lusk ('17) and Morgulis ('23) give an extensive review of the changes in the urine during starvation in man and animals.

In data from the adult organ weights in autopsy records of the Johns Hopkins Hospital and the New Orleans Charity Hospital, Bean and Baker ('19) found the kidney weights much influenced by the general state of nutrition (body weights not available). In 597 white males the kidneys varied from an average of 291 g. in the extremely emaciated group to 379 in the fat and obese groups. In 436 white females, the corresponding range (average) was from 277 to 448 g. In 252 negro males, the corresponding range was 252-333 g.; and in 228 negro females, 228-341 g. Obviously diseased organs were excluded.

Rubner ('19) stated that the underfeeding due to war conditions in Germany resulted in a decreased size of the kidneys and other organs. Roessle ('19), however, concluded from the organ weights in 700 soldiers that the kidney weight is but slightly, if at all, depressed by conditions producing general emaciation (chronic fevers, etc.). The general average weight of both kidneys was 306.7 g.; in a selected group of 89 cases with sudden death, representing a better norm, the average was 317.7 g.

Krieger ('20), on the other hand, from a smaller number of autopsy records (at Jena) representing various conditions involving malnutrition and emacia-

tion, concluded that the kidney weight is markedly decreased in such cases, though least among the chronic infections. In the accompanying table of average weights, 0.48 per cent of the body weight (Vierordt's norm for 20-25 years) is assumed as normal for the males. For females, Thoma's average of 276 g. is taken as the norm. All the cases included in the table are males, excepting the first group (6 males and 5 females). Cases directly involving the kidney (*e.g.*, renal tuberculosis) are excluded. Krieger states that the

AVERAGE WEIGHT OF KIDNEYS IN EMACIATED ADULTS (KRIEGER '20)

Cause of inanition	No. of cases	Normal weight, g.	Observed weight, g.	Percentage decrease	Percentage of body wt.
I. Without chronic organic disease. . . . .	11	286.0	182.6	36.0	0.546
II. Chronic diarrhea. . . . .	7	312.9	183.5	41.0	0.546
III. Malignant growths. . . . .	25	318.7	232.0	27.5	0.556
IV. Chronic general infections (not tb.). . . . .	31	318.7	268.0	15.5	0.724
V. General tuberculosis. . . . .	39	312.9	257.0	17.6	0.710
VI. Various cases in the aged. . . . .	20	{ 318.7 276.0 <sup>1</sup> }	221.4	{ 30.5 19.7 <sup>1</sup> }	0.518

<sup>1</sup> Allowing for age change; using Thoma's norm for 60-80 years.

individual variations in weight were greater in the kidneys than in the heart. The strongly atrophic kidneys were almost always hyperemic (excepting 2 cases of chronic diarrhea). Since in various cases of human fasting up to 30 days the urinary secretion remained nearly normal, Krieger concluded that an extensive simple atrophy of the kidney from inanition may cause no appreciable functional disturbance.

In order to see whether the war conditions had affected the organ weights, Weber ('21) compared the data from 1,257 autopsies at Kiel for the years from 1914 to 1918, inclusive. Only apparently normal organs were included. The body weights were not available. The average (without capsule) in the males for the right kidney was 135 g.; for the left, 145 g. In the females, the average for the right kidney was 122 g.; for the left, 128 g. On comparing the period of general good nutrition (1914-15) with that of subnutrition (1916-18), no significant difference was found in the average weight of the kidneys.

In **malnourished infants**, Parrot ('77) emphasized steatosis as the most characteristic change in the various organs, including the tubules of the kidneys. He also found venous thrombosis and uratic infarcts.

Ohlmüller ('82) recorded a weight of 25 g. for the kidneys in an atrophic infant of 8 weeks (body weight 2,381 g.), while in a well nourished control of the same age the kidneys weighed 32.3 g. (body weight 4,150 g.).

Thiercelin ('04) stated that the renal lesions in atrophic infants are often severe. The tubular steatosis (of Parrot) occurs as deposits of fatty granules or droplets in the cells of the convoluted tubules. Irregular deposits of fat may cause deformity or varicose appearance of the tubules. The glomeruli present no lesions, aside from congestion. In the pyramids, the fatty granules and droplets are more irregular. Thiercelin says the work of Simmonds ('96)

indicated that these renal lesions may be related to a true parenchymatous nephritis.

In 571 necropsies at the N. Y. Foundling Hospital, on children from newborn to 5 years, Bovaird and Nicoll ('06) concluded that in general the kidney weight varies directly with the body weight, although exceptions occur.

Lucien ('08) concluded that in athrepsia the kidneys are congested; and abundant deposits of urates usually color the infarcts in the tubules of Bellini a bright orange-yellow. In a more detailed study of the renal lesions in athreptic infants, Lucien ('08b) found the kidneys macroscopically normal in most cases. Capillary congestion, glomerular sclerosis, and granulations in the epithelium and lumen of the convoluted tubules and ascending limb of Henle's loops were noted. The granulations are due to urate of soda, forming yellow streaks (infarcts) in the tubes of Bellini. Tubular steatosis was not observed. Lucien concluded that the athreptic renal lesions are not specific, but may occur in all the infantile dystrophies.

Helmholz ('09) studied the histological changes in 6 cases of pedatrophie. "In den Nieren fand sich zumeist trübe Schwellung des Epithels, zweimal Kolloid-degeneration, sonst aber lagen normale Verhältnisse vor."

Schelble ('10) incidentally observed the renal histology in 28 cases of pedatrophie, but noted no constant or characteristic changes. Mönckeberg ('12) described the general atrophic changes in the kidneys and other organs resulting from malnutrition.

Maillet ('13) in athreptic infants noted slight renal lesions, including cloudy swelling or fatty degeneration in some convoluted tubules; occasionally pycnosis and cytoplasmic atrophy in the intermediate segments, and slight sclerosis of Henle's loops.

Mattei ('14) recorded the weights of the kidneys in several athreptic infants. He noted marked renal congestion and slight sclerosis of the glomeruli, but concluded that in general the kidney presents no constant lesions of importance. Lesage ('14) found a renal weight of 18 g. (normal 25 g.) in an atrophic infant of 4 months. Lesage and Cleret ('14) in congenital spasmodic atrophy of infants failed to find in the kidney the sclerosis which was characteristic in most organs.

Nobécourt ('16) reviewed the previous work on infantile atrophy, including the renal lesions, which are usually comparatively slight. The true parenchymatous nephritis sometimes found is ascribed to complications.

Marfan ('21) stated that in athreptic infants the weight of the kidneys appears variable, either normal or decreased. In infants dying before the end of the first month, the deposits of urate of soda (considered by Virchow as normal in the newborn) in the tubules of Bellini, calices, etc. are frequent and characteristic of malnutrition.

In famine-stricken children of various ages, Nicolaëff ('23) found the kidneys less atrophic than the liver, sometimes appearing normal, sometimes hyperemic. In hydremic, edematous subjects, the kidney on section may be pale. The renal epithelial cells appear swollen, with indistinct contours and small Malpighian glomeruli. The urine in these cases is not albuminous.

The weights of the kidneys in atrophic infants from various sources are shown by the graph in Fig. 96, plotted against body length. The larger dots represent original observations on Minnesota cases. It will be noted that in most cases the weights are below normal, although some cases are definitely above.

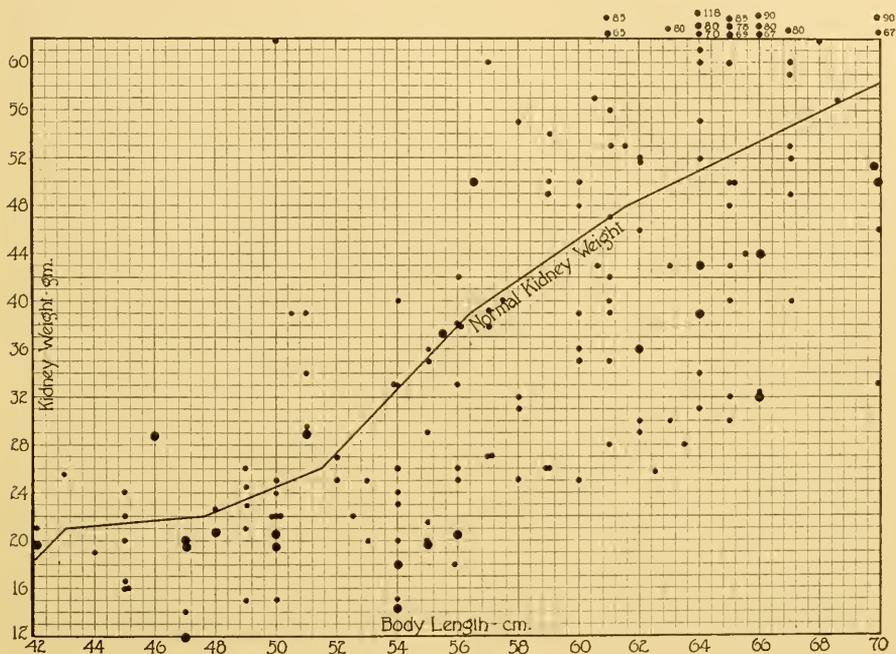


FIG. 96.—Graph showing the individual weights of the kidneys, according to body length, in atrophic infants. The larger dots represent original Minnesota cases; the others are from various sources. The curve of normal kidney weight is from data compiled by Prof. R. E. Scammon. Although most of the cases are below normal weight, there is much individual variation, and many are above normal.

In Table 2, the percentage changes in the average weights of the kidneys in atrophic infants are estimated in various ways, according to all available data. Thus in comparison with the normal for the corresponding final body weight, the kidneys averaged 20.5 per cent above normal (or 13.7 per cent for the Minnesota cases alone). Compared with the normal for the maximum body weight recorded during life, the kidneys averaged 1.5 per cent above normal. Compared with the normal for body length, the kidneys averaged 1.0 (or 7.6) per cent below normal; while according to age they averaged 19.4 (or 18.4) per cent subnormal in weight. The individual data for several of the Minnesota cases are given in Table 3. It would thus appear that in malnourished infants the kidneys in general are very resistant to loss in weight, ranking not far behind the brain in that respect.

Among the **animals**, numerous observations on the kidneys during total inanition (or on water only) will be presented in chronological order, excepting some studies of the changes related to the functional condition, especially

during hibernation and short fasting periods, which will be grouped together at the end of this section.

In starved dogs and rabbits, Collard de Martigny (1828) found the kidney tissue firm and anemic in appearance; the mucosa of the urinary bladder also pale.

Chossat ('43) estimated an average loss of 31.9 per cent in the weight of the kidneys in pigeons on total inanition with loss of about 40 per cent in body weight.

Heumann ('50) is said to have noted "granular degeneration" in the kidneys and liver of starved pigeons.

Bidder and Schmidt ('52) in a starved cat with loss of about 50 per cent in body weight found (in comparison with a control) an apparent loss of only 6.2 per cent in the kidneys; while the urinary bladder apparently *increased* from 2.50 to 5.36 g. in weight. Voit ('66), however, found an apparent loss of 25.9 per cent in the kidneys of a starved cat with 33 per cent loss in body weight.

In 47 adult starved rabbits with average loss of 39 per cent in body weight, Manassein ('68, '69) noted an apparent loss of 23 per cent in average weight of the kidneys. In 8 younger rabbits ( $3\frac{2}{3}$  months old) with loss of about 33 per cent in body weight, the apparent loss in kidney weight was 39 per cent. In 3 rabbits 23–25 days old, however, with loss of about 35 per cent in body weight, the kidneys apparently *gained* 13 per cent in weight. Two starved cats showed an apparent average loss of 47 per cent in kidney weight, while in 2 crows the loss was only 19 per cent. In 5 rabbits amply refed after a period of inanition, the kidneys appeared 4 per cent above normal in weight.

Manassein found constant albuminuria in the starving rabbits. The kidney tubules showed all stages of degeneration from cloudy swelling to complete disintegration. Some tubules were collapsed, others filled with fat droplets. The Malpighian corpuscles were frequently hyperemic. These changes were sometimes found persistent even in the rabbits refed after inanition.

In the **urinary bladder**, Manassein found a remarkable increase in average weight during inanition. In the 47 adult rabbits (body loss 39 per cent), the bladder gained 45 per cent; in the 8 rabbits  $3\frac{2}{3}$  months old (body loss 33 per cent) the bladder gained 126 per cent; in the 3 rabbits 23–25 days old (body loss 35 per cent), the bladder gained 83 per cent; in the 5 rabbits refed after inanition, the bladder appeared 56 per cent above normal. In 2 starved cats, the bladder weight appeared unchanged.

In various starved animals (mammals and birds), Bourgeois ('70) noted that the kidneys were pale, with average loss of 37 per cent in weight, or relatively slightly less than that of the whole body. The urinary bladder was contracted. Lépine ('74) stated that the kidneys of starved animals are often found normal. Carville and Bochefontaine ('75) found the kidneys very small in a starved dog; and Luciani and Bufalini ('82) found them atrophic, hard and fibrous. Falck ('75) in starved dogs of various ages found the kidneys firm and usually brownish in color, with atrophic adipose capsules. The *urinary bladder* appeared white; the mucosa wrinkled, with no lesions. The *urethra* was normal.

In starved rabbits, Mankowski ('82) observed that the kidneys appeared anemic, and Skoritschenko ('83) determined the changes in water content. Ochotin ('85, '85a, '86) studied the histological changes in rabbits with variable losses in body weight. In the extreme group, with body loss of 30-36 per cent, the kidney tubules showed marked degeneration, but unequally in different tubules. In some tubules, the epithelium appeared normal; in others the cells showed cloudy swelling, granular degeneration or fat droplets. The nuclei were variable in appearance. The Malpighian corpuscles were hyperemic. The connective tissue in places showed slight proliferation; the endothelium was entirely normal. In a rabbit with loss of only 4 per cent in body weight, the kidneys were normal. At loss of 10 per cent in body weight, renal degenerative changes appeared and became progressively more marked and frequent in the subsequent groups.

Isaëw ('87) observed parenchymatous degeneration in the kidney of starved dogs.

Morpurgo ('89, '89a) in starved rabbits of various ages (15 days to adult) found mitoses reduced in number in the youngest rabbit, and entirely suppressed in the others. In rabbits refed after a period of inanition, however, the mitoses reappeared in great abundance in both cortex and medulla. In a pigeon dead after 17 days of inanition, Morpurgo ('89b) found the average diameter of the renal convoluted tubules reduced from 28.31 to 24.13 $\mu$ ; and the height of the epithelial cells from 9.92 to 9.07 $\mu$ . The nuclei were but slightly decreased in average diameter, from 5.81 $\mu$  to 5.63 $\mu$ .

In rabbits 6-18 months of age, Morpurgo ('90) observed mitoses rarely in the kidneys of normal animals or during inanition, but more numerous upon refeeding. In the normal rabbits, the diameter of the renal epithelial nuclei averaged 7.29 $\mu$ ; in those starved to death, 6.95 $\mu$ ; in those refed after inanition, 7.35 $\mu$ .

Lukianow ('88, '89) studied the changes in the water content of the kidneys and other organs in starved pigeons. Tonninga ('93) similarly studied the loss of nitrogen content in fasting rats and rabbits.

During starvation (with or without water) in 3 rabbits and 1 kitten, Coen ('90) found the renal stroma unchanged. Especially in the convoluted tubules (to a less extent in Henle's loop) the epithelium in places showed cloudy swelling and degeneration. The cytoplasm atrophied more than the nuclei, which stained variably. Some fat droplets found in the renal epithelial cells might be remnants of those normally existing. The blood vessels in general appeared distended, with some hemorrhagic foci, and slight glomerulitis.

In various animals (cat, dog, rabbit, guinea pig, pigeon, frog, turtle, lizard) fasting with losses in body weight of 5, 10, 20 or 30 per cent, Statkewitsch ('94) found that in general the intensity of the lesions in the renal epithelial cells varies according to the length of the inanition. In the early stages, cloudy swelling appears in the convoluted tubules, later finely granular, and finally coarsely granular or fatty degeneration. Sometimes total cell disintegration occurs and granular-albuminous or hyalin cylinders, or fat droplets may be found in the lumen. The nuclear changes vary in different tubules and at

different stages. Hyperchromatosis occurs frequently even in the first half of the inanition period; later chromatolysis or pycnosis and karyorrhesis are frequent. The cell changes occur chiefly in the convoluted tubules and Henle's loop, while those of the tubuli recti and medulla show little or no change. (Statements by Perls, L. Popow, Ochotin and Steiger are also cited.) The renal cell changes are least marked in the pigeon, more distinct in the guinea pig, and most intensive in the rabbit, cat and dog.

Russo ('92) observed albuminuria in 1 malnourished dog, although not in 6 others similarly starved. Sacerdotti ('94) concluded that in fasting dogs, rabbits and guinea pigs, the removal of one kidney does not cause hyperplasia in the epithelium of the remaining kidney, if no inflammatory complication is present.

In groups of guinea pigs on absolute inanition with average losses of 10, 20, 30 and 36 per cent, Lazareff ('95) found corresponding losses of 1.80, 2.54, 10.23 and 11.00 per cent in the kidneys (see Table 5; averages for right and left combined). In the *urinary bladder*, the corresponding average apparent losses were 3.33, 0, 13.33 and 23.33 per cent (Table 5). It would thus appear that the loss in the bladder is relatively greater than that in the kidneys, but that in both the loss is relatively much less than that in the whole body.

Kusmin ('96) found that in fasting rabbits and guinea pigs at hyperthermia the kidneys lose in weight relatively less than the spleen, liver and intestines, but more than the heart and lungs. Hyperemia occurs, and sometimes hemorrhagic extravasations, with changes analogous to those in fever.

Weiske ('97) observed a loss of about one-fourth (slightly more in dry weight) of the kidneys in 3 rabbits on water only with loss of 35-41 per cent in body weight.

Lukianow ('98, '98a) found that in fasting white mice the nuclei of the kidney-cells show a much smaller decrease in volume than do the liver-cell nuclei. With loss of about 28 per cent in body weight, the renal nuclei apparently decreased 8.2-8.4 per cent in diameter, corresponding to an average loss of 23.03 per cent in volume.

Nemzer ('99) showed that in fasting white mice the organs undergo a variable decrease in nuclein-content, that of the kidneys showing the least decrease.

In 2 starved cats, with losses of 51 and 55 per cent in body weight, Sedlmair ('99) found that the kidneys had apparently lost weight in nearly the same proportion. The weight of the urinary bladder appeared very irregular, with a slight increase in one case, and a loss of 45 per cent in the other.

Traina ('04) reviewed the somewhat discordant results of previous investigators as to the changes in the kidneys during inanition. In rabbits subjected to acute and chronic inanition he noted that both renal cells and nuclei decrease in size, with some decrease also in Altmann's granules. Traina paid especial attention to the fatty droplets and granules, which occur normally in the kidney (as in other glands) and constitute the "sessile" or "permanent" fat which is relatively unaffected by inanition. Rubow ('05) likewise found no significant

change in the renal fat of starved dogs, examined both microscopically and by chemical analysis.

In rabbits with experimental toxic marasmus, Cesaris-Demel ('06) noted that the kidneys were reduced in size, with granular pigmentation in the convoluted tubules, but never in the Malpighian bodies and rarely in the renal connective tissues. Unusual destruction of red blood corpuscles constituted the source of the pigment.

Takaki ('07) studied the kidney-cells of mice and rats during inanition. No changes were found in the rod-like structures in the kidney-cells of the mouse, up to the third day of total inanition, with loss of 22.2 per cent in body weight. With progressive loss in body weight (up to 36 per cent in 5 days), the rods become shorter and thicker, or broken into fine or coarse granular fragments which may remain in rows parallel with the long axis of the cell. Fat droplets may occur normally or as a result of degeneration. Mice on water or dry bread only showed similar changes. Postmortem changes may simulate those due to inanition, with marked decrease in stainability of the cells. The secretory changes were also studied in refeeding experiments. Takaki concluded that the replacement of the rods by granules is a stage in the normal secretion; but although the fine granules are normal the coarse granules are pathological.

Roger ('07) determined the water content of the kidneys and other organs during inanition in rabbits, finding but slight changes.

Beeli ('08) found that in cats at various stages of inanition the kidney appears comparatively resistant in the earlier stages, but with marked reduction of about one-half (relatively equal to that of the body) at death from starvation. At loss of 9.6 per cent in body weight, the renal cells showed but slight changes. At losses of 31 per cent to 51 per cent in body weight, the cells of the convoluted tubules showed variable degenerative changes, with cloudy swelling, granulation, and irregular, feebly-staining or pycnotic nuclei. A distribution table for nuclei according to diameter in the various stages of inanition shows a slight tendency to decrease in size.

Adami ('08) reviewed the atrophic changes in the cells of the kidney and other organs during malnutrition.

Cesa-Bianchi ('09) made a careful study of the changes in the kidney- (and liver-) cells of the white mouse during fasting. He considered the rabbit unfavorable, on account of the frequency of spontaneous lesions. When the loss in body weight is 40 per cent, a decrease of 15 or 20 per cent is found in the thickness of the wall of the uriniferous tubules (cell boundaries indistinct), but the nuclei appear unchanged in size. During inanition the rods of the renal epithelium break up into parallel rows of granules, which finally increase in size and occupy the entire cell, with corresponding decrease in size and final disappearance of the liposomes. Nuclear changes (hyperchromatosis, chromatin clumping, karyorrhexis or pycnosis) appear late, usually followed by appearance of myelin in the cytoplasm, and lead rapidly to the death of the cell. He concluded:

“Zusammenfassend kann man feststellen, dass im Laufe der Verhungerung die Leber- und Nierenzelle demselben Mechanismus folgend, schwere Veränderungen erleiden: Ein Teil derselben, nämlich diejenigen, welche sich auf Kosten des Zytoplasmas und in den ersten Stadien der Verhungerung bilden, entsprechen in exacter Weise den Veränderungen, die durch verschiedene hypo- und hypertontische NaCl-Lösungen in denselben Elementen erzeugt werden. Die anderen schweren Veränderungen dagegen, welche sich auf Kosten des Zytoplasmas wie des Kernes, und zwar nur in den letzten Verhungerungsstadien bilden, entsprechen ganz genau den Strukturumänderungen, welche sich an denselben Elementen im Laufe der aseptischen Autolyse einstellen.”

Stefani ('10) found that while in normal dogs subjected to starvation the kidneys lose 25–30 per cent in weight, if one kidney is removed at the beginning the remaining kidney appears nearly normal in weight at the end of inanition. Thus the tendency to atrophy during inanition is counterbalanced by the tendency to compensatory hypertrophy (contrary to Sacerdotti '94).

In several dogs and a fox which died from protracted inanition, Morgulis, Howe and Hawk ('15) found the kidneys with variable form and extent of degeneration. Bowman's capsule was invariably thickened, “as in the case of nephritic kidneys.” The cells of the convoluted tubules appeared coarsely granular and always vacuolated. Vacuolation of cells was rare in Henle's loop. The nuclei appeared small and irregular. Casts (cellular and hyalin) were frequent. The cells of the collecting tubules were nearly normal.

In the kidney of starved guinea pigs, Rondoni and Montagnani ('15) observed slight congestion, rarely cortical hemorrhages. Sometimes the nuclei of the glomerular layer of Bowman's capsule and of the glomerular endothelium appeared deformed and pycnotic. In some cases the entire cortex was edematous, with granular coagulum in the spaces between the tubules.

In white rats which had lost nearly 50 per cent in body weight by starvation, Sundwall ('17) noted extreme congestion of all vessels, both glomerular and intertubular capillaries, with albuminous degeneration of the cells of the urinary tubules.

Jackson ('15) in adult albino rats on acute inanition (water only) with average loss of 33 per cent in body weight, or on chronic inanition (underfeeding) with loss of 36 per cent in body weight, found a loss of 26 or 27 per cent in the weight of the kidneys (Table 4). In younger rats the loss was still less, and on those held at constant body weight by underfeeding from 3 to 10 weeks of age there was even a slight increase (4 per cent) in the average kidney weight.

In still younger albino rats, underfed from birth to 3 or 10 weeks of age, Stewart ('18) found the kidneys 21–38 per cent above normal in weight; and in a later study ('19) in rats held at birth weight for 16 days by underfeeding the kidneys showed a markedly persistent growth, increasing 90 per cent in weight. In the stunted offspring of albino rats severely underfed during pregnancy, Barry ('20, '21) found the kidneys only 6 per cent above normal weight (Table 4).

In albino rats refed after underfeeding (at maintenance) from 3 to 12 weeks of age, Stewart ('16) found the kidneys nearly normal in proportion to the body

weight. In those underfed from birth for several weeks (resulting in greatly supernormal kidneys) and subsequently refed to body weights of 25-75 g., Jackson and Stewart ('19) found the kidneys had nearly recovered their normal proportionate weight in most cases, though sometimes still somewhat above normal (Table 7). In those refed to adult size after variable periods of early underfeeding, Jackson and Stewart ('20) noted nearly normal proportionate weight of the kidneys, excepting one group still 22.5 per cent above normal (Table 8).

In steers on various planes of nutrition, Trowbridge, Moulton and Haigh ('18) and Moulton, Trowbridge and Haigh ('22a, '22b) found the weight of the kidneys in all cases nearly proportional to the body weight, regardless of the plane of nutrition.

Asada ('19) in rabbits on absolute inanition for 11-20 days with loss of 28-52 per cent in body weight found intense congestion in the small arteries and capillaries of the kidney and other viscera. The renal and hepatic parenchyma showed cloudy swelling, vacuolation and a variable degree of cell-atrophy, but no fatty degeneration.

Kittelson ('20) made a careful volumetric study of the cortex and the medulla, together with counts of the total number of renal (Malpighian) corpuscles in the kidneys of albino rats after underfeeding from birth to 3 or 6 weeks, and also upon refeeding. He found that during underfeeding, especially when severe, the medulla is less retarded in growth than is the cortex. Normal proportions are restored upon refeeding. During the shorter underfeeding periods, the formation of new renal corpuscles ceases, although the anlagen of incompletely formed corpuscles become fully developed. The deficiency in the number of corpuscles is apparently over-compensated by an increase in size of the corpuscles. During the longer underfeeding periods, in which the body weight and kidney weight were permitted to increase somewhat, the formation of renal corpuscles continued until practically the normal total number was reached. Refeeding after a period of underfeeding apparently results in a hypertrophy of the renal corpuscles, and an increase in their number even beyond the normal.

Terroine ('20) made a careful study (primarily biochemical) of the various fats in the various organs of the body. In the kidney (rabbit, dog, pigeon) there appears to be no significant variation in fat-content, even up to death from inanition. Okuneff ('22) investigated the morphology of lipid substances in various organs of fasting rabbits, but was unable to demonstrate lipoids in the kidney-cells (in formalin-fixed frozen sections, stained with Sudan or Nile blue sulphate). Okuneff ('23) described simple atrophic and degenerative changes in the kidney-cells of fasting rabbits. In some cells the mitochondria appear to break up into granules, which may be transformed into droplets, sometimes even "Lipoidartung der Chondriosomen."

Ott ('24) found that in the leopard frog (*Rana pipiens*), during hibernation and subsequent fasting up to 60 per cent loss in body weight, the kidneys are affected differently in the two sexes. In the male, the relative loss in weight rarely exceeds that of the body; while in the female the relative loss is smaller,

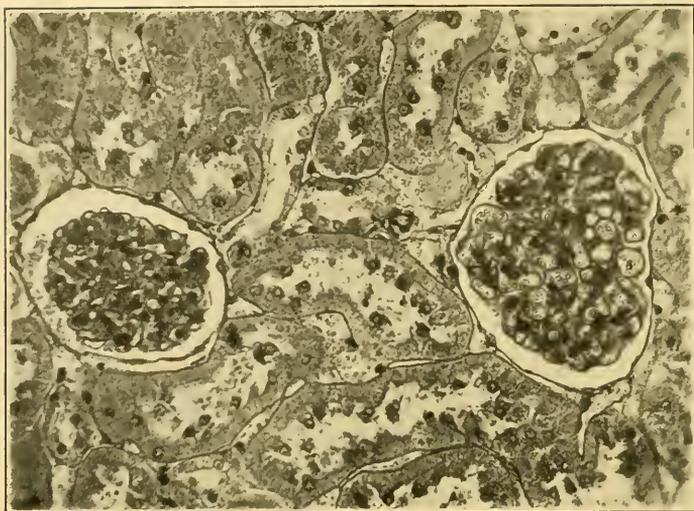


FIG. 97.—Photograph of a portion of a section from the kidney of a normal adult albino rat (S. 14), showing two renal (Malpighian) corpuscles and the adjacent cortical labyrinth (chiefly proximal convoluted tubules). Compare with Fig. 98. Zenker fixation; hematoxylin-eosin stain.  $\times 250$ .

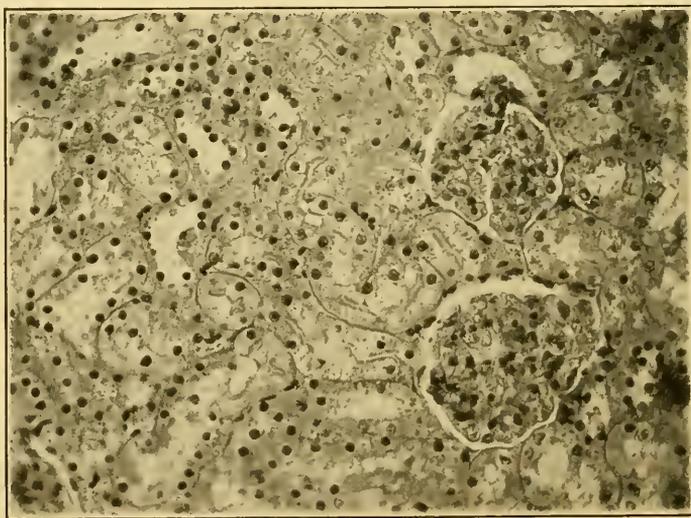


FIG. 98.—Photograph of a portion of a section from the kidney of an adult albino rat (S. 18), after 8 days of inanition on water only, with loss of 38 per cent in body weight. Estimated loss of about 26 per cent in weight for the kidney. Compare with Fig. 97, noting the apparent shrinkage of the renal (Malpighian) corpuscles and tubules. The cells show atrophic degeneration, with nuclear pycnosis or karyolysis. Zenker fixation; hematoxylin-eosin stain.  $\times 250$ .

especially in the later stages (Table 6). The percentage of dry substance in the kidney remains nearly constant.

Figures 97 and 98 are from photographs of sections showing typical changes in the renal cortex of the adult albino rat as a result of acute inanition (on water only).

**Functional Changes, Hibernation, Etc.**—Some structural changes observed during inanition or hibernation, and relating especially to the renal cell function, will now be considered.

Sauer ('95) studied the kidney-cells in the dog, rabbit, hedgehog, rat, mouse and guinea pig, contrasting the condition of relative anuria (produced by feeding dry food only; also by total inanition in rabbits and white mice) with that of polyuria (produced by intravascular injection of urea, etc.). He found no secretory changes in the brush border of the renal cells (as claimed by Disse '92); also no changes in the rod-like structures of Heidenhain. In the fasting (or thirsting) animals with urinary suppression, the cells appeared taller, and the lumen of the tubule smaller; after maximal secretion, the cells were reduced in height and the lumen became larger.

Zanier ('96) found no diminution in the granular "bioblasts" of Altmann in the kidney and liver-cells of the fasting frog or rat. Likewise Sjöbring ('00) saw no change in the mitochondria (chondriosomes) of rabbits fasting 1 or 2 days.

In the hibernating marmot, R. and A. Monti ('00) noted the appearance in the renal epithelium of numerous granules, which were thought to represent excretory substances. The brush border is an integral cell constituent, not merely a functional stage. The width of the tubular lumen varies according to functional condition.

Baroncini and Beretta ('00) found that in hibernating bats (*Myoxus*, *Vespertilio* and *Vesperugo*) the kidney-cells present a progressive degree of cloudy swelling in the renal labyrinth; also the appearance and progressive increase of fat droplets, and (sometimes) the exit of the nucleolus, in the convoluted tubules and loops of Henle. No changes were observed in the collecting tubules and the ducts of Bellini.

Disse ('00, '00a, '02) claimed that the functional changes in the renal epithelium can be ascertained only by comparing the structure during active secretion with that found in the quiescent condition. A study of these conditions in the bat (*Nannugo pipistrellus*) during activity and hibernation supports Disse's theory that the brush border represents a resting condition, being liquified and evacuated during renal secretion.

Ferrata ('05, '05a), however, could find no appreciable change in the brush border of the cells in the convoluted tubules and loops of Henle in the marmot, hedgehog, bat and tortoise (*Emys*) during activity and hibernation. In hibernation the lumen of the tubule becomes smaller and the cytoplasmic granules of all kinds more numerous. As previously mentioned, Takaki ('07) concluded that the granular metamorphosis of the basal cytoplasmic rods in the renal epithelial cells of fasting or thirsting white mice represents a stage in the normal process of secretion.

Kolster ('11) studied the mitochondrial changes in the renal cells of rabbits in which urinary secretion was reduced to a minimum by total inanition or dry food for 3 days. The central portion of the brush border apparently becomes homogeneous and swollen, not through imbibition of fluid, but in association with an increase in the cell mitochondria and related structures. The mitochondrial changes are described in detail.

Suzuki ('12) investigated the excretion of carmine in the renal epithelium of fasting and thirsting animals.

It is impracticable to mention in detail the results of the preceding investigations on the finer cytological changes, especially in the mitochondria, of the renal epithelial cells during hibernation and inanition, as resting conditions, in contrast with the active secretory condition. These results are reviewed fully by Arnold ('14). More recently, Azzi ('16) concluded that in rabbits on total inanition 24-48 hours the chondriosomes remain nearly unchanged, excepting in the ascending limb of Henle's loop and the collecting tubules, where the granules and filaments tend to become concentrated in the circumnuclear zone. In rabbits fasting 9-17 days, Okuneff ('23) finds in some renal cells degenerative changes in the mitochondria (chondriosomes) similar to those described in the liver.

#### (B) EFFECTS OF PARTIAL INANITION

The forms of partial inanition in which the kidneys have been studied include dietary deficiencies of protein (in malnutritional edema and pellagra), of salts (including rickets), of vitamins (including beriberi and scurvy) and of water (thirst).

The reasons for classifying **malnutritional edema** primarily as a protein deficiency were given in Chapter V. Kohman ('20) produced edema in rats on watery diets poor in proteins and fats. She stated that "There is some indication that the kidney cells are injured and therefore fail to eliminate the water. Although very little work was done on the kidney tissues, sections were made of a few kidneys and some albumin found in the tubules." Kohman's results were confirmed in general by Maver ('20) on dogs, rats and guinea pigs. McCarrison ('21), however, concluded from his experimental studies with variously deficient diets on monkeys and pigeons that malnutritional edema is not due to organic renal change.

In human "famine edema," and allied conditions, the consensus of opinion of numerous observers is likewise that the edema is not due to renal or cardiac insufficiency, but is more probably due to the direct effect of the malnutrition upon the vascular endothelium. Paltauf ('17) found the kidneys variable in weight, with congestion and signs of edema. Schittenhelm and Schlecht ('18, '19) found the kidneys nearly normal in size and condition. Oberndorfer ('18) noted total absence of renal fat droplets and glycogen. The kidneys appeared reduced in size in proportion to the heart (which was always small), although the urine was increased in amount. Mann, Helm and Brown ('20) reported the kidneys grossly normal in 200 necropsies. Prince ('21) found the

kidneys normal in autopsies on 45 cases. Lubarsch ('21) mentioned deposits of hemosiderin in the epithelium of the kidney and other glands. Fracassi ('22), however, observed albuminuria in cases of edema in war prisoners. In 2 cases, autopsy revealed marked increase in renal connective tissue, in some places more or less completely replacing the glomeruli and tubules. The kidneys also showed necrosis and granular degeneration of the greater part of the epithelium; a condition said to correspond to a (not entirely typical) chronic interstitial nephritis.

In **pellagra**, Fraenkel ('69-'70) reported the kidneys decreased in weight in 46 out of 52 autopsies. Lombroso ('92) stated that the kidneys are rarely normal, uremic conditions being common. He found the kidneys fatty in 21 cases; atrophic and cirrhotic in 33; cystic in 5; and with uric acid calculi in 1. Tuczek ('93) mentioned atrophic and fatty degeneration of the kidneys and other organs. Marie ('08, '10) concluded that the kidneys are usually subnormal in weight, often showing fatty degeneration of the parenchyma, with or without interstitial sclerosis. Nicholls ('12) in 8 African cases found the kidneys averaging only 3½ ounces each. Kozowsky ('12) in 16 cases found in the kidney congestion, cloudy swelling, fatty degeneration, pigmentation, etc. Raubitschek ('15) designated these degenerative changes in the kidney as "Nephritis pellagrosa." The marked renal changes in pellagra were also reviewed by Harris ('19).

In human **rickets**, Wohlaue ('11) concluded that the kidneys are neither structurally nor functionally disturbed, although certain characteristic urinary changes occur. Jackson and Carleton ('23), however, found the weight of the kidneys markedly (42-48 per cent) above normal in albino rats with experimental rickets. The interpretation of this hypertrophy is somewhat doubtful, however, since the rats on similar diets, but killed before the appearance of rachitic symptoms, also had kidneys 33 per cent above normal weight (Table 11).

**Vitamin Deficiencies.**—In the kidneys of rats on diets low in vitamin A, Davis and Outhouse ('21) found chiefly a cloudy swelling of the parenchyma in the collecting tubules; more pronounced in the second generation. In some places the cells of the tubules appeared "skeletonized" and the glomeruli shrunken. Osborne and Mendel ('17c) and Mendel ('20) found urinary calculi in the kidneys or bladder of 81 out of 857 albino rats on diets deficient in vitamin A. Meyerstein ('22) noted renal changes in young white rats on diets deficient in vitamins A and B. Beach ('23) described renal enlargement, with urate-filled tubules, in chicks on diets deficient in vitamin A. Herter ('97) found renal enlargement, hemorrhagic spots and granular degeneration of the secretory epithelium in pigs during fat starvation, probably involving deficiency in vitamin A.

In human **beriberi** (due to deficiency of vitamin B), Duerck ('08, '08a) gave a review of the lesions, with weights of the kidneys (usually subnormal) in 10 cases. Nephritis was not observed, but the kidneys were congested, sometimes with small hemorrhages. Strong and Crowell ('12) found acute parenchymatous degeneration of the kidney in the case studied. From 18 necropsies of infantile beriberi, Andrews ('12) concluded that the kidneys are

usually normal, excepting congestion. In some cases the tubules show albuminous or fatty degeneration, but no leukocytic infiltration. Padua ('19) found urinary calculi relatively frequent in malnourished Filipinos, and especially those with beriberi. Nagayo ('23) claimed that renal passive congestion occurs in human beriberi but not in experimental polyneuritis.

In experimental beriberi in white mice, cats, dogs, pigeons, and chickens, Schnyder ('14) could find no marked change in the kidneys, excepting congestion (stasis). Funk and Douglas ('14) and Douglas ('15), however, noted atrophy and degeneration in the renal parenchyma of pigeons with beriberi. Tasawa ('15) in chickens and pigeons found the kidneys sometimes hyperemic, sometimes anemic. Voegtlin and Lake ('19) found some degenerative changes in the kidney of cats and rats on diets producing polyneuritis.

McCarrison ('19, '19e, '21) in pigeons with polyneuritis on autoclaved rice diet (deficient in vitamins; also in proteins, etc.) found the kidneys but slightly changed in weight, and congested in 20 per cent of the cases. Histologically there appeared slight degeneration with cloudy swelling in the epithelium, and sometimes hemorrhagic extravasations. In monkeys on similar diets the kidneys were variable in weight.

In dogs on polished rice diet (producing polyneuritis), Brucco ('20) found in the renal convoluted tubules marked fatty degeneration, but no atrophy (as found in starvation). In pigeons and fowls with beriberi, however, Findlay ('21) observed no fatty degeneration, but cloudy swelling of the cells in the convoluted tubules, and congestion of the intertubular capillaries. In general, the kidneys showed relatively slight atrophy (Table 13). Souba and Dutcher ('22) and Souba ('23), on the other hand, obtained a marked loss in the weight of the kidneys in young chickens on diets deficient in vitamin B, producing polyneuritis and loss in body weight. Lopez-Lomba ('23) found the kidney weight unchanged in adult pigeons on vitamin-free diet.

In human **scurvy** (due to deficiency in vitamin C), Sato and Nambu ('08) noted that kidneys are usually normal in size, sometimes showing subcapsular hemorrhage. On section, the kidney appeared anemic. The urinary bladder was normal. Aschoff and Koch ('19) found the scorbutic kidney variable, with no characteristic changes. Interstitial and glomerular hemorrhages were observed in a few cases. Hess ('20) reviewed the literature on scurvy, including renal changes, of which congestion and hemorrhage appear most frequent.

In experimental scurvy of animals, Hart ('12) mentioned renal hemorrhages in scorbutic monkeys.

McCarrison ('19b, '21) in scorbutic guinea pigs found congestion and ecchymoses of the urinary bladder, especially of the mucosa, with hematuria in 1 case. Histologically there appeared congestion in all the coats, with hemorrhagic infiltration of the mucosa and degenerative changes in the lining epithelium. La Mer and Campbell ('20) found some evidence of increased weight in the kidneys of scorbutic guinea pigs. Bessen ('23) described a progressive increase in the kidney weight, amounting to 57.7 per cent above normal at death from scurvy (Table 12). There was also a marked, but more irregular, increase in the weight of the urinary bladder. Beginning even in the latent stage of

scurvy, Höjer ('24) found renal atrophy, often combined with necrosis and certain peculiar calcareous deposits.

In **aqueous inanition** (thirst), Schuchardt ('47) found a loss of 25 per cent in the weight of the kidneys in pigeons on dry barley diet, with loss of 34 per cent in body weight. In a dog on dry diet with loss of 20.9 per cent in body weight, Falck and Scheffer ('54) noted an apparent loss of only 8.7 per cent in the kidneys and ureter, but a loss of 34.9 per cent in the urinary bladder. In dogs on dry food, Bowin ('80) found the epithelium of the renal tubules somewhat atrophic and cloudy.

In a dog on dry diet with loss of 24 per cent in body weight, Pernice and Scagliosi ('95a) found the kidneys apparently normal in size, hyperemic, and with slightly nodulated external surface. The relation of cortex and medulla appeared normal. Microscopically the renal epithelial cells showed cloudy swelling and indistinct nuclei; some cells containing fine fatty granules. In places, the capsule space was filled with blood, compressing the glomerulus.

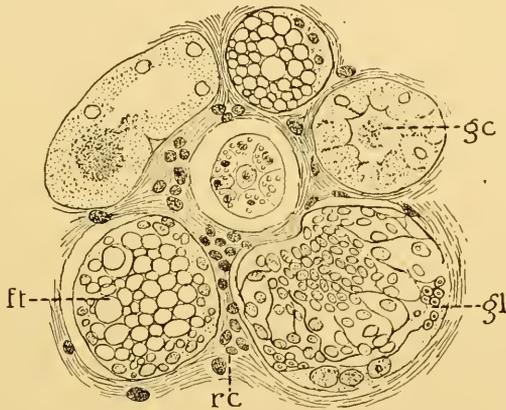


FIG. 99.—Portion of a section of the kidney from a young fowl on aqueous inanition (dry diet). *ft*, uriniferous tubules containing epithelial cells with "fatty degeneration;" *gc*, uriniferous tubule containing a granular cylinder; *gl*, an abnormal renal (Malpighian) corpuscle, showing capsule and glomerulus (glomerulitis?); *rc*, stroma, with small round cell infiltration. X400. (Pernice and Scagliosi '95a.)

Many uriniferous tubules were also filled with blood, and some contained hyalin cylinders. In many glomeruli the vascular endothelium appeared greatly proliferated; sometimes the capillary loops had lost their nuclei. Osmic preparations showed marked fatty degeneration in many glomeruli. Small round cell infiltration occurred around some of the glomeruli and tubules. The epithelial cells showed proliferation, which might indicate regeneration.

In 3 young chickens likewise fed a dry diet, the fresh kidney showed fatty-granular degeneration, especially in the convoluted tubules, with partial destruction of the epithelium, especially in the collecting tubules. In general, there was marked hyperemia and often hemorrhage in Bowman's capsules and in the renal tubules. Stained sections also showed small cell infiltration around the vessels and Bowman's capsule; and blood in the capsule spaces and tubules. Cylinders (hyalin and cellular) occurred in the lumen of the tubules; and the

epithelium showed degenerative changes and desquamation, sometimes apparently indirect cell-division. The capillary endothelium in places appeared hypertrophied or degenerated. Some of the renal changes found by Pernice and Scagliosi are shown in Fig. 99.

In frogs with partial withdrawal of the water from the body by dessication, Durig ('01) observed that the kidneys, in spite of a marked decrease in water content, showed a relative increase in weight due to the retention of insoluble urinary constituents.

In adult albino rats on dry diets, Kudo ('21) found in the acute thirst series (loss of 36 per cent in body weight) a loss of 23.8 per cent in the kidney weight; in the chronic thirst series (loss of 52.4 per cent in body weight) a loss of 33.1 per cent in the kidneys; and in a rat on total inanition (body loss 47.2 per cent) a loss of 41.7 per cent in the kidneys (Table 9). There was also an apparent loss in bladder weight of 40 per cent in the acute thirst series and of 47 per cent in the chronic thirst series.

In young albino rats held at constant body weight by a relatively dry diet for various periods beginning at about 4 weeks of age, Kudo ('21a) found that the kidneys show a marked increase in weight, varying from 35 to 65 per cent in the various groups (Table 10). This increase in weight appears relatively greater than that found by Jackson and Stewart in young rats held at constant body weight by simple underfeeding.

Some data on mitochondrial and other cytological changes in the renal epithelium on dry diets as well as total inanition (by Takaki '07, Kolster '11, Suzuki '12, and Arnold '14) were mentioned on a previous page, under functional changes, hibernation, etc.

Rosenfeld ('86) pointed out the danger that Oertel's obesity cure, involving a reduction of liquids in the diet, may produce degenerative changes in the kidneys, as well as in the heart and nervous system.

## CHAPTER XXIV

### EFFECTS ON THE FEMALE REPRODUCTIVE TRACT

The female reproductive tract is especially susceptible to the effects of inanition and malnutrition. The general effects on the body during pregnancy were noted in Chapters IV and V. The direct effects on the female tract are of special interest to the gynecologist in relation to the production of amenorrhea and sterility, which have recently been widespread in Europe because of the malnutrition resulting from war and famine. The repression of sexual development in the undernourished children likewise presents a problem of interest and importance in social medicine.

This chapter will include the effects of inanition upon the ovary and uterus. A few observations are available also for the uterine tubes (oviducts) in amphibia and birds. After a brief summary of the effects on the entire female reproductive tract, the data will be considered in detail separately for the ovary and the uterus.

#### SUMMARY OF EFFECTS ON THE FEMALE REPRODUCTIVE TRACT

In human females beyond the age of puberty, the reproductive system is especially susceptible to the effects of malnutrition, amenorrhea and consequent sterility being the characteristic result of severe inanition, either total or partial. Similar results appear during inanition among the lower animals.

The incapacity of the female reproductive tract through inanition is due primarily to the effect on the **ovary**. The atrophic and degenerative changes in the ovary concern especially the Graafian follicles, which undergo regression and atresia. In man and mammals, this prevents not only normal ovulation, but also the formation of corpora lutea, and therefore inhibits the endocrine activity of the ovary and the associated process of menstruation or related phenomena of the estrous cycle.

The more nearly mature follicles and ova are the most susceptible, and undergo prompt involution, with degenerative (occasionally cystic) changes and ultimately complete resorption. Yolk-rich ova in birds and amphibia are absorbed through phagocytic activity of the granulosa cells. The simpler and smaller follicles with the primordial ova appear more resistant, and mitoses continue in the follicle cells. If the inanition is not extremely severe or prolonged, the normal process of ovogenesis is promptly resumed upon adequate refeeding. In extreme cases, however, relative or complete sterility may result from the ovarian injury. It appears possible that in some cases the lesions of the ovum during inanition may affect sex-determination, or cause abnormalities in the offspring.

In the **young**, inanition usually causes a variable degree of atrophy in the ovary, or more rarely a slight persistent growth occurs. Chronic underfeeding results in the retardation or repression of sexual development in general. On adequate refeeding, as in adults, the normal weight and structure are usually recovered promptly, excepting extreme cases.

During **hibernation**, the ovaries in general appear resistant to inanition. The changes in the ovarian interstitial cells appear variable. During the migration of the fasting salmon, the ovaries undergo an enormous development at the expense of other tissues, notably the trunk musculature.

Various forms of *partial inanition* apparently produce in the ovary atrophic and degenerative changes similar to those during total inanition, although detailed data upon these effects are scanty.

The mammalian **uterus**, in addition to the cessation of menstruation and related phenomena of the estrous cycle (due to the disturbance of the ovarian endocrine function), may also present evidences of direct effects of inanition. The loss in weight usually appears marked, with congestion and degenerative changes. The uterine glands undergo atrophy, although mitoses persist in the gland cells. Similar atrophic changes likewise occur in the uterine tubes (oviducts) of inframammalian species.

Abortions or complete resorption of the embryo and membranes may result from severe inanition during pregnancy. Evans and Bishop find that the lack of a special dietary factor "X" results in abnormal placentation, with resorption of the implanted ovum, in the albino rat. Resorption has also been found during underfeeding (Barry).

## 1. OVARY

The effects upon the ovary will be considered under (A) total inanition (or on water only), and (B) partial inanition.

### (A) EFFECTS OF TOTAL INANITION, OR ON WATER ONLY

The data for the human species (adult and children) will be mentioned first; and the effects upon the lower animals will be taken up later.

**Human Adults.**—Although amenorrhea directly concerns the uterus, it is now known to be indirectly due to ovarian disturbance in most cases, and may therefore be mentioned in this connection. Gaspard (1821) noted that during a famine in France in 1817 the menses ceased in many women, and pregnancies were reduced to half the normal number. Lucas (1826) stated "Dass die Menstruation bei einer längeren Enthaltung von Nahrungsmitteln aufhöre, ist zu erwarten, und geht auch fast aus allen Geschichten einer langen Enthaltung von Speisen hervor."

Slavjansky ('70) noted that in certain emaciating diseases (tuberculosis, typhus abdominalis) in adult women there is amenorrhea, with atrophy and regressive changes in the ovarian ova and follicles.

Among several hundred women stricken by famine, Porter ('89) stated: "Menstruation was not observed in any of these patients, nor was any woman admitted to hospital pregnant. The Sanitary Commissioner, Dr. Cornish, records that only 39 births occurred among some 100,000 famine stricken who passed through the Madras relief camps in 1877. He also shows that the birth rate began to fall off early in the famine, and steadily increased, till some 9 months after the height of the famine it reached in the famine districts an annual ratio of 4-5, against an average of 29-30 per mille of population." Cornish concluded that the wasting of the mammary glands and ovaries in the women over 30 was so severe as to make the recovery of normal function impossible, but Porter thought this unlikely. It was apparently assumed, without direct proof, that the amenorrhea and sterility were due to the effects of starvation upon the ovary.

Frequent observations on famine amenorrhea were also made during the recent world war. Apparently amenorrhea during this war was first noted at Warsaw by v. Jaworski ('16), who called it "Amenorrhea ex inanitione," and ascribed the accompanying marked atrophy of the uterus also to the inhibition of ovarian follicle development. A similar amenorrhea was reported in Germany by Dietrich ('17), Ekstein ('17), Giesecke ('17), Graefe ('17), Hannes ('17), Hilferding ('17), Stickel ('17), Schweitzer ('17), Spaeth ('17), Ebeler ('17, '18), Siegel ('17), Vaerting ('18), Abel ('18), Beninde ('19), Bauereisen ('19), H. Koehler ('19), and Holmberg ('19); in Austria by Pok ('17) and Czerwenka ('17); and in Russia by v. Lingen ('21), Abel ('23) and Ivanovsky ('23).

While all found a great increase in the percentage of cases of amenorrhea, the statistics reported vary widely. A few instances may be cited, from gynecological clinics involving thousands of cases. Amenorrhea due to the ordinary causes is excluded. In Kiel, Giesecke ('17) found an increase from 0.19 per cent of all cases in 1914 to 0.31 per cent in 1915, 0.57 per cent in 1916 and 1.29 per cent (to May) 1917. In Vienna, Pok noted an increase from 0.037 for 1910-14 to 0.65 per cent in 1915 and 1.32 per cent in 1916; and (according to R. Koehler) to 13.5 per cent in 1917. In Leipzig, Schweitzer described an increase from 0.85 per cent in 1911-12 to 4 per cent in 1916-17. In Berlin, Stickel reported an increase from about 1 per cent in prewar times to 1.4 per cent in 1914-15 and 7 per cent in 1917. In Königsberg, Hilferding found an increase from 0.55 per cent in 1912 to 14 per cent in 1917. The differences were doubtless due partly to actual differences in the amount of inanition at different times and in different localities, but also in part to difference in the diagnosis and classification of cases. Thus cases showing an atrophy of the uterus were included by some authors, but excluded by others. There were also many borderline cases, such as oligomenorrhea, which were difficult to classify.

The amenorrhea was ascribed chiefly to insufficient nutrition, together with overwork in many cases, resulting in depression of the endocrine function of the ovary. Psychic depression was often considered a contributing factor, and Siegel ('17) even held it to be the primary cause of the amenorrhea. With the return to better food conditions in 1918 and 1919, the number of cases rapidly decreased, according to Holmberg ('19).

R. Koehler ('17, '18), on the basis of 2 necropsies, opposed the theory of Fraenkel ('17) that war amenorrhea is due to small-cystic ovaries produced by sexual abstinence. Koehler concluded that the ovarian changes prevent the ripening of follicles and the formation of corpora lutea. The uterine changes were considered secondary to the ovarian lesions, which in turn are probably caused by inanition, over-exertion and psychic shock.

H. Koehler ('19) likewise concluded from microscopic examination of the ovaries that war amenorrhea is due to the effect of malnutrition upon the ovaries, in which there is disappearance of the primordial ova and failure to form corpora lutea. In some cases the ovaries become small-cystic, in others they undergo fibrosis. Hoffmann ('20) examined 4 ovaries from cases of war amenorrhea; 2 appeared cystic, the other 2 merely atrophic. That ovarian function sometimes continued in spite of the amenorrhea is indicated by the occasional occurrence of conception during this condition, as was noted by Giesecke ('17), Pok ('17) and others.

Bauereisen ('19) reviewed fully the literature upon war amenorrhea, including (in addition to those above mentioned) additional data by Stoeckel ('17), Hamm ('18) and Schaefer ('18). Rubner ('19) reported retarded menstruation and deterioration of the female sex-organs as an effect of the subnormal diet on the German population. In the Russian famine, Ivanovsky ('23) noted that "In women menstruation ceased during the period of fasting. The sexual instinct became very weak and even disappeared entirely. The number of births decreased enormously." The question of malnutritional amenorrhea will be discussed further in connection with the effects upon the uterus.

In athreptic **infants**, Mattei ('14) found the ovary somewhat atrophic, weighing 0.30-0.60 g. instead of normally 0.60-1.0 g. On section, the germinal epithelium appeared normal.

The ovarian cortex contained chiefly primordial follicles; sometimes follicles more advanced in development, atretic, or cystic. These changes were also reviewed by Nobécourt ('16). Marfan ('21) likewise found the ovaries small in athreptic infants, but Nicolaeff ('23) states that they appeared normal in weight in famine-stricken children of various ages. Stefko ('23, '24) and Maslowsky ('23), however, find marked follicular atrophy (ova sometimes absent) with increased interstitial tissue.

The effect of malnutrition in causing retardation or arrest of sexual development has frequently been observed. Calmette ('19) noted arrested growth in the malnourished children in Lille during the period of occupation. The girls failed to mature sexually at the proper age, those at 18 years appearing only 13, and those of 14 appearing only 10 years of age.

From Table 3, it appears that in most cases the weight of the ovaries in atrophic infants (Minnesota cases) is considerably below the normal at birth (0.32 g.), but it is impossible to draw conclusions as to the extent of the atrophy, on account of the scarcity and irregularity of the data, as well as the lack of an adequate norm of postnatal growth of the ovaries.

Among the lower **animals**, data upon the effects of inanition on the ovaries are more numerous. These will be reviewed chronologically, excepting some

observations upon hibernation, etc., which are placed at the end of this section.

Nussbaum ('80) found that in underfed frog larvae with retarded growth of the body the gonads appeared to have persisted in development, so as to be as large as in full-fed controls.

Morpurgo ('88, '89, '89a) found mitoses persisting during extreme inanition in the ovary of rabbits of various ages, especially in the larger Graafian follicles. No differences were apparent in rabbits refed after a period of inanition.

Cuénot ('94) cited cases of sterility in cattle and sheep, as a result of undernourishment. Beneke, on the other hand, stated that fattened trout are not suitable for breeding, although they lay many eggs; hence fish raisers improve them by fasting.

The work of Motrochin, who is said to have studied degenerative lesions in the ovary during inanition, was inaccessible; likewise the work of Pyotroff ('97) on the changes in the ovaries of rabbits and dogs during starvation and refeeding. The latter reference, however, evidently corresponds to Petrow ('97).

Petrow ('97) made a careful study of the ovarian changes during fasting (body loss 20-47 per cent) in 3 dogs and 12 rabbits, the latter mostly sisters about 6 months old; also after refeeding and in normal controls. During starvation, the germinal epithelium was found partly lost. In the cortex, the primordial and developing follicles and ova appeared normal in number and structure, with persistent mitoses in the granulosa cells; but in certain areas of the medulla the epithelial cells presented albuminous (granular), later fatty, degeneration and finally complete necrosis. Vacuolation and fatty degeneration were also found persistent in the refed rabbits.

Lebrun ('02) held that inanition plays an important rôle in the maturation of the ovum in certain amphibia (*Alytes obstetricans* and *Salamandra maculosa*) and invertebrates. "L'état critique de la maturation est consecutif à une periode de jeûne, de semiasphyxie et de déshydratation du cytoplasme. L'oeuf mûr est une cellule affamée qui lutte contre la mort; le spermatozoïde est une cellule affamée qui cherche un aliment." This recalls the doctrine of Rolph ('84), which was mentioned in Chapter III.

Traina ('04) studied the fat content of the ovary in normal and fasting rabbits. He stated that Petrow ('97) overlooked the fact that fine fat droplets are normally present in the ovary (in the theca folliculi, stratum granulosum, yolk, etc.) and persist unchanged during inanition.

Pérez ('03, '03a) subjected female tritons (*Molge marmorata*) to complete inanition, up to 4 months, beginning just before the time to lay eggs. The ovaries show no marked changes in the earlier months, but later become hypere-mic. The follicle cells hypertrophy and absorb the ovum by phagocytic activity. The larger eggs, normally pale, become orange-colored. The nucleus of the ovum undergoes karyolysis. The ovum atrophies and is finally replaced by a connective tissue mass, including fatty droplets. Sometimes apparently leukocytes invade and dissolve the ovum, forming a cyst-like cavity. Thus there is a reversal of the normal process of ovogenesis, the food materials (yolk) being resorbed by the same follicle cells which originally nourished the ovum.

Blumenthal ('04) mentioned that in fasting frogs the ovary atrophies, though to a lesser degree than the testes and other organs.

Kahan ('04a) experimented for 2 years with 2 hens, 1 used as a normal control, the other subjected to starvation, with loss of about 50 per cent in weight, and then fully refed to normal weight. In the hen previously starved, the spring period of egg-laying began later and the eggs were smaller and weighed less than normal. The eggs were non-fertilized, hence their capacity for development was not tested.

Heape ('05) held that sex may be affected by quantitative or qualitative variation in the ovarian nutrition during the process of oögenesis.

Russo ('06, '06a) studied carefully the effects of nutrition and inanition upon the developing ova in the rabbit. The mitochondria normally present in the oöcytes, perivitelline space and cells of the corona radiata disappear during inanition. The ova normally contain certain specific deutoplasmic materials, staining black with iron-hematoxylin, which are increased by hypernutrition (lecithin injections), but disappear during inanition. The germinal epithelium of the ovary during inanition becomes atrophic, with pycnotic nuclei.

Comes ('07) likewise found the ovarian ova in the cat to be highly variable and plastic structures. In the zona pellucida and oöplasm there normally appear certain chromatic bodies, staining with iron-hematoxylin, and interpreted as trophic materials derived from the follicle cells for the nourishment of the developing ovum. These materials decrease or disappear during pregnancy or inanition.

Russo ('09) continued his studies on the effects of inanition upon the ovary of the rabbit, finding a disintegration and chromatolysis of the granulosa cells, thus furnishing a modified nutriment for the developing ovum; a process of possible significance in the determination of sex. Russo ('10, '10a, '10b) concluded that the rabbit's ovary contains two types of ova, capable of experimental modification: an anabolic type (female-producing), rich in lecithin globules; and a katabolic type (male-producing), containing fatty acid crystals. Russo ('10c, '12) found that during inanition the deutoplasmic materials (myelin globules derived from mitochondria) in the developing ovum may be profoundly modified. In the earlier stages of inanition these materials may be increased in amount; but later they are decreased, with deformity of the mitochondria and atrophy of the ovum and follicle cells.

Burkhardt ('12) described the resorption of the ova in non-copulating female *Rana esculenta*, the process being the same as during starvation. The zona pellucida disappears first, and the granulosa cells enlarge through absorption of the yolk granules. These cells send cytoplasmic processes into the yolk and become loaded with pigment. Blood vessels and mesodermic cells invade and resorb the pigmented degeneration products, as in the formation of a normal corpus luteum. Finally only a pigmented scar remains in the place of the resorbed ovum. Progressive changes, with ripening new ova, may occur simultaneously with the involution process.

Heidkamp ('09) observed marked involution of the female reproductive tract in fasting *Triton cristatus*. In a well-fed female 109 mm. long, the ovary was 21

mm. long; the diameter of the oviduct was 1 mm., and of numerous ripe ova, 1.3 mm. A female underfed 4 months was 91 mm. long; ovary 16 mm. long; diameter of oviduct 0.6 mm., and of the scanty ripe ova 0.8 m. In a third female, starved 6 months, the ovary measured 10 mm., the oviduct 0.5 mm., and the atrophic, yolk-poor ova 0.25 mm. He found that: "Der Hunger zuerst die dotterreichsten Eier zur Resorption bringt, und die übrigen Körperorgane demgemäss auf Kosten dieses reichen Nährmaterials eine Zeitlang ihren Fortbestand sichern."

Marshall ('10) stated that cows attain sexual maturity normally at one year of age, though later if malnourished. "But even starved and backward cows will receive the bull when 15 months old."

Marshall ('23) summarizes the evidence that fecundity in sheep is increased by special nutrition ("flushing"), which apparently increases the number of ova discharged; with the opposite result during malnutrition.

Kammerer ('13) noted that underfed *Salamandra maculosa* are retarded in growth of the body and of the sex-glands, which remain small, though accompanied by a massive fat-body. When placed under normal nutritional conditions, the sex glands soon become normal. Bardier ('13) reviewed the effects of inanition upon the ovary and other organs.

Aschner ('14) found that during inanition, disease, etc., there is a marked decrease or disappearance of the fatty granules in the interstitial cells of the ovary in dogs.

Nussbaum ('14) reviewed his earlier work ('06, '06a, '09) on the effects of inanition upon the ovary and testis in frog larvae. The results are variable (especially according to the season), the gonads being long persistent, though ultimately undergoing atrophy and resorption. The ripened cells are resorbed first, the oögonia and spermatogonia being more persistent. He remarked that: "Bei den Eiern ist die Resorption namentlich am Amphibienei gut verfolgt worden. Ruge u. a. haben gezeigt, dass die Aufsaugung des Dotters unter Mitwirkung der Granulosazellen vor sich geht."

Morgulis, Howe and Hawk ('15) found no apparent abnormality in the ovary of a dog as a result of protracted inanition. Ova were present in all stages of normal development.

In adult albino rats subjected to acute inanition, with loss of 33 per cent in body weight, Jackson ('15) found an apparent increase of 22 per cent in the weight of the ovaries. In rats underfed from age of 3 to 10 weeks, or 10 weeks to 8 months, however, Jackson ('15a) found the ovaries 27-54 per cent sub-normal in average weight (Table 4). Stewart ('18, '19) found that in newborn rats held at birth weight by underfeeding 16 days, the ovaries were slightly (5 per cent) above normal in weight; but with longer and less severe underfeeding, the ovaries increased to an average weight 54-83 per cent above normal for the corresponding body weight (Table 4). In the stunted offspring of rats underfed severely during pregnancy, Barry ('20, '21) noted nearly normal weight in the ovaries.

Stewart ('16) refed albino rats after holding them at maintenance (constant body weight) from 3 to 12 weeks of age, and found the ovaries 11.6 per cent

subnormal in weight at the end of one-half week; but above weight 43.2, 44.5, and 27.9 per cent, respectively, after 1, 2 and 4 weeks of refeeding. Thereafter they appeared nearly normal in weight. In rats underfed from birth to 3, 6 or 10 weeks, and then refed to 25, 50 or 75 g. in body weight, Jackson and Stewart ('19) found the ovaries somewhat variable in weight, but definitely (20-29 per cent) subnormal in those which had been subjected to the longer underfeeding periods (Table 7). In another series, underfed from birth to 3-10 weeks, or from 3 weeks for long periods, and then fully refed to the maximum attainable size, Jackson and Stewart ('20) found the ovaries always atrophic, averaging 32-61.5 per cent subnormal in the various groups (Table 8).

Some allowance must be made for the great variability in the weight of the ovary (on account of the changes during the estrus cycle), but the evidence clearly indicates that severe or prolonged underfeeding causes a profound atrophy of the ovary, which is sufficient to account for the marked degree of sterility usually found in such animals (Jackson and Stewart '18, '20). King ('18) likewise noted that malnourished female rats are usually sterile, but may regain their fertility when the general nutrition is improved. Osborne and Mendel ('17) found that in females stunted by underfeeding to the age of 6-17 months (body weight 90-108 g.), and then fully refed, the menopause is postponed long beyond the normal age and apparently vigorous young may be produced.

Swingle ('18) noted that in frog larvae (*Rana pipiens*) almost completely starved for over 100 days from the emergence from the egg capsule the development of the gonads and germ cells is almost entirely inhibited. In older (yearling) larvae of *Rana catesbiana*, the development of the gonads proceeded during starvation for 5 months and 10 days, so their microscopic structure appeared identical in test and control larvae, in spite of marked atrophy of the body as a whole and of the corpora adiposa.

Stieve ('18) found that in hens the ovarian activity and egg-laying are soon interrupted by imprisonment or inanition. Histologically the ovarian follicles were shown to undergo more or less rapid atresia, and the large ova with their yolk are resorbed in 5-10 days. Upon refeeding, new follicles and ova develop, but not until the yolk has been completely resorbed from the follicles in process of atresia. Stieve concluded that the germ cells are much more susceptible to environmental influences than is usually believed.

Stieve ('21) made further extensive investigation upon tritons (chiefly *Triton vulgaris*), and concluded:

“Zusammenfassend lässt sich sagen, dass Hunger und spärliche Fütterung vor der Brunst nicht schadet, sofern zu Beginn der Fortpflanzungszeit reichliche Nahrungszufuhr erfolgt. Während der Brunst selbst bedingt Hunger den Stillstand der Eiablage, jedoch nicht plötzlich, sondern erst nach einigen Tagen; bei spärlicher Ernährung ist die Zahl der abgelegten Eier gering. Sehr reichliche Fütterung vor der Brunst verhindert die Fortpflanzungstätigkeit, wohingegen sie während der Laichzeit die Eiablage steigert. Bei spärlicher Ernährung und beim Hunger wird stets zuerst der Fettkörper aufgebraucht, erst dann lassen sich schwerere Veränderungen am Eierstock nachweisen. Bei

der Mast vergrösserte sich der Fettkörper erheblich, während sich der Eierstock niemals sehr beträchtlich verkleinert."

L. Loeb ('17, '17a, '21) by underfeeding produced a "hypotypical" condition of the ovaries in guinea pigs, with retardation and regression in follicular development. The effects usually appear more marked in the younger animals, with smaller body weight. The epithelial elements (granulosa) are primarily affected, the smallest follicles being the most resistant. The connective tissue is more resistant, although in some cases two or more follicles may fuse through absorption of the perifollicular tissue. During follicular atresia, the ovum may undergo irregular segmentation. The rate of mitosis in the granulosa cells in the "hypotypical" ovary may remain nearly normal (Walsh).

McCarrison ('19, '21) in starved pigeons found a marked atrophy in the ovaries which lost in weight relatively about twice as much as the whole body.

Papanicolaou and Stockard ('20, '22) found that underfeeding (20 g. of carrots daily) in guinea pigs "produces a prolongation of the dioestrus and, at the same time, a congestion of the ovary and uterus and a degeneration of the graafian follicles." The result varies in different periods of the cycle. Shortly after ovulation, the small primary follicles are more resistant than the large graafian follicles which develop in the later stages of the dioestrus.

Champy ('21) claimed that in *Triton alpestris* two males were reduced to a sexually neutral condition by starvation. Upon refeeding, one presented, in the place of the testes, fatty bands including scattered spermatogonia; the other, killed 3 months later, had ovaries lying medial to the degenerated testes.

Evans and Bishop ('22) have shown that in the albino rat general underfeeding (Fig. 34), as well as various special dietary deficiencies, result in delayed estrus and disturbances of the ovulation rhythm. Moehl ('22) observed somewhat similar effects in underfed cattle.

In the leopard frog (*Rana pipiens*), Ott ('24) found relatively slight decrease in the weight of the ovaries during hibernation and subsequent inanition, up to a loss of 20 per cent in body weight. In later stages, with body loss of 30-50 per cent, the ovaries lost relatively more (89-95 per cent), as shown in Table 6.

**Hibernation and Seasonal Changes.**—The most remarkable instance is the well-known case of the salmon, which fasts for some months during its migration from the sea up the rivers to the spawning grounds. During this period there is an enormous growth of the ovaries and testes, the materials for which are derived by atrophy and resorption of other tissues, especially of the trunk muscles. This process was described by Miescher ('80, '97) for the Rhine salmon, by Paton (Gillespie) ('98) for the British salmon, and by Stone ('97) and Greene ('10) for the Pacific salmon. In the Rhine salmon, the ovaries during this fasting period are said to increase from 0.4 per cent to about 27 per cent of the body weight.

Gaule ('01) studied the seasonal variation in the weight of the ovaries, concluding that in *Rana esculenta*, as in the salmon, during inanition or hibernation other organs may be to some extent sacrificed to build up the sex-glands. This was confirmed by Gerhartz ('06), who concluded that the phenomenon

occurs only at a certain season or stage of the sex-cycle. As noted above, however, Ott ('24) found no increase in the weight of the ovaries in frogs kept without food (beginning in the fall) throughout the hibernation period and subsequently.

In hibernating bats, Cesa-Bianchi ('07) observed an apparent decrease or disappearance of the ovarian interstitial cells, with a redevelopment at the time of awakening and during the subsequent summer period. Van der Stricht ('12), in the bat, and Rasmussen ('18), in the woodchuck, found an enlargement of the interstitial cells of the ovary during the winter hibernating period, with a reduction to minimum size during the summer. Aschner ('14), on the other hand, found in the hedgehog (*Erinaceus europaeus*) a marked reduction in the fat-content of the ovarian interstitial gland during hibernation, with recuperation in the spring; while Mann ('16) noted no specific change in the structure of the sex glands of the gopher (*Spermophilus tridecemlineatus*) during hibernation.

#### (B) EFFECTS OF PARTIAL INANITION ON THE OVARY

**Protein Deficiency.**—Gaspard (1821) described a famine edema in France during 1817, due to subsistence on rough herbage, and probably involving protein deficiency. The menses ceased in many women, and conceptions were reduced to half the normal number.

Slonaker and Card ('18, '23a, '23b, '23c) found that albino rats on protein-poor vegetarian diet showed in both sexes a delay in the age of puberty, and a marked increase in sterility, so that by the third generation the line became extinct. Animals still capable of reproduction were restored to nearly normal conditions when placed on an omnivorous diet.

Kraus ('19) and others have noted amenorrhea and sterility as accompanying the edema from malnutrition during the world war. Rubner ('19, '20) ascribed the "war amenorrhea" (above mentioned with effects of underfeeding) in Germany to the great reduction in the protein content of the diet. It acts as a protection against further loss through hemorrhage. He stated, however, that it is also a question whether the formation of the ovum itself is normal.

Reynolds and Macomber ('21, '21a) and Macomber ('23) found that in albino rats the age of puberty is postponed and fertility greatly reduced by various deficient diets, including deficiencies in calories (general underfeeding), in vitamin A, or in protein and calcium. Certain peculiar conditions were observed in the ovaries, notably follicles apparently containing four ova, possibly due to premature segmentation.

Recently Evans and Bishop ('22) have shown that the onset of puberty and the ovulation rhythm may be disturbed by protein deficiencies, as well as other general or special dietary deficiencies.

In **pellagra** (considered primarily due to protein deficiency), Raubitschek ('15) stated that various inflammatory lesions occur in the female reproductive tract, including the ovary and uterus.

In experimental **rickets** in rats on diets with calcium deficiency, McCollum, Simmonds, Shipley and Park ('21) noted that the gonads appeared atrophic.

Jackson and Carleton ('22, '23) found the ovaries irregular in weight, though rarely atrophic to any marked extent, in albino rats at various stages of experimental rickets on various (chiefly phosphorus-poor) diets (Table 11).

Hatai ('15) found the ovaries 17.4 per cent subnormal in weight in albino rats fed on lipoid-free rations (deficient in fats and vitamin A). Evans and Bishop ('22, '22a, '23) discovered that a dietary deficiency in **vitamin A** in rats causes an ovarian disturbance resulting in a continuous production and desquamation of cornified cells by the vaginal mucosa. In spite of the ovarian dysfunction, normal follicles may for a time continue to mature, so that estrus and copulation may occur. Although implantation is normal, there is a reduction in the number born because fewer ova are delivered per ovulation. Reproductive failure is thus due to impairment of germ-cell vigor. They find also a distinct "fertility conferring factor X," as will be mentioned in connection with the uterus.

In young rats on vitamin-free (polished rice) diets, Tsuji ('20) found ovarian atrophy with degeneration of oviducts and premature ovulation. Meyerstein ('22) similarly noted atrophy and functional derangement in the ovaries and testes of albino rats on diets of potato or rye flour, deficient in vitamins A and B (as well as in other respects).

On diets deficient in **vitamin B**, Funk and Douglas ('14) found evidences of histological degeneration in the ovary and other glands of pigeons. Findlay ('21) noted that in fowls and pigeons with beriberi the ovary atrophies to a lesser extent than does the testis (Table 13). The ovarian follicles appear small and uniform in size, and the nuclei in some of the interstitial cells show degenerative changes. Ovarian atrophy in pigeons on a diet deficient in vitamin B was found also by Gotta ('23).

In experimental **scurvy** of guinea pigs, Bessesen ('23) found a progressive atrophy of the ovaries, which averaged 19.8 per cent subnormal in weight at death from scurvy (Table 12).

In a dog on dry diet (**aqueous inanition**), Pernice and Scagliosi ('95a) found the ovaries and uterus strongly congested, with atrophic, poorly-staining cells. Kudo ('21a), in albino rats held at constant body weight by relatively dry diets for various periods beginning at about 1 month of age, discovered a marked and progressive decrease in the weight of the ovaries (Table 10), amounting to 66.7 per cent below normal in the group on the longest test (9-13 weeks).

## 2. THE UTERUS

In the preceding section, it was mentioned that malnutritional amenorrhea, although concerning the uterus directly, is recognized in most cases as an indirect effect of ovarian (endocrine) disturbance. Observations concerning the occurrence of amenorrhea in connection with famine or similar conditions of malnutrition were cited by Gaspard (1821), Lucas (1826), Slavjansky ('70), Porter ('89), v. Jaworski ('16), Czerwenka ('17), Dietrich ('17), Ekstein ('17), Giesecke ('17), Graefe ('17), Hannes ('17), Hilferding ('17), Pok ('17),

Schweitzer ('17), Siegel ('17), Stickel ('17), Spaeth ('17), Ebeler ('17), Vaerting ('18), R. Koehler ('18), H. Koehler ('19), Holmberg ('19), Bauereisen ('19), Kraus ('19), Rubner ('19, '20), Beninde ('19), Hoffmann ('20), v. Lingen ('21) and others (see pp. 390-392).

The uterus has been observed to undergo a variable degree of atrophy during various conditions of inanition. Hewitt ('79) stated that in chronic starvation (quantitative or qualitative) the uterus undergoes "a peculiar softening and relaxation of the tissues," which may favor uterine flexures and amenorrhea (more rarely menorrhagia). Although little or no uterine atrophy was found by Hannes ('17), Dietrich ('17) and v. Lingen ('21), this was frequently observed by v. Jaworski ('16), Spaeth ('17) and Schweitzer ('17). Ebeler ('17) noted marked hypoplasia of the uterus in 14 out of 110 cases of war amenorrhea, Stickel ('17) in 27 out of 126 cases, and Czerwenka in 23 out of 59 cases. Graefe ('17) reported uterine atrophy in 45 per cent of the war amenorrhea cases; Giesecke ('17) found 38 per cent in 1916 and 47 per cent in 1917. By palpation, the uterus generally appeared firm in consistency, but flatter and smaller, with subnormal length when measured by a sound. According to v. Jaworski ('16a, '17) even uterine myomas were affected by the inanition-atrophy.

**Microscopic** examination of the uterine mucosa in cases of war amenorrhea by Pok ('17) and Hoffmann ('20) revealed an abnormal scarcity of uterine glands. Further data are given by Hofstätter ('18). Various stages of degeneration in the uterine glands were demonstrated by Graff and Novak ('21) in 30 cases.

As a result of the war famine, v. Jaworski ('17) found the relative frequency of uterine prolapse in the out-patient clinic at Warsaw nearly doubled on account of relaxation in the pelvic supporting tissues. Among 3,080 women, 27 per cent showed a variable degree of vaginal and uterine descent with more or less complete prolapse in 11 per cent. The **urethra** was often displaced, and atrophic relaxation of the urethral sphincter often caused incontinence of urine. The general disappearance of fat, together with the atrophic relaxation of the abdominal walls, frequently resulted in a general ptosis of the abdominal viscera, resembling the syndrome of Glenard's disease.

In famine-stricken children of various ages, Nicolaeff ('23) found extreme atrophy of the uterus, especially in the musculature, although the ovaries appeared normal in weight. Stefko ('23a) likewise noted uterine atrophy.

Among **animals** on total inanition (or on water only) Chossat ('43) noted a weight of only 0.13 g. in the oviduct of a pigeon with loss of 40 per cent in body weight, the average in 3 normal controls being 0.36 g.

Manassein ('69) recorded, without comment, in numerous starved rabbits the weights of the uterus, showing apparently a variable degree of atrophy.

Morpurgo ('88, '89, '89a, '90) in fasting rabbits of various ages found that in the uterus the mitoses usually do not appear materially reduced in number. They occurred chiefly in the epithelium of the glands, rarely in the muscle. The mitoses likewise appeared unchanged in the uterus upon refeeding after a period of inanition.

The reduction in the diameter of the oviduct in fasting *Triton* by Heidkamp ('09) was mentioned in connection with the ovary.

Papanicolaou and Stockard ('20, '22) observed that in underfed guinea pigs the uterus as well as the ovary appeared congested, with rare occurrence of uterine (gland) cysts.

Barry ('20, '21) discovered that if albino rats are severely starved during the first half of pregnancy, the embryos and membranes are resorbed; while in the second half of pregnancy the fetuses are born at term, but variably reduced in size. In the rabbit, Reeb ('05) and others have noted abortions produced by inanition, as mentioned in Chapter IV. Moehl ('22) likewise found more frequent abortions in underfed cattle.

Osterud ('23) noted that in the albino rat undernutrition markedly affects the uterine weight.

Ott ('24) found that in the leopard frog (*Rana pipiens*) during hibernation and subsequent inanition with loss in body weight up to 50 per cent, the oviducts undergo an atrophy relatively almost equal to that of the ovaries, with a final loss of 81 per cent (Table 6).

As shown by the data in Table 3, the weight of the uterus in atrophic human infants is very low, even when allowance is made for the normal postnatal decrease in uterine weight.

**Partial Inanition.**—Campbell ('07) found that on various abnormal diets (especially of meat), the uterus of the rat may undergo arrested growth with fibrosis and other abnormalities of structure. It is not clear what dietary deficiencies were involved.

The frequent occurrence of amenorrhea in connection with **malnutritional edema** (due chiefly to protein deficiency) was mentioned above in connection with the ovary.

In **pellagra**, as before mentioned, Raubitschek ('15) found inflammatory lesions of the uterus as well as of the ovary.

In albino rats on diets deficient in **vitamin B**, Hatai ('18) observed in the uterus "an unusual yellow color indicating the presence of some fatty degeneration or other pathological alteration." In **scurvy**, Hess ('20) mentions the occurrence of uterine hemorrhages.

As above mentioned, Evans and Bishop ('22, '22a, '23) found that a dietary deficiency in vitamin A causes a marked disturbance of the estrous cycle through a direct effect upon the ovary. They also ('22a, '23, '23a, '23b) claim the discovery of a hitherto unrecognized dietary factor "X," which is essential for reproduction, and is concerned with normal placentation. Upon diets normal in other respects (including vitamins A, B and C), but lacking this substance, the ovaries appear to function normally and the ova become fertilized and implanted, but the placentae are abnormal. "They may persist almost throughout gestation but show as early as the second day of their establishment beginning blood extravasations, which increase in extent. Resorption invariably overtakes the products of conception." Fertility is promptly restored by adding to the diet fresh lettuce or other "X"-containing substances. The existence of a distinct vitamin essential to reproduction was confirmed by Sure ('24).

As mentioned above, Pernice and Scagliosi ('95a) found that a dry diet (**aqueous inanition**) in the dog occasioned congestion and structural disorder

in the uterus as well as in the ovary. In young albino rats held at constant body weight by a relatively dry diet for various periods, beginning at about one month of age, Kudo ('21a) found the weight of the uterus somewhat variable in the earlier groups, but apparently a definite increase (26.7-34.8 per cent) in average weight in the two longest tests (Table 10). In young rats the uterus (unlike the ovary) therefore appears at an early age to present during inanition a persistent growth tendency, somewhat comparable to that found in various other organs during thirst as well as chronic underfeeding.

## CHAPTER XXV

### EFFECTS ON THE MALE REPRODUCTIVE TRACT

The effects of inanition upon the reproductive tract in the male are somewhat less obvious than those in the female, but equally important. Conditions of severe malnutrition may cause complete suppression of spermatogenesis, but fortunately the spermatogonia survive to renew the process upon the reestablishment of nutrition. The observations on the effects of inanition upon the male reproductive tract have been chiefly confined to the testis, with a few scattered data upon the accessory organs, epididymis, prostate, seminal vesicles, etc. After a brief summary, the results will be considered in detail under (*A*) total inanition and (*B*) partial inanition.

#### SUMMARY OF EFFECTS ON THE MALE REPRODUCTIVE TRACT

In general, the testes, like the ovaries, are very susceptible to the effects of inanition. The changes are variable according to age and species, as well as in different types of inanition.

During **total inanition** (or on water only) in adult man the decrease in **weight** of the testis usually appears roughly proportional to that of the body; while in lower forms (mammals and especially birds and amphibia) the loss is usually even greater. The same applies to some forms of **partial inanition**, especially in beriberi and aqueous inanition, though apparently not as a rule in rickets and scurvy, in which the testes may even increase in weight.

As to **age** differences, in the atrophic human infant there appears a variable degree of atrophy in the testis; but in other species (mammals, amphibia) the testis appears more resistant and at certain stages may even show a marked increase in weight while growth in body weight is repressed by inanition. This is comparable to the striking metamorphosis of the gonads in the fasting migratory salmon, and possibly in other species.

In **structure**, the effects of inanition upon the testis are equally striking. In the young, development is retarded or inhibited. In the adult, there is a progressive atrophy of the seminiferous tubules, with degenerative changes and decreased or (in extreme cases) completely arrested spermatogenesis. There is great variation in different tubules, some remaining more nearly normal and continuing spermatogenesis, while others undergo marked degeneration. Even in the same tubule, there is a notable difference in the resistance of the various cell-elements. In general, the spermatozoa are least resistant, and are the first to degenerate and disappear. Next come the spermatids and spermatocytes, which persist longer. Most resistant are the spermatogonia and Sertoli cells, which usually persist, often fused into a syncytium, and upon refeeding are able

to regenerate the normal seminiferous tubule. Although variably reduced in frequency, mitoses are usually found even at death from starvation. The cytological changes are those typical for atrophic degeneration, and occur in both total and partial inanition.

The changes in the stroma of the testis during inanition appear variable. The fibrous connective tissue may show proliferation (with round cell infiltration in thirst), but usually undergoes little change, occasionally showing pigmentation. The specific interstitial cells (of Leydig) likewise appear variable, sometimes appearing atrophic, in other cases hypertrophied, especially in beriberi and upon refeeding after inanition. The fat content of the interstitial cells (also in the Sertoli cells and the epithelium lining the seminal vesicles) appears to belong chiefly to the "permanent" or "sessile" lipoids, which are unaffected by inanition.

Of the **accessory organs**, the **epididymides** show (in rats) a persistent growth in the young during underfeeding, though a marked atrophy during chronic thirst. The human **prostate** usually appears relatively small in atrophic adults, though not in atrophic infants. A few data indicate an atrophy of the **seminal vesicles** (especially in fasting frogs).

#### (A) EFFECTS OF TOTAL INANITION, OR ON WATER ONLY

The data upon the effects in the human species (adult and infant) will be considered first, followed by those for the lower animals.

**Human Adults.**—No references to the effects of inanition upon the human male reproductive tract have been found in the earlier literature. Cohnheim ('89) stated that in relative amount of atrophy during inanition, the testes rank next to adipose tissue and the spleen, but it is not clear whether this conclusion was based upon human data. Von Hanseemann ('96) noted some increase in the interstitial cells in all human cachexias. Cordes ('98) found the process of human spermatogenesis to be depressed in various forms of acute illness, but spermatogenesis does not cease except in chronic malnutrition involving extreme cachexia. Thickening of the walls of the seminiferous tubules and increase in interstitial tissue may occur during malnutrition. After the age of puberty, both the seminiferous epithelium and the interstitial cells contain fat droplets of the "permanent" or "sessile" variety, which do not disappear even in extreme cachexia with tuberculosis or cancer.

Simmonds ('13, '21) stated that the condition of the sex glands is influenced by the general state of nutrition. In chronic cachexia (especially in tuberculosis), the testes are small and flabby. Spermatogenesis may be arrested in many chronic diseases (*e.g.*, alcoholism) which do not affect the external appearance of the testes. Pigment may occur in the seminiferous cells and the connective tissue, especially in senile atrophy.

In an adult man who died from starvation, Meyer ('17) noted that the bladder and *prostate* appeared normal.

Roessle ('19) found no indication of atrophy in the weight of the testes in soldiers with fever or other chronic disorders producing marked loss in body

weight. Krieger ('20), however, found the loss in testis weight fully as great relatively as the loss in body weight in various cachexias (assuming the normal at 46 g., which is slightly less than Vierordt's norm of 0.08 per cent of the initial body weight), as shown by the accompanying table.

WEIGHT OF THE TESTES IN EMACIATED MEN (KRIEGER '20)

Cause of inanition	No. of cases	Normal weight, grams	Observed weight, grams	Percentage decrease, per cent	Per cent of body weight, per cent
Chronic diarrhea.....	5	46	27.0	41.3	0.080
Malignant growths.....	12	46	32.8	28.7	0.078
Chronic infections.....	24	46	27.4	40.3	0.074
Tuberculosis.....	27	46	27.9	49.4	0.075

Krieger also noted that the *prostate* very often appeared unusually small (24 cases); while in 14 cases it was of medium size, and in 7 cases presented "Prostatahypertrophie im Alter."

The atrophy of the testis during inanition may explain the marked sexual depression observed by Miles ('19) and Benedict, Miles, Roth and Smith ('19) in 25 healthy young men on a reduced diet (two-thirds to one-half of the normal calory requirement) with loss of about 10 per cent in body weight in 2 months.

Rübner ('19) stated that as a result of the unfavorable nutritional conditions in Germany, *libido sexualis* was decreased in the male. He thought this might be associated with the extreme atrophy of the testes noted in malnourished men on the Eastern front. Spermatogenesis was also found much diminished. Impotence was noted by Abel ('23) as characteristic in the Russian famine.

During inanition in **infancy**, a few data are available. Ohlmüller ('82) observed a weight of 2.28 g. in the testes of an atrophic infant of 8 weeks (body weight 2,381 g.), while in a well nourished control of the same age (body weight 4,150 g.) the testes weighed 2.50 g. This would indicate but slight loss, possibly even a persistent gain in weight, depending upon the (unknown) previous body weight of the atrophic infant.

Simmonds ('13, '21) stated that before puberty the testis may be retarded in development during tuberculosis, late rickets, or similar conditions of malnutrition. The seminiferous epithelium and stroma may become pigmented, especially in atrophic nurslings.

Mattei ('14) gave weights for the testes in atrophic infants, indicating considerable variation. He concluded, however, that there is usually but slight change in size or appearance. Microscopically, the seminiferous epithelium appeared normal, but the blood vessels usually appeared congested, and the tunica albuginea and connective tissue stroma slightly thickened. The interstitial cells sometimes appeared pigmented, sometimes they showed atrophic cytoplasm. "Il y a en somme atrophie et dystrophie légère de la glande interstitielle du testicule."

Schlesinger ('20) found in numerous German boys during the war period a retardation of puberty in association with the retarded growth of the body in general on account of malnutrition.

Jaffé ('21) observed that in the normal testis during the first year the seminiferous tubules are close together, with but narrow strips of connective tissue stroma, and but few interstitial cells containing little or no fat. In victims of chronic diseases, the tubules are separated by broad, mostly edematous connective tissue; the interstitial cells remain unaffected. "Bei pädatorphischen Kindern ist das Bindegewebe oft nicht oder kaum vermehrt, dafür sind die Zwischenzellen mehr oder weniger stark vermehrt und weisen reichlichen Fettgehalt auf." Jaffé interpreted this to indicate that the interstitial cells play a rôle in endocrine metabolism.

In famine-stricken children 1-16 years old, Nicolaëff ('23) found the weight of the testis and epididymis normal (sometimes above) according to age. No spermatogenesis was found, even in those beyond the age of puberty. Stefko ('23 a, '24) and Maslowsky ('23) noted degeneration of the germ cells, increased interstitial tissue, and frequent cryptorchism.

Several observations upon the weight of the testes in atrophic Minnesota infants are given in Table 3. While variable, they all are below the normal for birth, and usually indicate a considerable degree of atrophy during inanition. The *epididymides*, on the contrary, are invariably much above the normal birth weight, apparently indicating a persistent growth in weight during inanition. In 3 cases, the weight of the *prostate* also appears considerably above the normal for birth weight, or corresponding body weight (Table 3).

Among the **lower animals**, the effects of inanition upon the testis have been noted frequently. Chossat ('43), however, failed to include the testis in his otherwise comprehensive study. Voit ('66) found that in a starved cat the testes apparently lost in weight relatively slightly more than the entire body. Manassein ('68, '69) concluded that in adult fasting rabbits with loss of about 39 per cent in weight the testes lost 45 per cent. Manassein grouped the testis with the liver and spleen among those organs which lose most heavily on account of relative inactivity during inanition.

Bourgeois ('70) observed that in various starved animals the *seminal vesicles* contain no sperm, and the testes appear atrophied; but he gave no quantitative data.

Morpurgo ('88, '89, '89a) found mitoses undiminished in number in the seminiferous tubules of the testis in an adult rabbit at death from 13 days of starvation. He also ('90) found no change in cell division of the testis in rabbits of various ages upon refeeding after a period of inanition. Thus the rate of mitosis in the seminiferous epithelium appeared independent of nutrition.

Grandis ('89, '89a), on the other hand, observed that in fasting pigeons (1-24 days without food or water) the process of spermatogenesis was affected within a few days. Probably those cells in process of spermatogenesis continued to maturity, but no new spermatozoa were developed after the 12th day. The spermatozoa remain in the seminiferous tubules, and begin to degenerate and undergo resorption when the loss in body weight exceeds 40 per cent. The spermatozoa suffer most; the cells of the seminiferous epithelium also degenerate,

but are more resistant, and those of the outer portion of the wall persist and appear embryonal in character, the tubules resembling those in young animals before puberty. Upon refeeding, these cells are able to regenerate new elements, even when the testis has lost two-thirds in weight.

Simonowitsch ('96, '97, '99) likewise found in the testis degenerative changes somewhat proportional to the length of inanition (complete or incomplete) in rabbits and guinea pigs. The parenchyma (seminiferous) cells undergo cloudy swelling, granulo-fatty degeneration, vacuolation and nuclear chromatolysis, with ultimate necrobiosis. The interstitial tissue shows edematous infiltration. The degenerative changes appear greater in incomplete (chronic) inanition, probably because of the longer time involved. These changes occur only in irregularly scattered areas, normal spermatozoa appearing in the other tubules and in the seminal vesicles. Sexual passion is retained for a considerable period, even after loss of 35 per cent in body weight. Upon ample refeeding, the degenerated areas disappear in 5-7 days, through regeneration of the persistent cells; and the interstitial tissue becomes infiltrated with fat.

Loisel ('01) studied the changes in the testis of a dog, emaciated by 26 days on water only. Spermatogenesis is completely arrested in most of the tubules, the epithelium being in various stages of retrogression, with some scattered fat granules. The phenomenon resembles the "metaspermato-genesis" in birds and (probably) in hibernating mammals. In both cases, pathological and physiological, the seminiferous epithelium tends to become reduced to a single type of cell, corresponding to the cells of Sertoli. These cells, under appropriate conditions, are able to regenerate the seminiferous epithelium.

Konstantinovitsch ('03) observed in the seminiferous epithelium (of rabbits?) fat droplets which appeared unchanged during starvation. This was confirmed by Traina ('04), who found the fat content of the testis unchanged in fasting rabbits. In adults, spermatogenesis continues unaffected until the loss in body weight reaches 20-25 per cent; and ceases only when the loss reaches 30-35 per cent. Even then, mitosis still continues in the spermatogonia and spermatocytes. The interstitial cells, including their fat content, remain unchanged during inanition. The *epididymis* cells also remain unchanged, including the cilia and the lipoidal granules. In the *seminal vesicles* of adult fasting rabbits, spermatozoa still occur. The fat granules of the lining cells remain unchanged; likewise the pigment granules (lipochromes). The fat content of the male reproductive tract therefore belongs to the "sessile" or "permanent" variety, unaffected by inanition.

Blumenthal ('04) studied the effects of inanition in mammals and (especially) the frog, noting that the testes become greatly atrophied. Ugrumow ('04) found that even moderate starvation of the male rabbit may produce low vitality in the offspring (*cf.* Morgulis '23).

As early as 1880, Nussbaum, in experiments on underfed frog larvae, noted that the sex glands may apparently continue development, in spite of retardation in growth of the body. Later ('06, '06a, '09, '14) Nussbaum found that in amphibia (frog and triton) inanition has a varied effect upon the testis and spermatogenesis (as previously mentioned for the ovary) according to the

time at which the inanition occurs. During the season of active proliferation of the sex-cells, the gonads (including testes and seminal vesicles) are very resistant to inanition. Under some conditions, growth and development may even continue at the expense of the rest of the body, in spite of starvation. Ultimately the sex glands are affected, however, and the final result is the same in all cases, the testes being reduced to spermatogonia and the ovaries to oogonia. Recovery is rapid upon refeeding.

Gerhartz ('06, '08) likewise found that in *Rana fusca* the marked resistance of the testes to inanition occurs only at a certain season, when development in preparation for the breeding season may continue at the expense of the remainder of the organism. During the fall and winter, however, the fully developed testes, and the accessory organs (*thumb swelling* and *seminal vesicle*) lose in weight during fasting in proportion to the entire body.

In the testes of cats at various stages of inanition, Beeli ('08) found an apparently marked decrease in weight, but no indication of degenerative changes at any stage. Fat droplets were noted in the peripheral portions of the seminiferous tubules, and also in the intertubular tissue; but there was no change in amount in the different stages of inanition. A distribution table according to size of the nuclei in the primary spermatocytes shows a shrinkage in diameter, the mode being 7.0-7.7 $\mu$  for the normal and 5.6-6.3 $\mu$  at death from starvation.

In the mouse and white rat (*Mus decumanus* var. *alb.*), Monterosso ('12) and Monterosso and Schlatter ('12) noted that the early stages of inanition may even stimulate the seminiferous epithelium (increase in lipoids and mitoses). More protracted inanition causes progressive degeneration, affecting first the last-formed elements, the spermatozoa; and involving progressively the spermatids and spermatogonia. The cells undergo nuclear pycnosis and chromatolysis, the chromatic material being ultimately transformed into fatty substances for nutritive purposes. The Sertoli cells are the last affected, and are very resistant; but their nuclei may disappear in extreme inanition (over 200 hours). Polynuclear giant cells, and also degenerating cells, may occur normally, but are much more numerous during inanition. The giant cells may arise by fusion of any of the cells in the seminiferous epithelium. The interstitial cells of the testis differ from the seminiferous epithelium in that their fat droplets disappear immediately when inanition begins (contrary to observations by earlier investigators).

In two dogs on incomplete inanition, Pořarkov ('13) found the amount of spermatic fluid reduced in 3 months (with loss of one-third in body weight) from 10 c.c. (normal) to 1 or 2 drops. Moreover the spermatozoa were deformed and lessened in vitality. The testis showed many tubules with Sertoli cells only. Spermatogonia were scarce, and presented signs of degeneration. Upon ample refeeding, the body weight was recovered in 2 months. The decrease in spermatic fluid continued at first, with gradual recovery later. Since the Sertoli cells are unable to regenerate, it was assumed that the regeneration was due to the few persistent spermatogonia; hence the slowness of recovery.

Kammerer ('13) observed that among *Salamandra maculosa* in captivity, whether full-fed or underfed, the gonads remained small and undeveloped, "verkümmert und von einem ungeheuren Fettkörper begleitet." Bardier ('13) reviewed the previous work on the effects of inanition upon the gonads.

Rondoni and Montagnani ('15) in fasting guinea pigs noted an apparent decrease in spermatogenesis. But few mature spermatozoa appeared in the seminiferous tubules, which were filled rather with granular or filamentous detritus. Morgulis, Howe and Hawk ('15) found no mitosis in the testes of dogs which had died from protracted inanition. The nuclei were large and round, with the chromatin usually massed on one side, resembling synzesis.

In adult albino rats, Jackson ('15) found in the acute inanition series (with loss of 33 per cent in body weight) a loss of 30 per cent in the testes; and in the chronic inanition series (body loss 36 per cent) a loss of 40 per cent in the testes (Table 4). In younger albino rats, held at constant body weight by underfeeding from 3 to 10 weeks of age, Jackson ('15a) noted an increase of 34 per cent in weight of the testes, with but little change in those similarly underfed from 10 weeks to 8 months of age (Table 4). In still younger rats, underfed from birth for various periods, Stewart ('18, '19) found still greater increases in testis weight, reaching (in the series held at birth weight for 16 days) the astonishing maximum of 374 per cent! In this series the *epididymides* were likewise 225 per cent above normal weight (Table 4). In the stunted offspring of severely underfed pregnant albino rats, Barry ('20, '21) found the testes only 16 per cent above normal (for corresponding body weight) (Table 4).

In albino rats amply refed after maintenance (constant body weight) by underfeeding from 3 to 12 weeks of age, Stewart ('16) concluded that the testes and *epididymides* were probably somewhat below normal weight for a few weeks, but became practically normal before the adult stage was reached. In albino rats underfed from birth to 3 weeks of age and then refed to 25 or 50 g. in body weight, Jackson and Stewart ('19) noted that the testes remained slightly (17-19 per cent) above normal weight, while in those refed to 75 g. body weight, the testes averaged 45-49 per cent subnormal (Table 7). The *epididymides* in the first case were nearly normal in weight, whereas in the second case they were 17-27 per cent subnormal (Table 7). In rats underfed from birth to 3 or 10 weeks, and then refed to adult stage, Jackson and Stewart ('20) found the testes 9-18 per cent above normal in weight; and in those refed after underfeeding from 3 to 20 weeks of age, or longer, the testes were 17-30 per cent above normal (Table 8). In all cases, the *epididymides* appeared 24-34 per cent above normal in the rats refed to adult condition.

In contrast with Nussbaum's results, Swingle ('18) observed in the larvae of *Rana pipiens* starved for over 100 days (from emergence from the egg capsule) an inhibition of growth and development in the gonads, including both germ cells and interstitial tissue.

In starved pigeons with loss of about 40 per cent in body weight, McCarrison ('19, '21) found an enormous loss of over 80 per cent in the weights of the testes (Fig. 35).

Siperstein ('21) studied the effects of inanition in the albino rat, finding that:

"In rats two days old starved for forty-eight to fifty hours, the testis increases markedly in weight, but mitoses are reduced in number and the normal process of histological differentiation is arrested. The seminiferous tubules remain nearly normal in diameter.

"During underfeeding for various periods beginning in rats three weeks old, mitosis continues in the cells of the seminiferous tubules, but the process of spermatogenesis is arrested at the primary spermatocyte stage, which persists even in rats over 400 days old. The spermatocytes degenerate and are resorbed, but if the number formed exceeds those destroyed, the testis may increase in weight. Multinucleated giant-cells are formed during the process of degeneration. The spermatogonia and Sertoli cells usually persist unaffected, except in very extreme cases, where a complete degeneration and disintegration of the seminiferous epithelium may occur. If the underfeeding begins after sexual maturity, the seminiferous tissue is much more resistant and normal spermatogenesis may persist for a long time. The seminiferous tubules may increase slightly in diameter in the shorter tests, but usually appear sub-normal in size in the longer experiments.

"Acute inanition in adult rats, with 30-47 per cent loss in body weight, produces degenerative changes in a few, irregularly scattered, tubules. All the other tubules show apparently normal structure and spermatogenesis, although there is a general decrease in their size. The degenerative changes are initiated by a desquamation of the epithelial cells into the lumen of the seminiferous tubule, followed by pycnosis and karyolysis. The process involves first the spermatids and spermatozoa, then the secondary and primary spermatocytes, and finally the spermatogonia. The Sertoli cells are the most resistant. During the degenerative process, multinucleated giant-cells arise, apparently by fusion of the degenerating spermatocytes.

"During inanition, mitosis is very persistent in the seminiferous epithelium, both in young and adult rats. It may occur even in tubules where nearly all the cells are more or less degenerated. Amitosis was not observed. A condition resembling synizesis was frequently observed in the spermatids in both controls and test rats.

"Refeeding after prolonged inanition (beginning in rats at three weeks of age and extending to twelve to twenty weeks) results in a rapid improvement in the structure of the testis, although it may lag behind in weight for awhile during the preliminary stages of reconstruction. Spermatogenesis returns to normal in a short time, the tubules gradually increase to normal diameter, and spermatozoa appeared in thirty-seven days.

"There is a definite hypertrophy of the interstitial tissue and an increase in the number of interstitial cells of the testis during the regenerative period on refeeding after inanition (in growing rats). No hypertrophy of the interstitial tissue was found accompanying atrophy of the seminiferous epithelium during inanition in either young or adult rats. The structure of the interstitial tissue and the size of the nuclei apparently remain nearly normal during acute and

chronic inanition, except in extreme cases, where degenerative changes in the cells may occur."

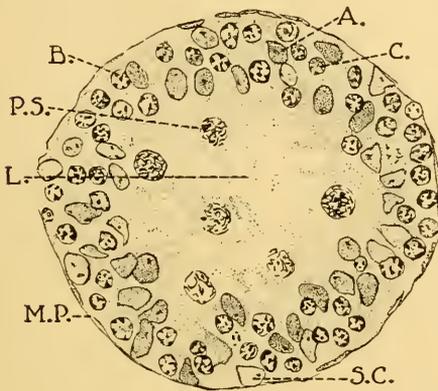


Fig. 100

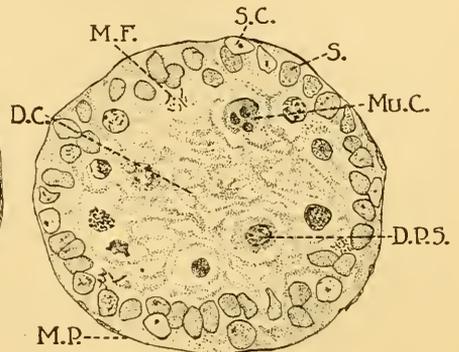


Fig. 101

FIGS. 100 and 101.—Showing the effects of inanition upon the testis in the young albino rat.  $\times 514$ . Figure 100 shows a cross section of a seminiferous tubule in a normal albino rat (Si 6.0) 3 weeks old. Figure 101 is a similar section in a rat (S. 7.32) held at constant body weight by underfeeding from 3 to 10 weeks of age. A, B, C, Allen's cell types of spermatogonia; D. C., degenerated cytoplasm; D.P.S., degenerating primary spermatocyte; L, lumen; M.F., mitotic figure; M.P., membrana propria; Mu.C., multinucleated cell; P.S., primary spermatocyte; S, spermatogonia; S.C., Sertoli cell. (Siperstein '21.)

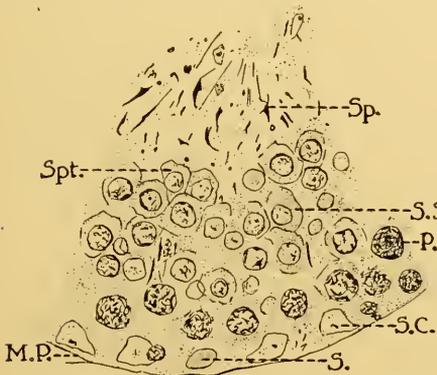


Fig. 102

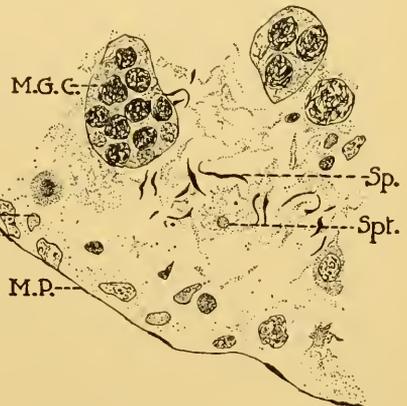


Fig. 103

FIGS. 102 and 103.—Showing the effects of inanition upon the adult testis in the albino rat.  $\times 514$ . Figure 102 shows a portion of a seminiferous tubule in cross section from a normal rat (St 5.2) 8 weeks old (practically adult structure). Figure 103 shows the corresponding structure in an adult rat (S. 25) after 9 days inanition on water only, with 35 per cent loss in body weight. M.G.C., multinucleated giant cells; M.P., membrana propria; P.S., primary spermatocytes; S, spermatogonia; S.C., Sertoli cell; Sp., spermatozoa; Spt., spermatid; S.S., secondary spermatocytes. (Siperstein '21.)

Figure 100 shows the normal seminiferous tubule in the albino rat at 3 weeks of age, and Fig. 101 the changes in a rat held at constant body weight by underfeeding from 3 to 10 weeks of age. Figure 102 shows the structure of

an adult seminiferous tubule, and Fig. 103 the effect of acute inanition in an adult albino rat.

The claim of Champy ('21) to have reduced male *Triton alpestris* by starvation to a sexually neutral condition, with transformation to a female in one case upon refeeding, was mentioned in Chapter XXIV.

Okuneff ('22) found no change of the lipoidal substance in the interstitial cells of Leydig or in the Sertoli cells of the testis in fasting rabbits (confirming Traina). Later ('23) he reported that the seminiferous epithelium and the interstitial cells remain unchanged in all respects, including their mitochondria (chondriosomes).

Stieve ('22) discovered that the male goose (gander) loses about one-fourth in body weight during the period just preceding and at the breeding season. "Die dem Gesamtorganismus entzogenen Substanzen werden offenbar zum Aufbau der Keimzellen verwendet." If this interpretation be correct, the phenomenon is evidently comparable to that during the migration of the fasting salmon. The case of the male fur-seal (cited in Chapter IV) perhaps belongs in the same category.

In the leopard frog (*Rana pipiens*) during hibernation and subsequent inanition with losses of 10-60 per cent in body weight, Ott ('24) found a slight loss (7 per cent) in the average weight of the testes during hibernation. Thereafter the loss in testis weight ran roughly parallel with the body weight. In the late stages, the loss in the testis appeared relatively greater, reaching 89 per cent in the group with loss of 60 per cent in body weight (Table 6).

**Hibernation and Seasonal Changes.**—The case of the migration of the salmon up the rivers to the spawning grounds (Miescher '80, '97; Stone '97; Paton '98; Greene '10) has already been mentioned in previous chapters. During this fasting period of several months the testes and ovaries develop enormously at the expense of the remainder of the organism, especially the trunk musculature. Somewhat comparable phenomena in the gander and the fur-seal were mentioned above.

In the frog, regular seasonal changes in weight and structure of the testis have been described by Ploetz ('90) and Gaule ('93) for *Rana temporaria* and *Rana fusca*. Nussbaum ('06, '06a) described the conditions in *Rana fusca*, also in *Triton*. Ploetz and Nussbaum found the maximum size of the frog testis in August, the minimum in the spring. Athanasiu and Dragoin ('08) described an infiltration of fat in the basal cells of the seminiferous tubules (also some intertubular) in winter frogs. As emphasized by Nussbaum and Gerhartz, the effects of inanition upon the testes vary greatly according to the time at which it occurs, especially in forms undergoing seasonal changes.

The work of Ganfini ('02) on the interstitial cells of hibernating animals was inaccessible.

Mann ('16) found no specific changes in the sex glands of the gopher (*Spermophilus tridecemlineatus*) during hibernation. Hansemann ('96, '98) found that spermatogenesis ceases in the hibernating marmot, and that the interstitial cells almost entirely disappear. Rasmussen ('17 '18) found cyclic changes in the interstitial cells of the ovary and testis of the woodchuck (*Marmota monax*),

which undergo gradual enlargement during the hibernation period, with differentiation of mitochondria and lipoidal granules.

### (B) EFFECTS OF PARTIAL INANITION

The effects of partial inanition upon the testis may involve dietary deficiencies in the protein (including pellagra and malnutritional edema), in salts (including rickets), in vitamins (A, B or C), and in water (aqueous inanition).

**Protein Deficiencies.**—Most of the data available under this heading refer to mixed deficiencies, in which a shortage of protein is more or less prominent. Abderhalden ('19) found that male rats (white and white-black) on maize diets usually live only 40-50 days, with unfavorable effects upon reproduction. The males appeared less affected than the females, however, and in some cases were able to fertilize normal females even after 8 weeks on maize diet.

Slonaker and Card ('18, '23a), on the other hand, found that in young albino rats on a relatively protein-poor vegetable diet, pubescence was delayed more in the males than in the females, and sterility in adults was greatly increased. Conditions were markedly improved by the addition of animal protein (milk, eggs, etc.) to the diet.

Reynolds and Macomber ('21, '21a,) and Macomber ('23) experimented with albino rats on diets variously deficient (in general calories, protein, vitamins and calcium, separately or combined). By matings with normal rats it was determined that in both sexes the age of puberty is postponed, and the fertility lowered, by the deficient diets. Diets with double deficiency appeared in general more unfavorable than those with any single deficiency.

Malnutritional edema was produced by Kohman ('20) in rats on watery diets deficient especially in protein and fats. In the males, there was a marked decrease in the size of the testes, which was easily detected in the living animal. In human war edema, Reach ('19) observed atrophic testes incompletely descended in many cases; and Lubarsch ('21) noted hemosiderin deposits in the perivascular connective cells of the testis.

In **pellagra**, Raubitschek ('15) found usually no characteristic changes in the testis and *epididymis*.

In human **rickets**, Juaristi ('19) stated that the *penis* is long and hangs flaccid. In rats with experimental rickets, McCollum, Simmonds, Shipley and Park ('21) noted that the gonads were atrophic. Jackson and Carleton ('23) found the weight of the testis irregular, but usually not decreased, in albino rats with experimental rickets; and the *epididymis* usually appeared above normal in weight (Table 11).

As previously mentioned, Reynolds and Macomber ('21) found markedly lowered fertility in rats on diets deficient in calcium (or otherwise). In the discussion of this paper, W. Blair Bell cited the correlation between fertility and calcium content of the blood, as shown by his experiments with hens 15 years ago.

**Vitamin Deficiencies. Vitamin A.**—In rats fed *lipoid-free* rations (deficient in fat and in vitamin A), Hatai ('15) found the testes 44 per cent below normal

weight, with an absolute decrease of 23 per cent during the 6 months of experiment. In young rats on vitamin-free (polished rice) diets, Tsuji ('20) noted atrophy of the testis and degeneration of the seminiferous tubules.

Davis and Outhouse ('21) found the testis normal in most cases in rats on diets deficient in vitamin A (producing xerophthalmia). Emmett and Peacock ('22), however, noted atrophy of the testes in chickens on similar diets. Reynolds and Macomber ('21, '21A) and Macomber ('23) found that sterility in both sexes of rats is increased by diets deficient in vitamin A, as well as by other deficiencies. Meyerstein ('22) noted hypoplasia of the seminiferous epithelium and a relative increase of interstitial tissue in young white rats on diets deficient in vitamins A and B.

**Vitamin B.**—There is a large amount of evidence indicating that the testes are especially susceptible to a dietary deficiency of vitamin B. Funk and Douglas ('14) found evidences of degeneration in pigeons with experimental beriberi, and Tasawa ('15) likewise observed atrophy of the testes in a large number of chickens and pigeons on polished rice diet. The above mentioned results of Tsuji ('20) and Myerstein ('22) in young rats may depend chiefly upon vitamin B deficiency.

Drummond ('18) similarly noted suppression of spermatogenesis in young rats (black variety of *Mus norvegicus*) on diets deficient in vitamin B. Osborne and Mendel ('18c) also found a lack of fertility in rats reared on similar diets: "Twenty-five per cent of these animals ultimately reached a very large size but all failed to breed when mated with rats raised on the yeast diets, and only four proved fertile with rats raised on the ordinary 'mixed food' fed our stock colony. Even changing the rats from yeast-vitamin diet to this stock diet failed to render them fertile. Professor H. H. Donaldson kindly examined the reproductive organs of these animals and reported that in the testes of the four animals which he had examined he found no spermatozoa, no tubular tissue, and an excess of interstitial tissue."

Ezra Allen ('19) in similar rats received from Osborne and Mendel found the testes one-half to two-thirds below the Wistar norm for weight. There was a total degeneration of the germ cells (similar to that produced by alcoholization or X-ray exposure), but a persistence of the Sertoli cells in the form of a syncytium, and also a large increase in the quantity of interstitial tissue. Likewise Meyerstein ('22) reported specific atrophy of the gonads in albino rats on diets of potato or rye flour, with restoration of normal conditions upon the addition of vitamins A and B.

In chickens on diets deficient in vitamin B, Houlbert ('19) found atrophy of the testis with pigmentation of the interstitial cells and arrested spermatogenesis. Growth and development of the secondary sex characters (spurs, comb and tail feathers) were also inhibited, but normal conditions were restored upon the addition of the missing vitamin. Dutcher ('20) similarly found that in white Leghorn cockerels on polished rice diet, the testes become very atrophic (with maximum loss of 80 per cent), in some cases even without loss in body weight. Upon removing one atrophic testis and adding green alfalfa to the diet, the remaining testis approached normal. Atrophy of the testis in fowls,

due to deficiency of vitamin B, was also noted by Dutcher and Wilkins ('21), by Damianowich ('21), by Souba and Dutcher ('22) and by Souba ('23).

In pigeons on autoclaved rice diet, as during inanition, McCarrison ('19, '21) found an astonishing atrophy of the testes, with loss of more than 80 per cent in weight (Fig. 35). In monkeys on similar deficient diets, the loss in weight of the testes was less marked, but still relatively greater than in the body as a whole. Novaro ('20a) noted degeneration of the seminiferous epithelium and hypertrophy and hyperplasia of the interstitial cells in pigeons on diets lacking vitamin B.

Further observations on the atrophy of the testes in pigeons on diets deficient in vitamin B were made by Portier ('20, '20a). In order to eliminate seasonal and individual differences, a portion of the right testis was first removed as a control. Then after various periods of avitaminosis, the remainder of the right testis, and also the left (which had not suffered trauma), were removed and examined. During the first 15 days, there is a beginning proliferation of the intertubular connective tissue. The tubules have kept nearly normal diameter, but spermatogenesis is disturbed and arrested in some cases, with more or less degeneration in some spermatids. In 25 days more, the connective tissue has proliferated, causing atrophy of the interstitial cells. The tubules have greatly decreased in diameter (from  $300\mu$  to  $42\mu$ , in some cases). The spermatozoa disappear by degeneration *in situ*, and the lumen contains only fragments of desquamated, degenerated cells. The walls of the tubules include spermatogonia and spermatocytes (many with nuclei in synapsis). The degenerative changes are somewhat different in winter pigeons, where normally there is no spermatogenesis.

The effects of avian beriberi upon the testis were also studied by Findlay ('21) in pigeons and fowls. The seminiferous tubules showed marked shrinkage, the lumen being filled with debris, including normal spermatozoa. There was no clear differentiation between spermatogonia, spermatocytes and syncytial (Sertoli?) cells, for many of these had lost their lipid content. The interstitial cells of Leydig still contained some lipid, but the nuclei often appeared swollen and vesicular. The changes were similar to those found during total inanition. As shown by Table 13, the loss in weight appeared greater in the testes of the pigeons (82-85 per cent) than in the fowls (60-61 per cent). Atrophy of the testis and degeneration of the seminal epithelium in pigeons on a diet deficient in vitamin B were also described by Gotta ('23). In adult pigeons on a vitamin-free diet, Lopez-Lomba ('23) found the testes nearly normal in weight up to the 14th day, followed by an immense hypertrophy between the 14th and 22nd days, returning to slightly below normal by the 30th day.

**Vitamin C.**—Hess ('20) found no statements in the literature as to the effects of *scurvy* on the testes or ovary. Bessesen ('23) observed an apparent marked increase in the weight of the testes in scorbutic guinea pigs, varying from 31-76 per cent at various stages, excepting at death from scurvy, where it was only 4.8 per cent above normal (Table 12).

**Aqueous Inanition.**—In a dog on dry diet with loss of about 21 per cent in body weight, Falck and Scheffer ('54) noted a loss of 23.5 per cent in the weight of the *penis* and testes (together).

In a dog on dry bread with loss of 24 per cent in weight, Pernice and Scagliosi ('95a) found a dry and atrophic appearance of the testis, *epididymis* and *prostate* at autopsy. The *seminal vesicles* and *ductus deferens* were anemic and contained scarcely any seminal fluid. The microscopic structure was not described in this case; but in 3 young chickens on dry maize diet the testes appeared hyperemic, and the tunica albuginea presented small cell infiltration, extending into the testis along the septula between the lobules. The tubules were decreased in diameter. Their cells also appeared small and atrophic, poorly-staining, with no mitosis in the spermatogonia. Spermatozoa were absent.

In adult albino rats on relatively dry diets, Kudo ('21) in the acute thirst series (with loss of 36 per cent in body weight) found a loss of but 15 per cent in the testes; while in the chronic thirst series (body loss 52 per cent), the testes lost about 60 per cent. In a rat on total inanition (body loss 47 per cent) the testes lost 37 per cent. The *epididymides*, in the same acute thirst series, lost 30 per cent; in the chronic thirst series, 65 per cent; and in total inanition, 56 per cent (Table 9).

In young albino rats held at constant body weight by a relatively dry diet for various periods, beginning at about 4 weeks of age, Kudo ('21a) found a progressive loss in the weight of the testes, amounting to 68 per cent in those on experiment 7-8 weeks. A similar, though usually less marked loss occurred also in the *epididymides*, amounting to 30.5 per cent in the extreme group (Table 10). The results for the testes differ markedly from those found by Jackson and Stewart during simple underfeeding, where at the same ages the testes showed a persistent increase in weight (Table 4).

## CHAPTER XXVI

### EFFECTS ON THE SUPRARENAL GLANDS

A prominent characteristic of the suprarenal (adrenal) glands is their marked apparent resistance to the effects of both total and partial inanition. An interesting feature (occasionally found also in other endocrine glands) is their tendency to hypertrophy, rather than atrophy, in various conditions of malnutrition. After a brief summary, the effects of inanition upon the suprarenal glands will be considered in detail under (*A*) total inanition and (*B*) partial inanition.

#### SUMMARY OF EFFECTS ON THE SUPRARENAL GLANDS

The data concerning the changes in the suprarenal glands during inanition appear usually discordant and conflicting. Some of these differences are due to variations in the type of degree of inanition, others to variations in species, age and individuals, as well as to the technique used by different investigators. Some of the variations (in lipoids, chromaffin substance, etc.) may be due to correlated but variable conditions elsewhere in the organism. In general, further research is required in order to clear up many unsolved problems concerning the effects of inanition upon the suprarenal glands.

As to the **weight** of the suprarenal glands, in human adults during total inanition (complete or incomplete), the available data indicate little or no loss, but rather an increase in most cases. In atrophic infants, on the other hand, a marked atrophy of the suprarenals appears characteristic. In adult fasting animals, as in man, the suprarenals appear relatively resistant to loss in weight, usually manifesting a very marked increase (sometimes over 100 per cent), contrasting strongly with the atrophy typically found in most of the other viscera. In young animals, the persistent increase in suprarenal weight may be even greater, especially at certain stages of inanition and development, although a marked atrophy occurs during prenatal inanition (rat). Upon refeeding, mitosis (which is suppressed during inanition) is resumed, and the hypertrophied suprarenals promptly decrease to normal size, sometimes even below normal.

Notable enlargement of the suprarenal glands also occurs in various forms of partial inanition, especially with dietetic deficiencies in protein (malnutritional edema), in salts (experimental rickets), and in vitamins (especially in beriberi and experimental scurvy). In rats on dry diets (thirst) the results are similar to those during total inanition.

The enlargement of the suprarenal during inanition appears due to hypertrophy in some cases of the cortex; in others, of the medulla, or of both. Congestion of the blood vessels (sometimes hemorrhage) is characteristic in both cortex and medulla, and this may in some cases cause an increase in weight, in spite of actual atrophy of the parenchyma.

The changes in **structure** appear equally variable during inanition (including hibernation), with frequently conflicting data. In the *cortex*, there is a variable degree of cell atrophy in some regions, especially in the *zona fasciculata* and *zona reticularis*. The characteristic fat content is frequently described as persistent or sometimes even increasing during inanition, though in other cases a variable decrease is claimed. In some regions (*zona glomerulosa* and outer *fasciculata*) there is often a tenacious persistence of the lipoids, even to death from starvation. The losses also appear variable in the different elements of the suprarenal fat (neutral fats, cholesterolin, phosphatids, etc.) which may explain some of the apparent discrepancies in results. The pigment is variable, frequently increased. The cortical changes appear somewhat similar in the various types of both partial and total inanition.

In the suprarenal *medulla*, the atrophic and degenerative cell changes during inanition appear less marked and frequent than in the *cortex*. Interest has centered mainly in the chromaffin substance, with conflicting results. Most investigators have described a decrease in the chromaffin reaction during inanition, especially in the later stages, although in some cases the reaction persists apparently undiminished even up to death from starvation. Post-mortem changes may account for the marked decrease in chromaffin reaction described by some authors. Associated with the enlargement of the suprarenal gland, there is usually a marked increase in the total epinephrin content during beriberi, but apparently a decrease during scurvy. Fibrosis and inflammatory changes have been described in the medulla during pellagra.

#### (A) EFFECTS OF TOTAL INANITION, OR ON WATER ONLY

The data for man (adult and infant) will be presented first, followed by those for the lower animals.

**Human Adults.**—In man, no observations upon the effects of inanition on the suprarenal glands have been found in the earlier literature. Orth ('93) stated that a decrease in the fat (lipoids) of the human suprarenal occurs during inanition. Beneke ('94) likewise concluded that "Allgemeine Ernährungsstörungen veranlassen entsprechende Veränderung der Nebennieren; fettreich erwachsene Personen haben auch sehr fettreiche Nebennieren, während bei Kachexie das Fett verschwindet." Stilling ('98) and Hermann ('05) also found a decrease in the suprarenal cortical fat (lipoids) in man during inanition from wasting diseases, such as tuberculosis. This view was also supported by Babes and Jonesco ('08), who found a diminution of suprarenal fat in various abnormal conditions in man and rabbits (to be mentioned later).

The opposite conclusion was reached by Napp ('05), who found the amount of suprarenal fat in human adults generally independent of the nutritive condition. The suprarenal fat sometimes appeared scanty in well nourished individuals, and frequently it was found abundant in the emaciated. Especially in toxic conditions (including tuberculosis), no correlation was found between suprarenal fat and general nutrition. Kawamura ('11) similarly concluded: "Bei der Inanition habe ich—mit Ausnahme des Falles von chronischer Peritonitis—

keine Verminderung des Fettgehaltes konstatieren können, sondern im Gegensatz zu den anderen Autoren reichlich Fett gefunden."

Landau ('13) found that there may even be an *increase* in suprarenal lipoids in some cases of human inanition, such as stenosis from pyloric ulcer, and in other pyogenic conditions; but a reduction in suprarenal lipoids was found in tuberculosis and in septic-toxic conditions in general. The suprarenal lipid content is considered secondary to the lipid content of the body in general, but shows no evident relation to the general nutritive condition.

Meyer ('17) in a man who died of starvation noted that "In some portions the glomerular cells of the adrenal are mere webs and great cell disintegration is present. The atrophy is very marked and many shadowy cells are seen. The parenchyma contains many open spaces; the medulla is not only greatly reduced in size, but is greatly vacuolated, and almost completely destroyed in places."

Roessle ('19) concluded from a large series of necropsies on soldiers that the suprarenal may undergo changes such as edema or exhaustion of its lipid content, but he established no relation between these changes and emaciation. Byrne ('19) in 8 necropsies on soldiers dying from underfeeding in a prison camp found the suprarenals about 50 per cent enlarged (which agrees with recent experimental data to be mentioned later). The enlargement seemed to be chiefly in the cortex.

The data of Krieger ('20) likewise show an increased weight of the suprarenal glands in emaciated soldiers (excepting in diarrheas), as shown by the accompanying table. This, however, adopts v. Gierke's norm of 11.6 g. for the weight of both suprarenals, which is lower than Vierordt's (14.8 g.) or Roessle's (14.1 g.).

AVERAGE WEIGHT OF (BOTH) SUPRARENAL GLANDS DURING VARIOUS CONDITIONS OF MALNUTRITION (KRIEGER '20)

Cause of inanition	No. of cases	Normal weight (v. Gierke), grams	Observed weight, grams	Percentage change, per cent	Percentage of body weight, <sup>1</sup> per cent
Chronic diarrhea.....	5	11.6	10.6	-17.2	0.030
Malignant growths.....	9	11.6	14.1	+21.5	0.038
Chronic infections.....	23	11.6	14.3	+23.2	0.0386
Tuberculosis.....	24	11.6	12.3	+ 6.6	0.0334

<sup>1</sup> Normal according to Vierordt is 0.02 per cent.

Pellegrini ('20) observed a slight apparent decrease in the suprarenals of war prisoners who died from inanition. Leupold ('20?) concluded that after the completion of growth neither acute nor chronic diseases have any influence upon the weight of the suprarenal glands. Schilf ('22) has recently analyzed the data from 1,227 necropsies (at Jena) including 423 from the war period. He concludes that in general the suprarenal weight is independent of the nutritive condition of the body, although it appears somewhat decreased in the tuberculous group.

In the **infant**, Beneke ('94) remarked that "zart gebaute schwächliche Kinder haben schmale, fettlose Nebennieren; kräftige, guternährte dagegen fetthaltige." In athreptic infants, Thiercelin ('04) described hemorrhages as characteristic in the suprarenal glands, sometimes causing a considerable increase in volume. He cited a case observed by Parrot in which the suprarenal was ruptured by distension due to hemorrhage.

In infantile marasmus, Thompson ('07) noted incidentally that the suprarenal cortex appeared normal; the medulla small in size, with cells swollen or in places replaced by connective tissue.

Lucien ('08, '08a) found the weight of the suprarenals in athreptic infants greatly reduced, a minimum of 1.05 g. being noted. The color is darker than normal, and the consistence firm. Stained sections (fixation in formalin or Flemming's fluid) reveal various changes. There is a slight thickening of the fibrous capsule and trabeculae, with a sclerosis of the cortex, especially in the reticular zone, and to a less extent in the medulla. The cortical cells become atrophic, especially in the reticular zone, and lose their lipoidal content (except in the most external part of the zona fasciculata). The blood capillaries in the zona reticularis are distended, and a few pigmented cells occur. The changes resemble those described by Bernard and Bigart in tuberculosis, and indicate a hyposecretory condition of the suprarenals, associated with a profound intoxication of the organism.

Helmholz ('09) in the suprarenals of atrophic infants noted merely a thinning of the cortex with a slight increase in the connective tissue.

Mattei ('14) gave individual weights for the suprarenals in 7 athreptic infants, and made a careful histological study. The suprarenal weight was usually below normal (assumed as 3 g.), the ratio to body weight being 1:1,400 to 1:2,000 (normal 1:750). Mulon's method shows a reduction in the amount of fat in the cortical cells. Otherwise the glomerular and fasciculate zones in general are but slightly changed, although some cords appear swollen and clear, and others present cells and nuclei in various stages of atrophic degeneration. In the zona reticularis the blood vessels appear enormously distended, and sometimes ruptured, with scattered atrophic parenchyma in the hemorrhagic effusion. In the medulla there likewise appears a marked congestion, and also a notable increase in the connective tissue. The chromaffin cells are in clumps or islets, some normal in structure and staining reactions, others swollen or atrophic, presenting various stages of degeneration, sometimes containing hematogenous pigment. "Telles sont les altérations glandulaires surrénales les plus ordinaires au cours de nos observations. Il est utile et intéressant de remarquer que les lésions prédominent d'une façon très nette dans la médullaire et dans quelques boyaux cellulaires de la réticulée."

Lesage and Cleret ('14) found sclerosis as the characteristic change in most of the organs in congenital spasmodic atrophy of nurslings; but the suprarenals appeared normal in structure. Nobécourt ('16) reviewed the previous work on the changes in the various organs, including the suprarenals, in atrophic infants.

Lewis and Pappenheimer ('16) confirmed the occurrence of a normal post-natal involution of the suprarenal cortex, which had often been confused with pathological changes by the earlier investigators. They found no constant change in the relative sizes of the suprarenal cortex and medulla in children emaciated by malnutrition.

Marfan ('21) remarked that the suprarenal glands are small in atrophic infants. Huebschmann ('21) claimed that in acute nutritional disturbances of infants there is a characteristic fatty infiltration of the liver, correlated with a disappearance of lipoidal substances in the suprarenal glands. The cause was held to be an auto-intoxication through abnormal products of intermediary cell metabolism.

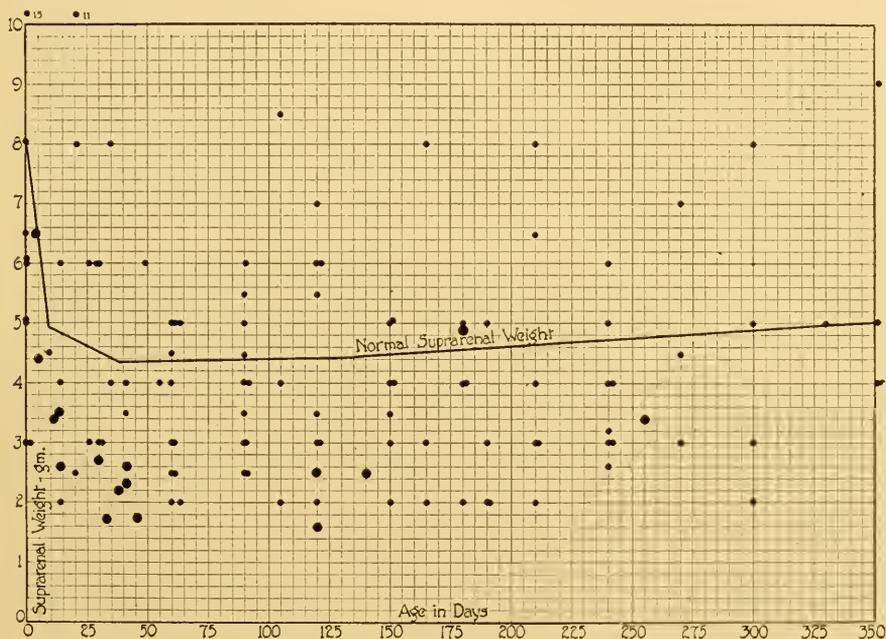


FIG. 104.—Graph showing the individual weights of both suprarenal glands, according to age, in atrophic infants of the first year. Curve of normal suprarenal weight from data compiled by Prof. R. E. Scammon, showing the rapid normal postnatal decrease, followed by a slow increase. The larger dots represent original Minnesota cases; the others are atrophic infants from various sources. While there is a wide individual variation, in most cases the suprarenals are clearly subnormal in weight.

In famine-stricken children 1-16 years old, Nicolaeff ('23) found the suprarenal glands sometimes apparently hypertrophied, but usually 5-37 per cent subnormal in weight according to age. Microscopic examination showed abundance of cortical lipoids. Stefko ('23, '23a) noted marked suprarenal changes. Stephani ('23) found the fat changes inconstant.

The weights of the suprarenal glands in all available cases of atrophic infants during the first year of life are shown in Fig. 104. It will be noted that the postnatal involution occasions a normal decrease in weight from 8 g. at birth to about 4.4 g. by the end of the first month, with a very slow increase thereafter. In most cases, the weight of the suprarenals in the atrophic

infants is still lower as a result of inanition. The larger dots represent Minnesota cases. The weights for some of these cases are also given in Table 3.

In all cases where full data were available, Jackson ('22) estimated the loss of weight for the suprarenals in atrophic infants upon various bases, with the results shown in Table 2. In comparison with the normal for the final body weight, the average loss in the weight of the suprarenals was 43.3 per cent (or 53.1 per cent in the Minnesota cases alone). Compared with the normal for the maximum body weight during life, the loss in suprarenal weight was 60.5 per cent. In comparison with the normal for the corresponding final body length (height) the loss in suprarenal weight was 56.9 per cent. According to age, the suprarenals averaged 38.5 (41.7) per cent subnormal. This includes the cases shown in Fig. 104.

The data for the **lower animals** are more numerous. The earlier literature will be considered in chronological order; the later data for the cortex, medulla; weight and hibernation are listed separately.

Chossat ('43) in fasting pigeons with loss of 40 per cent in body weight noted in 3 cases a weight of 0.01 g. for the suprarenal glands; while in 2 controls the weights of 0.06 and 0.02 (average 0.04) g. This would indicate a very marked loss in the suprarenals.

Manassein ('68, '60) recorded without comment (in his Table 12) data indicating that in 47 adult fasting rabbits, with loss of about 39 per cent in body weight, the suprarenal glands showed an average *increase* of 16 per cent in weight; in 8 young fasting rabbits,  $3\frac{2}{3}$  months old, with loss of about 33 per cent in body weight, the suprarenals gained 51 per cent; while in 3 still younger fasting rabbits (23-25 days old), with loss of about 35 per cent in body weight, the suprarenals apparently gained 89 per cent in weight! In 5 rabbits refed after a period of inanition, however, the suprarenals appeared 23 per cent subnormal in weight.

Lépine ('74) stated that during inanition in animals the suprarenals appear nearly normal.

Martinotti ('92, '92a) found the suprarenal glands enlarged and congested in fasting guinea pigs. The blood not only distended the vessels but also infiltrated the intercellular spaces of the cell cords. After 3 or 4 days of inanition, the number of mitoses in a section of the cortex was found greatly increased (20-25), as likewise in animals refed after a few days of inanition.

Barbèra and Bicci ('00) found in rabbits starved 7 days with loss of 34 per cent in body weight a reduction in average diameter of the suprarenal cortex nuclei from  $7.238\mu$  to  $4.817\mu$ , a decrease of 33.4 per cent. In the medulla, the nuclei were reduced from  $7.773\mu$  to  $5.587\mu$ , a decrease of 28.25 per cent. Similar results were obtained in dogs starved 17-26 days, with loss of 29-36 per cent in body weight. Changes in the cytoplasmic and nuclear structure were also described.

The subsequent investigations concerning the effects of inanition on the suprarenals (in animals) have usually centered around either the changes in the cortex, especially in its fat content, or in the medulla (chromaffin tissue). These two phases will therefore be considered separately.

**Cortex and Fat Content.**—As already mentioned, during human inanition or malnutrition in adults a decrease of cortical lipoids was claimed by Orth ('93), Beneke ('94), Stilling ('98), Hermann ('05) and Babes and Jonesco ('08); but denied by Napp ('05), Kawamura ('11) and Landau ('13). In athreptic infants, a decrease in cortical lipoids was claimed by Lucien ('08, '08a), Mattei ('14) and Marfan ('21). As a result of animal feeding experiments, Ewald ('02) concluded that the fat content of the suprarenal gland is independent of the (transient) stages of digestion, but is in general proportional to the general nutritive condition of the individual. Controls were full fed on mixed diet, while test rabbits were placed on water only for 5 or 6 days; mice similarly 3 or 4 days. Unless starved to death, the animals were then killed, and the fat content of the suprarenal cortex was found greatly reduced in amount by inanition.

On the other hand, Federici ('03) found no manifest decrease in the suprarenal cortical fat in a guinea pig starved to death by progressive underfeeding for 15 or 20 days; and Konstantinovitsch ('03) stated that the abundant cortical fat is retained in starving rabbits, guinea pigs and mice. Traina ('04) by a careful study with modern fat stains (osmic, sudan III and scarlet red) in fasting rabbits, young and adult, found a decrease in size of the cells in the suprarenal cortex, but no decrease in their fat content, which belongs to the "sessile" or "permanent" variety. Bonnamour ('05, '05a) even claimed a considerable *increase* in the amount of cortical fat (especially in the glomerular and reticular zones) in the starving rat, guinea pig, cat and rabbit. A different result appeared in hibernation (to be mentioned later).

Beeli ('08) found some atrophy in the cells of the suprarenal cortex in cats subjected to various degrees of starvation, but no change in the fat content. The nuclei also decreased in diameter, as shown by the distribution table. The mode in the normal cat was 6.3-7.0 $\mu$ ; at death from starvation, 4.2-4.9 $\mu$ . The cells and nuclei in the medulla were less affected.

In agreement with Ewald (and most of the earlier investigations on the human suprarenal), Babes and Jonesco ('08), however, maintained that there is a diminution and displacement of the cortical fat in man and animals in various conditions of inanition. "Dans la mort par inanition, il y a sans doute une certaine diminution de la graisse chez le lapin, la graisse etant un peu plus dans ces cas, dans la partie superficielle de la couche trabeculaire."

Ciaccio ('10) found certain "siderophile" cells of the suprarenal cortex in the hedgehog and dormouse increased in number after 5 or 6 days of inanition. The cortical lipoids were also abundant, in contrast with the condition after hibernation (to be mentioned later).

Landau ('13) likewise found no decrease in the total lipoid content of the suprarenal cortex in man, cat and guinea pig during inanition, although differential stains indicate a decrease in cholesterin in all but the outer zone. In the fasting guinea pig, there is an extension of the lipoid-containing layers. In white rats fasting 2-8 days, Wegelin ('13) similarly found no essential decrease in the total lipoid content of the suprarenal cortex.

Ponomarew ('14), on the contrary, obtained in white mice during complete inanition (also on carbohydrate or protein diets) a decrease in the suprarenal fats. These often disappear completely in the zona fasciculata and zona reticularis, though a small quantity is constantly retained in the zona glomerulosa (and spongiosa). This applies in general to the neutral fats and fatty acids.

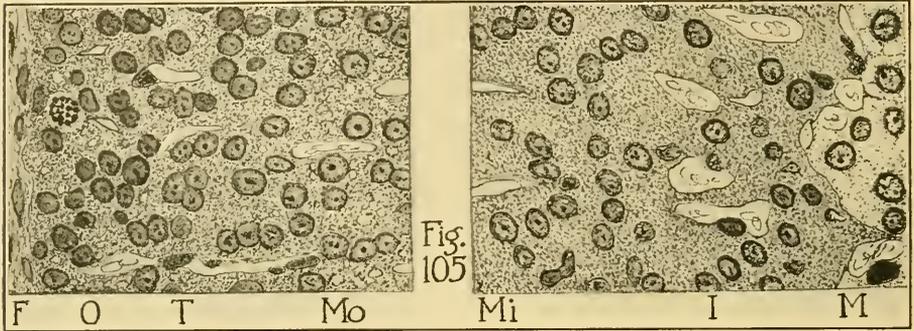


FIG. 105.—Portion of a section of the suprarenal gland of a normal male albino rat (J. 1.1) 3 weeks old. Most of the middle part of the cortical zone is omitted. *F*, fibrous capsule; *O*, outer zone (glomerulosa); showing one cell in mitosis; *T*, transition band, nearly lipid-free; *Mo*, outer part, and *Mi*, inner part of middle zone (fasciculata); *I*, inner zone (reticularis); *M*, small portion of medulla. Zenker fixation; hematoxylin-eosin stain.  $\times 300$ . (Jackson '19.)

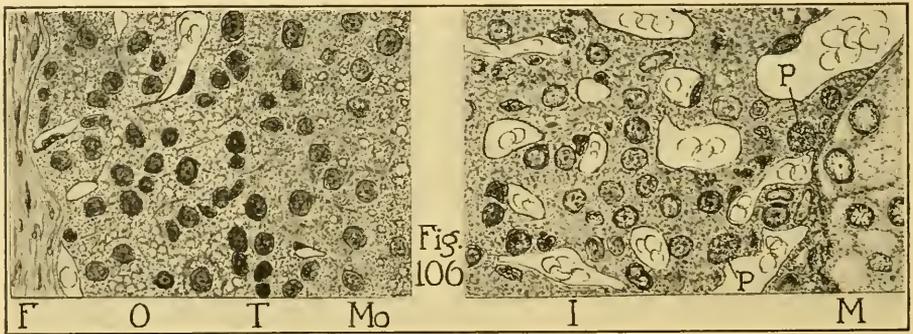


FIG. 106.—Portion of a section of the suprarenal gland of a male albino rat (S. 7.31) held at constant body weight by underfeeding from 3 to 10 weeks of age.  $\times 300$ . For explanations see Fig. 105. There is a progressive differentiation of lipoidal vacuoles in the outer zone (*O*), and of pigment (*P*) in the inner zone (*I*); also some cell atrophy, with hyperemia and increased degeneration in the inner cortical zone. (Jackson '19.)

The lipoids (cholesterin, phosphatids, etc.), which lie on the surface of the neutral fat droplets, disappear in the same order, but in the last stages of starvation appear relatively less abundant than the neutral fats. Ponomarew favors the infiltration theory (versus the secretion theory) of the origin of the suprarenal fats.

Rondoni and Montagnani ('15) in guinea pigs on complete inanition (water only) or incomplete inanition likewise noted a reduction in the cortical fats (osmophile and sudanophile); also congestion, atrophic degeneration in some

cells, and a decreased amount of pigment in the zona reticularis. Rothschild ('15), however, found an increased cholesterol content in the suprarenals, as well as in the blood, liver and bile, of fasting rabbits.

Jackson ('19) studied the effects of inanition upon the suprarenal in both young and adult albino rats. The ratio of cortex to medulla is not materially

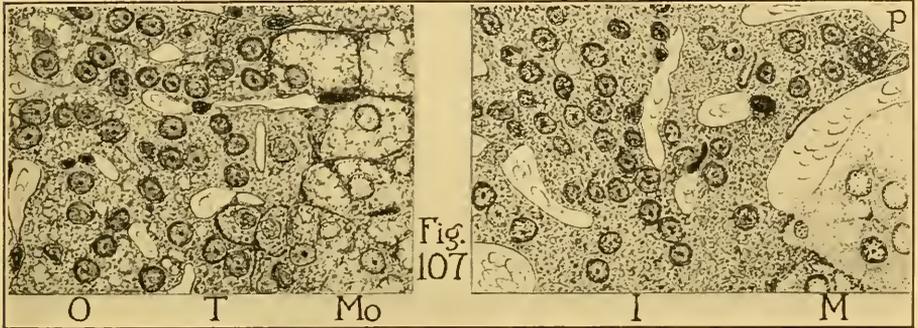


FIG. 107.—Portion of a section of the suprarenal gland of a normal male albino rat (St. 47.5) 10 weeks old.  $\times 300$ . For explanations, see Fig. 105. This represents the normal adult structure. Lipoidal vacuoles are well marked in the outer zone (O), and outer part of the middle zone (Mo), but rare in the transition band (T). A mass of pigment (P) is visible in the inner zone. (Jackson '19.)

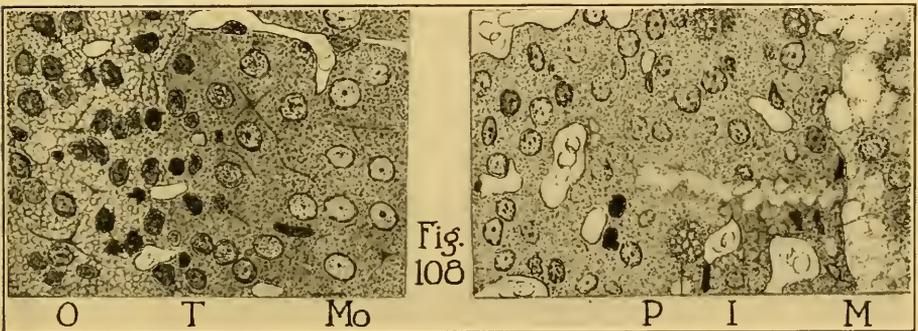


FIG. 108.—Portion of a section of the suprarenal gland of an adult male albino rat (J. 1.5) subjected to chronic inanition 5 weeks, with loss of 34 per cent in body weight.  $\times 300$ . For explanations, see Fig. 105. The lipoidal vacuoles have disappeared, except in the outer zone (O). There is marked atrophy with nuclear and cytoplasmic degeneration in the inner cortical zone (I). Three pigment masses (P) are visible. (Jackson '19.)

changed during inanition. Hyperemia is marked in the zona reticularis. In young rats during underfeeding the change in size of cortical cells and nuclei is variable, some increasing, some decreasing, some remaining unchanged. The cortical cells develop liposomes (as normally) but in variable amount (Figs. 105 and 106). In some cases, many cells undergo atrophic degeneration, especially toward the inner zone. Pigment appears in unusual abundance. Mitosis is more or less completely suppressed, but upon refeeding it is resumed, and normal conditions are nearly restored in two weeks.

In adult albino rats, the cells in the various cortical zones of the suprarenal appeared variably atrophic in acute or chronic inanition (Figs. 107 and 108). The atrophy occurs chiefly in the cytoplasm, increasing the nucleus-plasma ratio. The pigment remains unchanged. The fat granules (liposomes) are

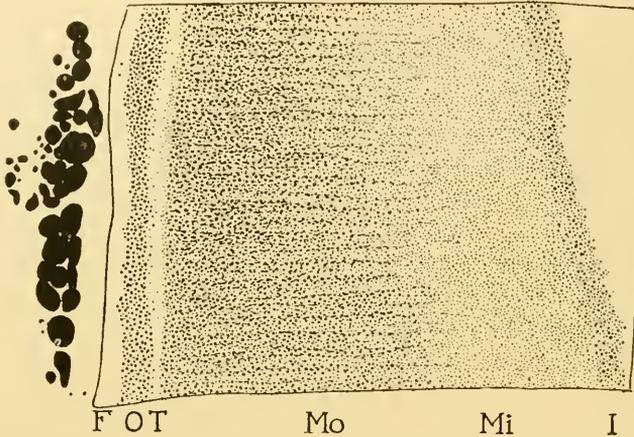


FIG. 109.—Portion of a section of the suprarenal gland in a normal adult albino rat (F. 3.1). Formalin fixation; frozen section stained with Herxheimer's scarlet red. Liposomes are most abundant in the outer cortical zone and the outer half of the middle zone. *F*, fibrous capsule; with large fat droplets in the tissue outside; *O*, outer zone (glomerulosa); *T*, transition band, relatively lipid-free; *Mo*, outer part of the middle zone (fasciculata); *Mi*, inner part of the middle zone; *I*, inner zone (reticularis); *M*, medulla.  $\times 90$ . (Jackson '19.)

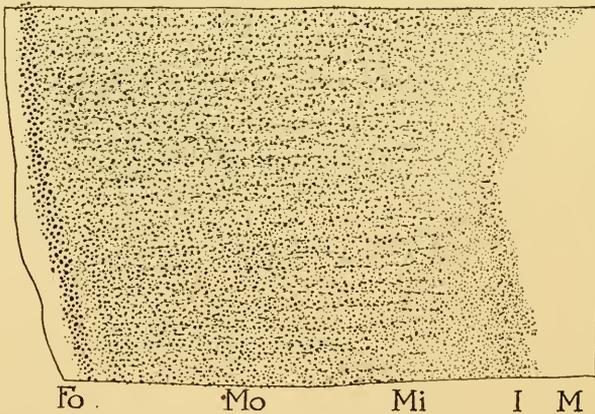


FIG. 110.—Portion of a section of the suprarenal gland of an adult male albino rat (F. 3.2) after 9 days of inanition on water only, with loss of 34 per cent in body weight.  $\times 90$ . Technique, etc. as in Fig. 109. There is no apparent decrease in the liposomes, which appear more uniformly distributed throughout the cortex. The light band at the transition between the outer and middle zones is obscured. (Jackson '19.)

may persist for a considerable period, and even appear more extensively and uniformly distributed than normally (Figs. 109, 110); but in extreme stages they are usually greatly reduced, though persisting tenaciously in the outer zone (Figs. 108, 111).

Recently Okuneff ('22) starved rabbits 9-15 days with loss of 30-40 per cent in body weight, and found that the suprarenal cortex contained fat, both isotropic and anisotropic lipoids, in variable (usually considerable) amount. In connection with the increased weight of the suprarenals, there is probably an increase in the amount of lipoids, especially of cholesterin, associated with hypercholesterinemia. Giglioli ('22), however, holds that the abundant sudanophile material found in the suprarenal cortex of fasting dogs represents not lipoids, but either neutral fats or cholesterol derivatives. Thus the term "lipoid" appears to be used differently by different authors.

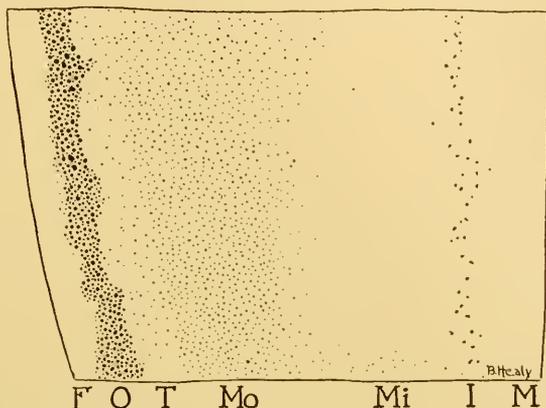


FIG. 111.—Portion of a section of the suprarenal gland in an adult male albino rat (F. 4.2) after 12 days of inanition on water only, with loss of 43 per cent in body weight.  $\times 90$ . Technique, etc. as in Fig. 109. The liposomes still persist in the outer zone (O), but have nearly disappeared elsewhere. A few are barely visible in the outer half of the middle zone (Mo), and in the inner zone (I). (Jackson '19.)

**Medulla and Chromaffin Substance.**—The variable change in the chromaffin reaction of the suprarenal medulla in atrophic infants, as observed by Mattei ('14), was mentioned above. In *animal* experiments, Venulet and Dmitrowsky ('10) found but slight decrease in the chromaffin reaction in a fasting rabbit with loss of only 6 per cent in body weight; but nearly complete or total loss of the chromaffin reaction with loss of 27.6-37.7 per cent in body weight. This was not confirmed by Luksch ('11), who found no decrease in the chromaffin reaction, or epinephrin content, by histological or physiological tests, in rabbits fasting 10-14 days. Kuriyama ('18) likewise found no marked change in the epinephrin content of 7 starved rabbits.

On the other hand, Borberg ('12) found a decrease in the intensity of the chromaffin reaction in a fasting cat and guinea pigs, especially at death from starvation. He also cited similar results by Kose and Kawashima. Rondoni and Montagnani ('15) likewise noted a decreased chromaffin reaction in the suprarenal medulla of guinea pigs after acute or chronic inanition. Pellegrini ('16) also found a decreased chromaffin reaction, especially in the later stages of fasting, although there was no definite correlation with the duration of inanition or the loss in body weight.

In adult albino rats with acute or chronic inanition, Jackson ('19) observed a marked atrophy of the cells in the suprarenal medulla, with some degenerative changes, though less marked than in the cortex. The chromaffin reaction is apparently retained undiminished up to death from starvation (Fig. 112), however, although a postmortem decrease in the reaction may occur.

Vincent and Hollenberg ('20, '21) obtained somewhat variable results as to the amount of chromaffin tissue in the suprarenal medulla of fasting pigeons, rats and dogs. In the early stages of inanition, there may even be an increased amount of adrenin (epinephrin), while in later stages the amount is usually

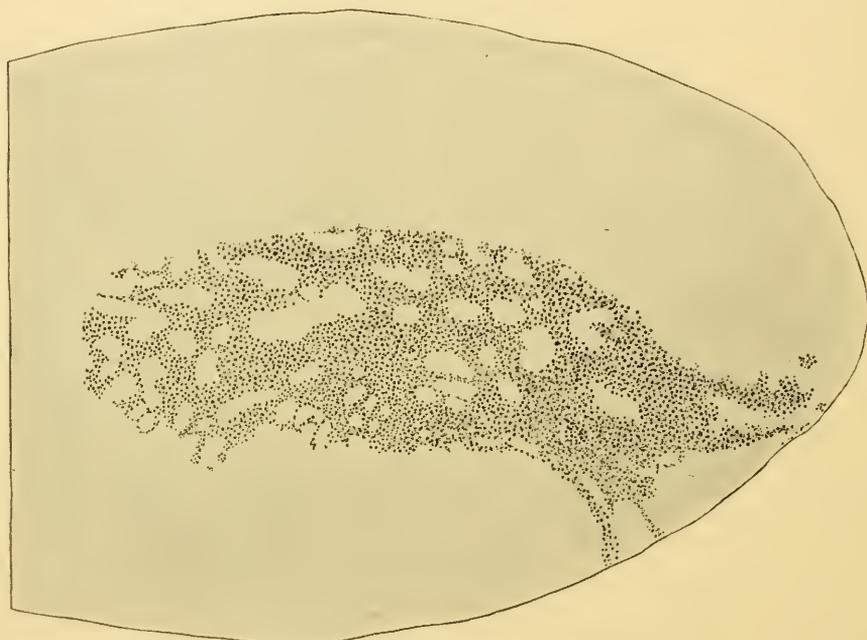


FIG. 112.—A longitudinal section of the suprarenal gland in an adult male albino rat (F. 9.3) after 10 days of inanition on water only, with loss of 33 per cent in body weight. Fixation in Müller's fluid; frozen section (unstained). The normal chromaffin reaction has been retained in the medulla, which in this case extends to the surface at the hilus.  $\times 80$ . (Jackson '19.)

greatly reduced. Physiological tests by McCarrison ('21) indicated an increased (total) amount of epinephrin in the enlarged suprarenal glands of fasting pigeons.

**Weight.**—As above mentioned, a tendency to increased weight of the suprarenals during inanition in the human adult was found by Byrne ('19) and Krieger ('20) (excepting diarrheas), although Leupold ('20?) found no change and Pellegrini ('20) a slight decrease in weight. In atrophic human infants, however, a marked loss in suprarenal weight was noted by Lucien ('08, '08a), Mattei ('14), Marfan ('21) and Jackson ('22).

Some earlier observations upon the weight of the suprarenals in fasting animals were also mentioned above; those of Chossat ('43) on the pigeon indicating a decrease, while those of Manassein ('69) and Martinotti ('92, '92a) indi-

cated an increased weight in the suprarenals of the fasting guinea pig. An increase was confirmed by Rondoni and Montagnani ('15). Some of the more recent investigations upon the weight in fasting animals will now be considered.

In adult albino rats on acute inanition (water only) with loss of 33 per cent in body weight, Jackson ('15) found an apparent average increase of 2 per cent in the weight of the suprarenal glands; while in a series on chronic inanition, with loss of 36 per cent in body weight, the suprarenals lost 9 per cent (Table 4). In younger rats, held at constant body weight by underfeeding from 3 to 10 weeks of age, Jackson ('15a) noted an increase of 26 per cent in the suprarenal weight. In still younger rats held at birth weight by underfeeding for 16 days, Stewart ('18, '19) found an increase of only 5 per cent in suprarenal weight; but if the underfeeding was continued up to 3 or 10 weeks, with increase of body weight to 10 or 15 g., the suprarenals were found above normal weight 60 and 114 per cent, respectively! (Table 4). In the stunted offspring of underfed pregnant albino rats, Barry ('20, '21) found the suprarenal glands 52 per cent subnormal in weight (for corresponding body weight). As shown in Table 4, this series illustrates how the resistance to loss in organ weight may vary according to age.

In albino rats refed for various periods after underfeeding from 3 to 12 weeks of age, Stewart ('16) found that the (enlarged) suprarenals lagged behind and lost in relative weight, dropping even below normal during the first month, in agreement with the data of Manassein ('69) for refed rabbits. Later the glands apparently regained normal weight, however. In albino rats underfed from birth to 3, 6 or 10 weeks, and then refed to 25, 50 or 75 g. in body weight, Jackson and Stewart ('19) found the suprarenals nearly normal in weight, or slightly above (Table 7). In another series refed to maximum (adult) weight after early inanition periods, Jackson and Stewart ('20) noted slightly subnormal weights in those underfed from birth to 3 or 10 weeks, and slightly supernormal weights in those underfed from 3 weeks for long periods (Table 8).

McCarrison ('19, '21) found the suprarenal glands of fasting pigeons nearly doubled in weight, in spite of a simultaneous decrease of nearly 40 per cent in body weight (Fig. 35). This result was confirmed by Vincent and Hollenberg ('20, '21), who found the suprarenal weight in fasting pigeons doubled in weight in 15 days and nearly doubled in dogs after a longer period. In fasting rats, the suprarenal hypertrophy appeared even greater, thus differing from the results of Jackson ('15). They found the *relative* average weights (percentage of body weight) for the suprarenals as follows:

In normal rats:	3 males, 0.0167 per cent; 3 females, 0.0170 per cent.
Starved 2-3 days:	2 males, 0.0188 per cent; 3 females, 0.0190 per cent.
Starved 10-12 days:	4 males, 0.0565 per cent; 2 females, 0.0600 per cent.

The changes in the suprarenal gland according to nutrition have recently been reviewed by Castaldi ('22). It does not appear clearly established whether the hypertrophy noted by various authors during ordinary inanition is due to an increase in the cortex, in the medulla, or in both.

**Hibernation.**—Valentin ('57) in a hibernating marmot with loss of 8.3 per cent in body weight observed an apparent loss of 39.13 per cent in the suprarenal glands; and in another, with loss of 35.5 per cent in body weight, a loss of 45.65 per cent in the suprarenals. Carlier ('93) mentioned a total absence of pigment granules in the suprarenal gland of the hibernating hedgehog. In the suprarenal cortex of the hibernating frog (*Rana esculenta*), Stilling ('98) observed a persistence of the fat droplets throughout the entire winter. A special type of acidophile, finely granular cells, found in the cortex of the summer frogs, disappears in winter. The cells of the suprarenal medulla continue the characteristic chromaffin reaction during the winter, although this reaction becomes somewhat masked by the development of unstained vacuoles, especially in the periphery of the cytoplasm.

In the suprarenal glands of various hibernating bats, Baroncini and Beretta ('01a) described (1) a progressive decrease in the cortical fat; (2) cloudy swelling of the entire gland, especially the zona fasciculata and the medulla; and (3) apparent emigration of the nucleus, in the zona fasciculata. Federici ('03) found no change in the cortical lipoids in hibernating bats and dormice. Bonnamour ('05, '05a) found (contrary to the results during ordinary inanition) a decrease in the fat of the suprarenal cortex in hibernating hedgehogs and marmots, also absence of pigment (confirming Carlier), but no emigration of the nucleolus. Ciaccio ('10) also noted a scarcity of lipoids in the suprarenal cortex of the hibernating hedgehog and dormouse. Mann ('16) found fairly definite seasonal variations in the suprarenal glands of the hibernating gopher (*Spermophilus tridecemlineatus*), but concluded that these are not a specific factor in causing hibernation.

### (B) EFFECTS OF PARTIAL INANITION

The effects of partial inanition upon the suprarenal glands include those of deficiencies in protein (malnutritional edema and pellagra), of salts (scurvy), of vitamins (A, B and C) and of water.

**Protein Deficiencies.**—Although **malnutritional edema** is probably in most cases due to a mixed deficiency, it is classified primarily as a protein deficiency, for reasons stated in Chapter V. Although this disorder has long been known, under various names, the corresponding changes in the suprarenal have only recently been recognized. Paltauf ('17) in malnourished, emaciated adults, with or without edema, noted fat and doubly refractive lipoid substances in the suprarenal cortex. Hülse ('18) and Schittenhelm and Schlecht ('18, '19) in famine edema and allied conditions noted an enlargement of the suprarenal glands, in striking contrast with the atrophy of the body and of most of the viscera.

The possible relation of malnutritional edema to the changes in the suprarenals was emphasized by McCarrison ('20a, '21). He found that in pigeons fed autoclaved rice (deficient in proteins, fats, vitamins and salts) edema, as well as polyneuritis, frequently occurs, especially in the younger animals and in those with the greatest enlargement of the suprarenals. The relation of the

suprarenal changes to the production of edema appears somewhat uncertain, but McCarrison concludes that "In the presence of a diet deficient in vitamin A and B, in protein, and excessively rich in starch, oedema-production is associated with derangement of adrenal function both as to its cortex and as to its medulla. This disturbance of function is evidenced by great enlargement of the glands, dispersal of lipoids from the cortex, and an increased epinephrine-content of the medulla." Cramer ('23), however, found no marked changes in the suprarenal glands of young rats on a tryptophan-deficient diet, with thyroid lesions and myxedema.

Hypertrophy of the human suprarenal glands in association with malnutritional edema was also noted by Bigland ('20), Menzies ('20), and others (reviewed by McCarrison '21). Enright ('20) appears to be the only observer finding an atrophy of the suprarenals in war edema. Tallquist ('22) also claimed that tests in fatal cases showed adrenal and thyroid insufficiency.

In **pellagra** (considered primarily due to protein deficiency), changes in the human suprarenals have often been noted. Harris ('10) found capillary hemorrhages, cellular infiltration and destruction, with extreme fatty (?) change in the medullary cells. Kozowsky ('12) mentioned capillary hemorrhages. Nicholls ('12, '13) observed that the suprarenals are not shrunken, but gave no weights. Raubitschek ('15) stated that the suprarenals usually show no characteristic changes, although Finotti and Tedeschi found nearly constant "kleinzellige Infiltrationen und Bindegewebswucherungen auf Kosten der Drüsenelemente." Sundwall ('17) in one case found no distinct pathological change; although there was slight sclerosis, with much lipoid substance in the zona fasciculata and much pigment in the zona reticularis.

Modinos ('16) in cases of pellagra in Egypt noted that the suprarenals were nearly double the normal size, but this was not confirmed by Wilson ('16). Morse ('16) in one case found the suprarenal cortex nearly normal; but the medulla showed moderate atrophy and fibrosis, with dilated blood spaces. The chromaffin cells were somewhat reduced in number. There appeared an infiltrative chronic inflammatory reaction, with focalized collections of lymphocytes and a few plasma cells. Roaf ('20) stated that the suprarenals are slightly lighter in pellagra than in other wasting diseases. Boyd ('20) observed no characteristic changes at necropsy, although the clinical features of pellagra suggest a profound suprarenal inadequacy.

In attempts to produce experimental pellagra, Rondoni ('15) found the suprarenals deficient in adrenalin in guinea pigs on maize diet, and various changes (degeneration and sclerosis) in structure were described by Rondoni and Montagnani ('15) and Rondoni ('22). Rondoni ('19) stated that the suprarenals form 0.12 per cent of the body weight in normal guinea pigs; 0.22 per cent in the maize-fed; 0.27 per cent in the oat-fed; and 0.18 per cent in those starved. The enlargement therefore appeared even greater in partial inanition than in total inanition.

In **ricketts**, Cattaneo ('05) was unable to confirm Stoeltzner's ('04) theory of a suprarenal and adrenalin deficiency as an etiological factor. Stoeltzner ('09) still maintained that the suprarenals are primarily affected, and abnormally

small in rachitic children. In rats with experimental rickets, however, Jackson and Carleton found a marked hypertrophy of the suprarenal glands, ranging from 42 to 62 per cent above normal in the various groups (Table 11) .

**Vitamin Deficiencies.**—Cramer ('20, '20a) found that in mice and rats dying on a vitamin-free diet the suprarenal lipoids have almost completely disappeared and are restricted to the outermost layers of the zona glomerulosa. The medulla shows an almost normal epinephrin content.

On diets deficient in **vitamin A**, Emmett and Allen ('20) found ophthalmia but no notable change in the suprarenal glands of the rat, although Emmett and Peacock ('22) noted apparent suprarenal hypertrophy in chickens (especially in the young) on similar diets. Herter ('97) found suprarenal enlargement in pigs during fat starvation, involving deficiency in vitamin A.

**Vitamin B.**—In infantile **beriberi**, Andrews ('12) noted congestion of the suprarenal glands. In one adult case, Strong and Crowell ('12) found the suprarenals normal in size; the cortex yellowish and the medulla relatively prominent. In pigeons with experimental beriberi (polyneuritis), Funk and Douglas ('14) incidentally noted "signs of degeneration" in the suprarenals and other viscera. Tasawa ('15) mentioned hypertrophy of the suprarenal medulla as a characteristic of human beriberi. Nagayo ('23) similarly contrasts the hypertrophy of the suprarenal medulla in human beriberi with the hypertrophy of the cortex in experimental polyneuritis.

The observations of McCarrison ('19, '19a, '20, '21) upon the suprarenals of pigeons on autoclaved rice diet with edema and polyneuritis were mentioned above (under protein deficiency). In these cases the suprarenals were found greatly enlarged (involving a hypertrophy of the medulla, at least), with an increased total adrenalin content. In one series, the initial and final average weights of the pigeons were 245–255 g. in the controls; 239–168 g. in 12 with dry beriberi; and 232–158 g. in 10 with hydropic beriberi. The corresponding average weights of the suprarenals were 23.2 milligrams in the controls; 36 milligrams in dry beriberi; and 67.6 milligrams in hydropic beriberi.

Kellaway ('21) likewise obtained enlarged suprarenals and increased adrenalin in pigeons on polished rice diet. The enlargement was prevented by the addition of yeast, but not by the addition of protein or fat. Findlay ('21) also obtained a definite hypertrophy of the suprarenals in both pigeons and fowls on polished rice diet, the enlargement being greater than during simple inanition, and more pronounced in the females (Table 13). Aside from a variable degree of congestion, no marked change was noted in the structure of cortex or medulla. On administration of a curative dose of vitamin B, a decrease in the weight and lipid content of the suprarenal was noted. Enlargement of the suprarenal glands in pigeons with beriberi was also found by Korenchevsky ('23a). In adult pigeons on a vitamin-free diet, Lopez-Lomba ('23) noted a decrease in suprarenal weight in the first 14 days, a return to normal before the 23d day, with a marked hypertrophy in the final period (to 30 days).

Brucco ('20) stated that dogs become emaciated with paralytic symptoms on polished rice diet. The suprarenals pass through a stage of hyperfunctioning, after which they undergo degeneration. Van Driel ('20) claimed that during

deficiency of vitamin B, there is an atrophy of all the endocrine glands excepting the hypophysis and the suprarenals, which produce more than the usual amount of adrenalin.

In a series of 200 young chickens, Souba ('23) found that in those on diets deficient in vitamin B (resulting in polyneuritis and loss in body weight) there was no increase in absolute weight of the suprarenals, but a marked increase in relative (percentage) weight.

**Vitamin C.**—In infantile *scurvy*, Jacobsthal ('00) and Schödel and Nauwerk ('00) found no gross or microscopic lesions in the suprarenal glands. In 6 necropsies of adult scorbutics, Bierich ('19) found the suprarenals normal in all except one, in which the medulla was enlarged. Aschoff and Koch ('19) noted an increased lipoid content in the suprarenal cortex. Hess ('20) reviewed the literature, indicating that suprarenal hemorrhages frequently occur in human scurvy, but not the enlargement found in experimental scurvy (by McCarrison).

In experimental scurvy of monkeys, Hart ('12) found the suprarenal glands normal, excepting calcareous granules in the cortex, especially near the junction with the medulla. McCarrison ('19d, '21) in scorbutic guinea pigs found in the suprarenals (1) congestion and increased weight, doubled in extreme cases; (2) hemorrhagic infiltration of the cortex, especially in the periphery, and cellular degeneration in both cortex and medulla; (3) adrenalin content reduced one-half, in spite of increased size of the gland. Bassett-Smith ('20) found the weight of the suprarenals in scorbutic guinea pigs nearly three times that in normal controls. La Mer and Cambell ('20) similarly found the suprarenal weight approximately doubled, in relation to body weight minus the alimentary canal. The increase appeared directly proportional to the length of time on the scorbutic diet. An enlargement of the suprarenals in scorbutic guinea pigs was also noted by Robb, Medes, McClendon and Graham ('21).

Morikawa ('20) observed the following changes in the suprarenal glands of scorbutic guinea pigs: (1) increased weight; (2) increase in lipoidal content of the cortex; (3) reduction in the amount of doubly refractive fat; (4) poverty of lipoids in the middle portion of the zona fasciculata, with a rich content in the outer and inner portions.

This distribution of the lipoids in the suprarenal cortex of scorbutic guinea pigs was in general confirmed by Iwabuchi ('22), who claimed, however, a decrease in the total lipoid content. He also described frequent degenerative changes in the middle portion of the zona fasciculata ("Aufquellung des Zelleibs und Pyknose des Kerns"). Mitoses were also frequently noted. Capillary congestion occurred, especially in the zona reticularis, and sometimes hemorrhages. The medullary cells appeared atrophic, and the chromaffin reaction had almost completely disappeared. Rondoni ('22) found the suprarenals greatly enlarged and congested in scorbutic guinea pigs. Peiper ('22) also noted that the suprarenal cortex of guinea pigs at death from scurvy is very deficient in lipoids, which appear in small patches. On recovery from scurvy, after 14 days the outer layer of cortical cells was found saturated with lipoid, from which finger-like

projections of lipoid-containing cells later extended down to the deeper layers of the cortex. Höjer ('24) found a simple (cortical) atrophy, at first in connection with hyperemia.

Bessesen ('23) made an extensive study of the weights of the suprarenal glands in guinea pigs at various stages of scurvy (Table 12). After 5 days on scorbutic diet, the suprarenals averaged 8.1 per cent above normal; at 10 days, 7.4 per cent below normal; at 15 days, 9 per cent above normal; at 19 days (beginning scurvy), 78.8 per cent above normal; and at death from scurvy (21-54 days), 270.1 per cent above normal (for corresponding final body weight). In another group of guinea pigs which had recovered from scurvy by addition of orange juice to the diet, the suprarenal glands still averaged 29.3 per cent above normal.

During **aqueous inanition**, on a dry diet, Kudo ('21) found in adult albino rats of the acute thirst series, with body loss of 36 per cent, a loss in the suprarenals of 21.3 per cent; and in the chronic thirst series, with body loss of 52 per cent, a loss of 27.1 per cent in the suprarenals; while in a rat on total inanition, with loss of 47 per cent in body weight, the suprarenals lost 16.6 per cent (Table 9). In young albino rats held at constant body weight by a relatively dry diet for various periods beginning at about four weeks of age, Kudo ('21a) found a progressive increase in the suprarenals, amounting to 71.4 per cent for the males and 66.2 per cent for the females, in the groups tested for the longer periods (Table 10). Thus the results are somewhat similar to those during total (complete or incomplete) inanition.

## CHAPTER XXVII

### EFFECT ON THE THYROID AND PARATHYROID GLANDS

The variably atrophic changes in the thyroid gland during inanition doubtless account for the typical decrease in basal metabolism during various conditions of malnutrition. Iodin deficiency, however, results in simple goiter, a fact of great importance in preventive medicine. The parathyroid glands similarly tend to hypertrophy during rickets, although they undergo slight atrophy in other types of inanition. After a brief summary, the details will be reviewed separately for the thyroid and the parathyroid glands.

#### SUMMARY OF EFFECTS ON THE THYROID AND PARATHYROID GLANDS

**Thyroid Gland.**—During total inanition (or on water only) in adult man or animals, there is typically a definite atrophy of the thyroid, but the loss in **weight** is somewhat variable, usually relatively less than that of the whole body. In the young, the changes in thyroid weight are still more variable. In atrophic infants, there is a profound thyroid atrophy in most cases. In malnourished young animals, the weight is variable; sometimes there is little or no loss, or even a slight gain, but never the persistent growth found in many other organs. During partial inanition in adults, a variable loss in thyroid weight is characteristic (in deficiencies of protein, vitamins and water); although there may be irregular enlargement in scurvy, and a very marked hypertrophy in iodine deficiency, the apparent cause of simple goiter in man and animals.

In **structure**, the thyroid changes during inanition are variable, but typically there is more or less hyperemia, with atrophy of the parenchyma and increase of stroma (sclerosis). In the follicles, the epithelial cells may show simple atrophy, or progressive stages of degeneration, with cytoplasmic vacuolation, loss of granulation, etc., and typical nuclear degenerative changes. There may be desquamation of degenerated cells, and in extreme cases a total disintegration of follicles. The fat granules in the thyroid cells appear uninfluenced by inanition. The colloid is extremely variable, in some cases reduced in amount, in others increased so as to distend the follicles.

During **hibernation**, the thyroid apparently undergoes atrophic changes correlated with a condition of functional depression.

During **partial inanition**, the thyroid changes in structure are in general similar to those during total inanition. The congestion and markedly degenerative changes are frequently (perhaps always) due to infections, which often complicate the late stages of inanition. Hemorrhages sometimes occur, especially in scurvy. In the thyroid hypertrophy due to iodine deficiency, the changes are variable according to species and stage of inanition. Apparently a follicular hyperplasia with shortage of colloid is usually characteristic of the earlier

stages, with an abundant accumulation of colloid in the later stages. Normal structure is regained upon the addition of iodine to the diet.

**Parathyroid Glands.**—From the somewhat scanty data, we may conclude that in adults (human and animal) during inanition in general the parathyroids probably tend to decrease in volume, with a variable degree of atrophy (and degeneration in extreme cases) in the parenchyma, and of increase in the fibrous stroma. Similar changes occur during inanition in the young, with decrease in size of the parathyroids in atrophic infants, but apparent hypertrophy in young rats. Hypertrophy of the parathyroid glands appears to be characteristic also in rickets.

### 1. THE THYROID GLAND

The effects of inanition upon the thyroid gland will be considered under (A) total inanition (or on water only), and (B) partial inanition.

#### (A) EFFECTS OF TOTAL INANITION, OR ON WATER ONLY

The data for the human species (adult and infant) will be presented first, followed by those for the animals.

**Human Adults.**—For human adults, the data are scanty. Erdheim ('03) described in the thyroid cells small fat droplets or granules which appear unaffected by the general nutritive condition of the body. Bardier ('13) stated that the (colloid?) secretion of the thyroid continues throughout the period of inanition. Meyer ('17) in a case of human starvation found the thyroid epithelium well preserved but atrophic and flattened; and the follicles usually distended with colloid.

Rössle ('19) observed no notable decrease in the weight of the thyroid gland in malnourished adults. Krieger ('20) estimated a marked decrease in various groups (soldier material) assuming the normal to be about 34 g. (in agreement with Rössle and Vierordt). The average results of Krieger are shown in the accompanying table. Thus the thyroid atrophy appears relatively

WEIGHT OF THE ADULT HUMAN THYROID GLAND IN VARIOUS CONDITIONS OF MALNUTRITION  
(KRIEGER '20)

Cause of inanition	No. of cases	Normal weight, grams	Observed weight, grams	Percentage decrease, per cent	Percentage of body weight, <sup>1</sup> per cent
Chronic diarrhea.....	5	34	18.0	47.0	0.0536
Malignant growths.....	10	34	27.0	20.6	0.0647
Chronic infections.....	23	34	23.0	32.3	0.0621
Tuberculosis.....	25	34	21.8	35.8	0.0589

<sup>1</sup> The normal is 0.05 per cent (Vierordt).

nearly as great as that of the entire body. Considerable variation was found in the amount of colloid in the follicles.

Tallquist ('22), Curschmann ('22a) and others explain the marked decrease in the frequency of exophthalmic goiter during the war as due to the thyroid atrophy and functional depression resulting from inanition.

In the **fetus** or newborn of malnourished mothers, Perrando ('02) noted a decreased weight in the thyroid gland, with "cirrhotic atrophy," including flattening of the follicular epithelium.

In atrophic *infants*, Thompson ('07) found the thyroid weight reduced to 1 g. The follicles were filled by detached epithelial cells, with no colloid, and the interfollicular stroma was abundant. Lucien ('08) also noted thyroid atrophy in athreptic infants: "Les follicules thyroïdiens sont étouffés par la sclérose envahissante." Helmholtz ('09) likewise found an increase in the fibrous stroma, with atrophic follicles and flattened, partly desquamated cells in 3 out of 6 cases. Nearly all the lumina contained some colloid.

A similar thyroid atrophy was found by Alezais and Mattei ('13) and by Mattei ('14) in 15 athreptic infants. The thyroid was greatly reduced in size (not above 1.6 g.) with a characteristic interstitial sclerosis, but no nuclear proliferation, fibroblasts, plasma cells or new vessel formation. The follicles, epithelium and colloid present various stages of atrophy, degeneration and disintegration. Lesage ('14) noted a thyroid weight of 1 g. (compared with the normal of 5 g.) in an atrophic infant of 4 months. Lesage and Cleret found sclerosis the fundamental lesion in the thyroid and other glands in congenital spasmodic atrophy. The thyroid lesions in atrophic infants were reviewed by Nobécourt ('16) and Marfan ('21).

In famine-stricken children 1-16 years old, Nicolaeff ('23) found the thyroid gland very atrophic, 45-70 per cent subnormal in weight according to age. Microscopic sections showed follicular aplasia, with flattening and desquamation of the epithelium. The glandular atrophy results in hypothyroidism. Similar effects were described by Stefko ('23a).

Some individual data for the thyroid weight in atrophic (Minnesota) infants are included in Table 3. It is evident that although there is much individual variation, the weight of the thyroid gland is usually much below even the normal birth weight (2.44 g.). In some cases, however, the weight of the gland appears nearly proportional to the body weight.

Among **animals** the data are more numerous and will be reviewed in approximately chronological order, excepting a few observations during hibernation, which are placed at the close of this section.

In a starved dog, Voit ('94) found the thyroid gland nearly 50 per cent larger than in a normal control, probably due to individual variation.

Barbèra ('02) and Barbèra and Bicci ('03) studied the thyroid gland in 3 rabbits and 1 dog subjected to total inanition, with loss of 30-34 per cent in body weight. No data on the weights of the thyroid were given, but the cells appeared atrophic, the loss being greater in the cytoplasm than in the nucleus. The nuclei became relatively elongated, (the average being  $5.73 \times 4.99\mu$  in the controls and  $5.75 \times 3.84\mu$  in the starved rabbits. In the dog, both diameters of the nucleus were reduced. Colloid formation appeared to continue normally, but the intercellular substance was reduced in amount.

Traina ('04) found that in starved rabbits the thyroid cells lose about 30 per cent of their initial volume, the loss being relatively greater in the cytoplasm than in the nucleus. The fat granules in the atrophic parenchyma cells remain unchanged in number, position, form and size.

Missiroli ('10, '11, '12) described the thyroid structure in rabbits as correlated with the stages of digestion. When food is withheld, the colloid is no longer eliminated, but accumulates and distends the thyroid follicles. In some cases of prolonged fasting, the colloid is said to undergo "fatty degeneration." In advanced stages of inanition, the cells atrophy and the interstitial connective tissue appears increased. Upon refeeding, the accumulated colloid is rapidly eliminated. Missiroli also found a hypofunctional condition of the thyroid in fasting dogs, with restitution upon refeeding with egg albumin (but not with sugar or butter fat).

Mrs. Thompson ('11) described marked changes in the thyroid gland of a dog starved a few days, which "seems to make the structure of the gland tend towards that of the parathyroid," but it is doubtful whether the changes were due to the brief inanition. Vincent ('12) also figured and described the changes in the thyroid of a starved dog. Gans ('15) reported negative findings in the thyroid and parathyroid glands of malnourished puppies. Rondoni and Montagnani ('15) likewise found no appreciable change in the histological structure of the thyroid gland in fasting guinea pigs.

Jackson ('15) in adult albino rats on acute inanition (water only), with average loss of 33 per cent in body weight, found no apparent loss in the weight of the thyroid glands; while in the chronic inanition series, with loss of 36 per cent in body weight, the thyroid loss was 22 per cent. In young albino rats underfed at constant body weight from 3 to 10 weeks of age, Jackson ('15a) found a loss of 24 per cent in the thyroid; and a loss of 62 per cent in those similarly underfed from 10 weeks to 10 months of age (Table 4). Stewart ('18, '19) in newborn albino rats underfed for various periods found the thyroid glands slightly (4-8 per cent) above normal weight; but Barry ('20, '21) found the thyroid 29 per cent subnormal in weight in the stunted offspring of severely underfed pregnant albino rats (Table 4). It thus appears that at no stage does the thyroid gland during inanition present the persistent growth tendency which is found in most of the other viscera, excepting the thymus and lungs.

In young rats fully refed after underfeeding (at maintenance) from 3 to 12 weeks of age, Stewart ('16) found the thyroid glands increased in weight though apparently not fully recovered in four weeks. In rats underfed from birth to 3, 6 or 10 weeks and then refed to 25, 50 or 75 g., Jackson and Stewart ('19) found the thyroid slightly subnormal at first, but nearly normal later (Table 7). In rats severely underfed from birth or 3 weeks of age, and later refed to maximum (adult) body weight, Jackson and Stewart ('20) found the thyroid gland variable in weight, either above or below normal (Table 8). The thyroid gland normally appears quite variable in weight in the rat, and difficulties in the dissection technique render conclusions still more uncertain. Thus Vincent and Hollenberg ('21) from a few observations found an apparent

marked increase in the weight of the thyroid in adult fasting rats, in disagreement with the results above mentioned.

A special study of the histological effects of inanition upon the thyroid gland of the albino rats was made by Jackson ('16), the results being summarized as follows:

"In young rats held at maintenance for several weeks (and hence in a condition of chronic inanition), the histological changes in the thyroid are varied. The follicular epithelium is atrophied, with reduction in height. The nuclei are rarely hypochromatic (various stages of karyolysis), but hyperchromatosis is more typical, the nuclei usually presenting some stage of pycnosis. In the earlier stages the nucleus may be nearly normal in size and structure, excepting a pale, homogeneous coloration of the nuclear background. In more advanced stages, the nucleus diminishes in size, with deepened coloration, forming a dense, deeply-staining, homogeneous mass (typical pycnosis). In extreme cases the nucleus becomes fragmented (karyorrhexis). Neither mitosis nor amitosis is found.

"The cytoplasm is usually reduced in amount considerably more than the nucleus. The cytoplasm may show no marked change in structure (simple atrophy), but usually becomes rarefied, with a marked vacuolization ('hydropic degeneration') and loss of the normal granulation. This is especially marked in the few cells where the cytoplasm has lost but little in volume. In some cases the cytoplasm may become homogeneous ('colloid' type) and in advanced stages may disintegrate, forming irregular, deeply-staining (eosinophile) masses of varied appearance.

"The intrafollicular colloid may show no abnormal changes. Advanced stages of degeneration in the follicular epithelium, however, are accompanied by dissolution and disintegration of the colloid. The colloid is often replaced by desquamated epithelial cells in various stages of degeneration, and the entire follicle may collapse into an irregular mass.

"The interfollicular connective tissue (stroma) usually shows no very marked change in structure, but is often increased in volume by an infiltration of ground substance, giving a somewhat edemic appearance. On this account, the whole thyroid gland may show but little loss in absolute weight, although there has been a marked atrophy of the parenchyma.

"In the adult rats subjected to acute and chronic inanition, the changes in the structure of the thyroid gland are likewise varied, but in general similar to those found in the younger rats. The interpretation of the changes in the older rats is more difficult, on account of the frequent occurrence in the normal (control) rats of degenerative changes somewhat similar to those found in advanced stages of inanition.

"These changes, involving desquamation and degeneration of the follicular epithelium, have frequently been observed in the thyroids of rats both normal and under various abnormal conditions. They also occur as pathological changes in various other glands. It is suggested that the similarity of these cell-changes may possibly be due to cell-inanition as a common underlying factor."

The effects of inanition upon the structure of the thyroid gland in young albino rats are shown by a comparison of Fig. 113 (normal at 22 days) with Fig. 114 (condition in a rat underfed from 3 to 10 weeks of age).

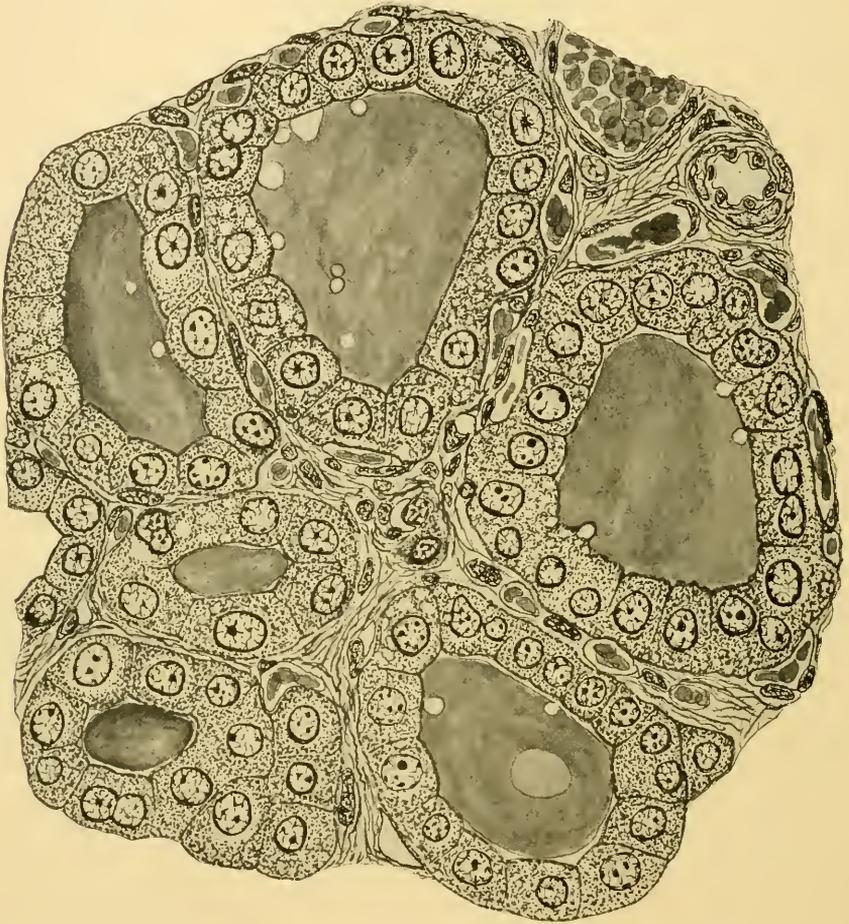


FIG. 113.—A small portion of a section from the thyroid gland in a normal albino rat (S. 9.47) 22 days old. Zenker fixation; hematoxylin-eosin stain.  $\times 750$ . The normal histological structure is shown, with several follicles containing colloid. Follicular epithelium cuboidal; cytoplasm abundant and granular, with a few scattered vacuoles. The fibrous stroma is scanty, with a rich blood-vascular plexus. (Jackson '16.)

McCarrison ('21) observed a marked decrease in the weight of the thyroid gland in starved pigeons, though relatively less than that in the whole body (Fig. 35).

Trowbridge, Moulton and Haigh ('18) and Moulton, Trowbridge and Haigh ('22a) concluded that in steers the thyroid ("neck sweetbread") is somewhat reduced in weight in the poorly nourished.

Okuneff ('22) in the thyroid gland of the rabbit found the fatty cell granules small and scarce, but (confirming Traina '04) unchanged during inanition with loss of 30-40 per cent in body weight.

**Hibernation.**—Peiser ('06) concluded that the secretory activity of the thyroid gland in bats decreases during hibernation. The follicular epithelium was found flattened, "colloid cells" lacking, and the colloid reduced to a small amount. A hedgehog killed in February also showed no colloid in the thyroid follicles.

Adler ('14) likewise observed an atrophy of the thyroid gland with a disappearance of follicular colloid in hibernating bats, and concluded that the decreased thyroid secretion might cause the phenomena of hibernation. Adler

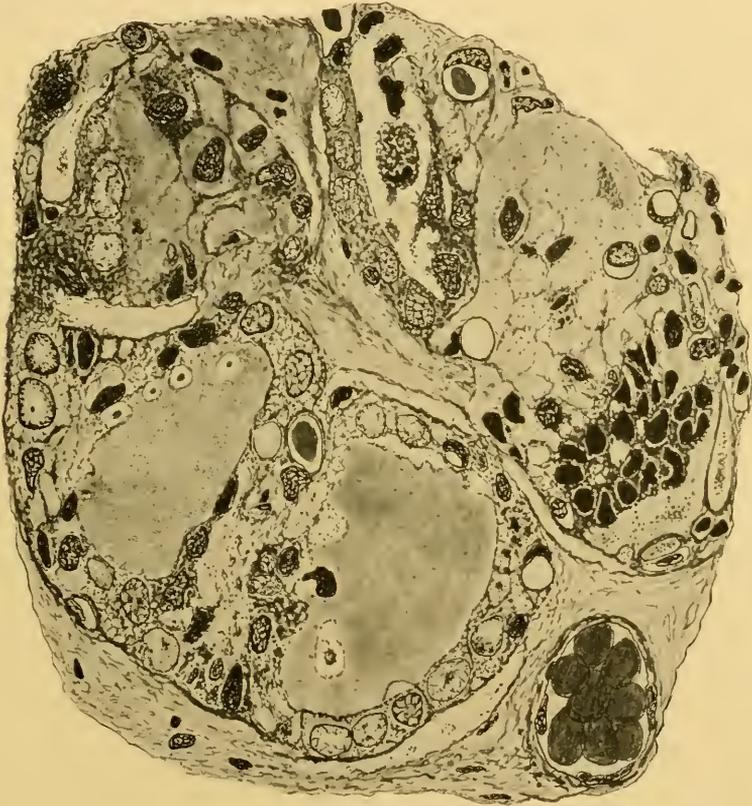


FIG. 114.—A portion of a section of the thyroid gland in an albino rat (11.64) held at constant body weight by underfeeding from 3 to 10 weeks of age. This area shows advanced stages of follicular degeneration, with cells in various stages of degeneration and disintegration. There is a tendency to desquamation of the epithelium, with destruction of the colloid and obliteration of the follicular lumen. Some of the nuclei appear karyolytic, although karyopycnosis predominates and karyorrhexis frequently appears.  $\times 750$ . Technique, etc. as in Fig. 113, which is to be compared. (Jackson '16.)

('20) described various grades of atrophic regressive changes in the thyroid follicles of hibernating bats, involving in extreme cases a complete destruction of the follicles. Upon the awakening in the spring, new follicles develop from the remaining interfollicular cell-masses. In hibernating hedgehogs, similar but less marked changes were found.

## (B) EFFECTS OF PARTIAL INANITION

The effects of partial inanition upon the thyroid gland have been noted in protein deficiency (malnutritional edema and pellagra), salt (especially iodine) deficiencies, deficiency of vitamins (B and C) and aqueous inanition (thirst).

**Protein Deficiencies.**—In human **malnutritional edema**, Paltauf ('17) found the thyroid gland usually diminished in size, weight 10–15 g.; rarely larger. Oberndorfer ('18) likewise found the thyroid gland extremely small, sometimes not exceeding 12 g. in weight. Histologically the follicles were atrophic, with thickened colloid and indications of hyposecretion. Lubarsch ('21) mentioned hemosiderin deposits in the epithelium of the thyroid and other glands. Tallquist ('22) found the thyroid usually much decreased (sometimes to  $\frac{1}{3}$ ) in size and ascribed the effects of malnutrition in famine edema and similar disorders largely to endocrine (especially thyroid and suprarenal) insufficiency. Curschmann ('22, '22a) likewise emphasized the atrophy of the thyroid gland as a factor in malnutritional edema.

In young rats fed on a diet with maize (tryptophan-deficient) replacing the casein, Cramer ('23) found marked histological changes in the thyroid gland, with cutaneous myxedema, indicating hypothyroidism. He noted that, according to Kendall, the active principle of the thyroid gland, thyroxin, is an iodine derivative of tryptophan.

In **pellagra** (considered primarily due to protein deficiency), Agostini ('02) ascribed the occurrence of infantile myxedema and arrested development to thyroid lesions from maize toxins. Valtorta ('12) noted the frequency of goiter and cretinism in pellagrous countries and described the changes in the thyroid gland. Rossi ('13) found no histological changes in the thyroid gland, but according to Raubitschek ('15), Agostini found typical atrophy of the thyroid, which was even considered as the cause of pellagra. Morse ('16) in one case also described lesions resembling "chronic productive interstitial thyroiditis with compensatory reaction on the part of the thyroid follicles." There was marked fibrosis with small areas of round cell infiltration, and islands of degenerating thyroid follicles.

Sclerosis and other lesions of the thyroid gland were observed by Rondoni ('15, '22) in guinea pigs on *maize-diet*, which, however, is known to be deficient not only in protein, but also in various salts, vitamins, etc. Likewise uncertain as to causation are the hyperemia and hyperplasia of the thyroid described by Watson ('10) and Tanberg ('10) in rats on a meat diet. Mellanby and Mellanby ('21) also found that in puppies the thyroid glands were small and normal in structure when cod liver oil was the only fat in the diet, but showed more or less hyperplasia on other fats, especially on butter (which caused five-fold increase in weight). It is possible that these changes may depend upon dietary differences in mineral or vitamin content, as well as in fats.

Murray ('23) found in puppies with **rickets** produced by unhygienic environment hyperplastic changes in the thyroid gland, similar to those seen in some infections. These changes were not found in the rachitic-like disorder

produced by calcium deficiency, and were prevented by the addition of cod liver oil to the diet.

The importance of **iodin deficiency** in the hyperplasia of the thyroid gland in dogs was demonstrated by Marine ('07). He found that canine goiters improve rapidly upon the administration of iodine, with (1) reduced prominence of the fibrous stroma; (2) nearly complete disappearance of the columnar epithelium, with return to the normal, low cubical type; (3) nuclear change from large, pale, vesicular type to small and deeply staining; (4) increase in the amount of stainable colloid.

Smith ('17) concluded that an iodine deficiency in the diet of pregnant swine causes hyperplasia and hypofunction of the fetal thyroid gland. This results in maldevelopment of the fetus, the affected pigs being born full sized, but weak, and hairless, with poorly developed hoofs, edematous skin, etc. The thyroid gland in these pigs appeared "dark red, sometimes almost black, and presents a constant enlargement which varies only in proportion to the acuteness of the malady. A histological examination of the thyroid shows a uniform hyperplasia and a distension of the blood-vessels." The iodine content of these glands was found very low, and the disease was prevented by the addition of iodine to the diet of the pregnant sows. Similar cases occur frequently in sheep, and occasionally in cattle and horses. Smith also cited Fenger's observation that the fetal thyroid (in slaughtered animals) is often found hypertrophied, with low iodine content. Hart and Steenbock ('18a) likewise concluded that hairless pigs are caused by fetal goiter due to deficient intake of iodine.

Marine and Kimball ('21) emphasized the lack of iodine as the cause of simple goiter, small doses of iodine being effective in prevention or cure. "Anatomically a wide range of changes may be present, depending on the species of animal and on the stage (duration) of the disease. It always begins with a decrease in the colloid material and a hypertrophy of the epithelial cells, at first cubical, later columnar, with infoldings and plicatures. In man and fowls, the stage most commonly observed is characterized by an abundance of colloid material—the so-called cystic or colloid goiter of the older writers—while in dogs, cattle, sheep, pigs, fish, etc., the accumulation of colloid is seen only in the late regressive or quiescent stages." Hayden, Wenner and Rucker ('24) produced goiter in rats by restricted iodine in the diet.

McClendon ('22) and McClendon and Williams ('23) studied the relation of the incidence of human goiter among the drafted men in the recent war to the amount of iodine in the drinking water of the corresponding districts of the United States. The evidence indicates that the prevalence of goiter is inversely proportional to the supply of iodine. They state that Chatin (C. R. Acad. Sc., Par., 1850) advanced the hypothesis that simple goiter is correlated with a low iodine-content of the drinking water.

McCarrison ('22) likewise concludes that "The factors which give rise to goiter center around the supply of iodine and the needs of the thyroid gland for iodine," but he points out that there are various factors which may bring about the insufficiency of iodine. Mellanby ('22) states that while a deficiency of iodine causes a thyroid enlargement in animals (dogs), this deficiency does not

usually occur on the human diets in England. Bayard ('23) and Olin ('24) support the theory of iodine deficiency as the cause of endemic goiter.

Although **oxygen** is not, strictly speaking, a nutritional factor, it is of interest in this connection to note that Martin, Loewenhart and Bunting ('18) found thyroid hyperplasia, with hydropic and hyalin degeneration of the cells in rabbits, as a result of decreased oxidation.

**Vitamin Deficiencies.**—In infantile **beriberi**, Andrews ('12) found but slight changes in the thyroid gland, aside from congestion.

In pigeons with experimental beriberi, Funk and Douglas ('14) noted definite "signs of degeneration" in the thyroid and other glands. Douglas ('15) described great individual variations in the thyroid of normal pigeons, as well as in those on polished rice diet, producing beriberi. In extreme stages, the follicles may be partly or wholly disintegrated. The variations apparently depend in part upon the general condition of nutrition. Drummond ('18) observed very small thyroid glands in some young rats (black variety of *Mus norvegicus*) greatly emaciated at death on a diet deficient in vitamin B.

McCarrison ('19, '20, '21) found that in polyneuritic (beriberi) pigeons the thyroid gland undergoes a moderate atrophy, the decrease in weight being less than during total inanition (Fig. 35). Like Douglas, he found marked variations in the histological structure, even in normal pigeons. He ('21) concluded: "Excluding, then, infective processes, which so constantly reveal their presence in the body by initiating pathological changes in the thyroid gland, I find this organ, so far as can be judged by histological study, to be amongst the least affected of all organs by the deficient dietary. The changes which are attributable to this cause consist in mild or moderate degrees of congestion and in necrobiosis of a relatively small proportion of the secretory cells. Confusion as to the changes directly attributable to the dietetic deficiency is apt to occur unless complicating infections are excluded. It is to these that pronounced congestion, necrosis, and denudation of the alveolar epithelium are directly due and not, as I had previously concluded, to the dietetic deficiency; although such deficiency is indirectly responsible for them, since it renders the thyroid very liable to attack from bacterial agencies." Similar changes were observed in the thyroid gland of monkeys and guinea pigs on variously deficient diets.

Brucco ('20) concluded that in dogs on a polished rice diet, the thyroid (like the suprarenal), after a transient stage of hyperfunction, undergoes degeneration. In young rats on a vitamin-free (polished rice) diet, Tsuji ('20) noted thyroid atrophy, with secondary changes in other organs, ascribed to hypothyroidism.

In pigeons and fowls on a polished rice diet, Findlay ('21) found but slight decrease in weight of the thyroid gland, similar to that during inanition (Table 13). The gland appears anemic. Histologically the structure may remain normal, or the follicular epithelium may be degenerated. Souba ('23) noted that in young chickens on diets deficient in vitamin B there is a slight loss in thyroid weight, somewhat proportional to the loss in body weight. In adult pigeons on a vitamin-free diet, Lopez-Lomba ('23) found the thyroid weight

below normal during the first 9 days, above normal in the second week, and markedly atrophied in the third and fourth weeks.

**Scurvy.**—Rondoni and Montagnani ('15) described hemorrhagic lesions of the thyroid gland as characteristic in scorbutic guinea pigs. McCarrison ('20a, '21) likewise found enlargement and hemorrhages. Aschoff and Koch ('19) observed no changes in the thyroid gland in necropsies of human adults with scurvy. Bessesen ('23) found an irregular enlargement of the thyroid in the various stages of experimental scurvy in guinea pigs (Table 12).

**Aqueous Inanition.**—In a dog on a dry diet with loss of about 21 per cent in body weight, Falck and Scheffer ('54) noted an apparent loss of 30 per cent in the weight of the thyroid gland.

In adult albino rats on relatively dry diets, Kudo ('21) found in the acute thirst series (with loss of 36 per cent in body weight) a loss of 23.9 per cent in thyroid weight; in the chronic thirst series (body loss of 52 per cent) a loss of 33.1 per cent in thyroid weight; while in total inanition (body loss of 47 per cent) the thyroid loss was 41.7 per cent (Table 9). In young albino rats held at constant body weight by a relatively dry diet for various periods, beginning at about 4 weeks of age, Kudo ('21a) found a variable loss in thyroid weight (8–26 per cent) in all but the longest test, in which it was slightly above normal (Table 10).

## 2. THE PARATHYROID GLANDS

The comparatively few data on the effects of inanition upon the parathyroid glands will be considered in the usual order: first the effects of total inanition in man (adult and infant) and animals, followed by the effects of partial inanition.

In the **human parathyroid** cells, Erdheim ('03) found small fatty (singly refractive) granules, which, like those in the thyroid gland, appear uninfluenced by the general nutritive condition of the body.

Pepere ('06) in his extensive monograph on the parathyroids mentioned briefly the effects of inanition in dogs starved 9–27 days and in 2 human cases of death from inanition following esophageal stricture. In the dog, there was atrophy of the parenchyma, especially of the cytoplasm, with vacuolation and loss of the characteristic granules, and deeply staining nuclei. In the human parathyroid, the effects were similar.

In a man who died from starvation, Meyer ('17) found the parathyroid parenchyma somewhat atrophic in appearance, containing much colloid in some places. Other portions showed faintly-staining acidophile cells in various stages of degeneration.

In **atrophic infants**, Thompson ('07) described parathyroid atrophy of two types: (a) degenerative and (b) sclerotic. In type (a) there is marked congestion. The epithelial cells are extensively degenerated, larger and more irregular; nuclei swollen; cell boundaries usually thickened or syncytial. In the more common type (b), there is sclerosis, with increase of the interstitial stroma. Mast cells occur frequently in the connective tissue. There are

islets of crowded epithelial cells, usually syncytial, and chiefly of the "principal" cell type.

In 7 athreptic infants, Harvier ('09) found the parathyroid glands normal in 5; but in 2 cases there was somewhat marked sclerosis, with the parenchyma cells in "pseudo-vesicular" groups, some containing colloid. In one case, numerous small hemorrhages occurred in the inferior parathyroids.

Helmholz ('09) likewise found the changes in the parathyroids in 6 atrophic infants less extensive than those described by Thompson. The glands appeared decreased in size, but microscopically unchanged, except a slight increase in connective tissue along the blood-vessels. "In dem Parenchyma waren keine Unterschiede von den normalen zu erkennen."

Mattei ('14) found the parathyroids of athreptic infants notably decreased in volume with marked general fibrosis (sclerosis), and variable cytoplasmic changes in the parenchyma cells. The results of the earlier investigations on the parathyroid in atrophic infants were summarized by Nobécourt ('16).

**Animals.**—Alagna ('08) described a cystic condition of the parathyroids in a dog killed after a long fasting period, but this condition was probably not due to the inanition.

In the hibernating gopher (*Spermophilus tridecemlineatus*), according to Mann ('16), "The very slight and inconstant changes noted in the parathyroids do not warrant any positive conclusion."

Jackson ('16) found in albino rats that:

"The parathyroid glands appear to be relatively larger in the female. They apparently belong to that group of organs in which growth persists in young rats, even when held at maintenance (constant body weight) by under-feeding. In adult rats during acute and chronic inanition, the reduction in the size of the parathyroids is nearly proportional to that of the body as a whole.

"In histological structure, the parathyroid gland is relatively more resistant than the thyroid to inanition. The changes in the structure of the epithelial cells are somewhat similar to those described for the thyroid, though in general less marked. In many of the cells there is apparently no decrease in the average size, but some (especially those degenerated) show marked shrinkage. The nuclei may remain nearly normal in size and structure, though usually exhibiting various stages of (rarely) karyolysis or (more frequently) karyopycnosis. No cell-division is found. The cytoplasm may be either somewhat reduced in amount, sometimes deeply-staining ('oxyphile'), or may remain nearly normal in volume, with marked vacuolization ('hydropic degeneration'). The stroma may remain normal in amount, but is occasionally increased in volume by infiltration of ground substance."

Among the various types of **partial inanition**, the most conspicuous changes in the parathyroids have been found during **rickets**. Erdheim ('14) described a marked enlargement of the parathyroid glands in rats with spontaneous rickets. In human rickets, Ritter ('20) found that hypertrophy of the parathyroids appears less common in the early cases than in those of long standing, in which perhaps recuperation is beginning. Instead of the normal light "Hauptzellen," the parathyroid cells are of the dark cell type, with frequent

hyperemia and fibrosis, sometimes also edema. Luce ('23) found that in young rats fed on calcium-deficient diet there is a progressive enlargement of the parathyroid glands, which is due to hyperplasia (not hypertrophy) of the cells. Parathyroid hyperplasia sometimes occurred also on diets deficient in **vitamin A** in young rats, though not in adults.

In infantile **beriberi**, Andrews ('12) found but slight changes in the parathyroids, aside from congestion. Findlay ('21) similarly observed normal appearance of the parathyroids in pigeons and fowls with beriberi, although the *postbranchial body* had undergone slight atrophy. McCarrison ('21) also found no marked change in the parathyroids of polyneuritic pigeons, unless complicated by infections, in which case congestion and cell necrosis occurred (as in the thyroid gland). In 3 monkeys on a diet of autoclaved rice and butter, the parathyroids showed intense congestion and in one case hemorrhagic infiltration. When onion was added to the diet (either with or without the butter) the parathyroids appeared normal.

In two cases of *infantile scurvy*, Ritter ('20) found the parathyroids normal in microscopic appearance and microscopic structure.

## CHAPTER XXVIII

### EFFECTS ON THE HYPOPHYSIS

Although as yet but imperfectly known, it appears that the changes produced in the hypophysis (pituitary gland) may be responsible for some of the general phenomena of inanition and malnutrition. After a brief summary, the effects of inanition upon the hypophysis will be considered in detail under (*A*) total inanition and (*B*) partial inanition.

#### SUMMARY OF EFFECTS ON THE HYPOPHYSIS

Although the data concerning the effects of inanition upon the hypophysis are comparatively scanty, it appears that during total inanition, or on water only, in the human species (adult and infant) there is a definite loss in **weight**, though as a rule relatively less than in the body as a whole. This usually applies also to adult animals (rat), but in the young during chronic underfeeding at constant body weight there may be a continued increase in weight of the hypophysis, amounting to a maximum of 33 per cent.

**Volumetric analysis** shows during inanition in the rat certain changes in the relative size of the hypophysis lobes, in proportions of parenchyma and of vascular stroma, and in nucleus-plasma ratio; these changes varying according to age and type of inanition.

In **histological structure**, only slight changes during inanition have been observed in the neural and intermediate lobes; but in the anterior lobe there is a variable degree of atrophy and degeneration of the parenchyma cells, with a tendency to loss of the specific cell granulation. Mitosis, which is frequent in the young, is more or less completely suppressed by inanition, but is resumed promptly upon refeeding, with ultimate recovery of normal size and structure of the hypophysis.

During **hibernation**, atrophic changes of questionable significance have been described in the hypophysis, but the findings in the most recent work have been negative in character. Upon awakening in the spring, even before feeding, hypertrophy of the hypophysis and cell-changes associated with the rutting season may occur.

From the few observations during **partial inanition**, the hypophysis apparently decreases in weight in experimental rickets, increases in scurvy, and undergoes little or no change in beriberi and aqueous inanition. The histological changes in the hypophysis during partial inanition appear uncertain or inconstant.

## (A) EFFECTS OF TOTAL INANITION, OR ON WATER ONLY

The data for the human species (adult and infant) will be presented first, followed by those for the lower animals. A few observations on the pineal body are also included. The data on the animal hypophysis are chronologically arranged, excepting some concerning hibernation, which are placed at the close of this section.

**Human Adults.**—Erdheim ('03) described in the cells of the anterior lobe of the human hypophysis small fatty granules, which, like those of the thyroid and parathyroids, are apparently independent of the general nutritive condition of the body.

In a man who died of starvation, Meyer ('17) found great congestion and hemorrhagic areas in the anterior lobe of the hypophysis. The epithelium showed marked reduction and degeneration, similar to that in the suprarenals. The characteristic chromophile granulation was faintly evident, and a few small masses of colloid were found.

Roessle ('19) stated that no atrophy (decrease in weight) was evident in the hypophysis of soldiers emaciated by chronic fevers, etc. Krieger ('20) held that, in general, the available data are too few to determine whether the hypophysis participates in the general atrophy of the body during inanition; although in general infections, the hypophysis weight is below the general average, as shown by the accompanying table.

WEIGHT OF THE ADULT HUMAN HYPOPHYSIS IN VARIOUS CONDITIONS OF MALNUTRITION  
(KRIEGER '20)

Cause of inanition	No. of cases	Average age, years	Average weight of hypophysis, milligrams
Chronic diarrhea.....	2	29	575
Malignant growths.....	4	44	643
Chronic infections.....	14	26	550
Tuberculosis.....	10	27	598

In **athreptic infants**, Lucien ('08) found lesions in the various endocrine glands, including the hypophysis, which "ne sécrète pour ainsi dire pas de colloïde." Mattei ('14) found the individual weights of the hypophysis in 8 atrophic infants below 3 months of age as shown in the accompanying table.

WEIGHT OF THE HYPOPHYSIS IN ATROPHIC INFANTS (MATTEI '14)

Age	Sex	Body weight, grams	Hypophysis weight, grams
16 days.....	f.	2,260	0.06
22 days.....	m.	2,300	0.06
18 days.....	m.	2,890	0.09
30 days.....	m.	2,400(?)	0.09
11 days.....	m.	2,200	0.10
45 days.....	f.	2,740	0.10
3 months (?).....	f.	2,500 (?)	0.10
37 days.....	m.	3,100	0.18

In all except the last case of Mattei, the weight of the hypophysis is markedly below the normal (0.13 g.) for the newborn. The actual degree of atrophy of the hypophysis is uncertain, however, since the final body weights are likewise below the normal birthweight, and the previous body weights are unknown. Mattei concluded that the weights of these hypophyses are normal (for corresponding body weight).

Mattei also described in detail the histology of the anterior, intermediate and posterior lobes of the hypophysis, but it is not clear as to just what features represent departures from the normal. In the anterior lobe, colloid was usually abundant. In 12 out of 15 cases, the cells were nearly all of the chromophile type, which was interpreted as indicating hyperactivity of the glandular secretion.

In Table 3 are included some original individual weights of the hypophysis from necropsies of atrophic Minnesota infants. It will be observed that the weights are all considerably below the normal for the hypophysis at birth (0.13 g.), even in infants whose final weight was above 3,200 g. It therefore appears that the hypophysis undergoes a marked loss in weight during inanition.

Among the **animals**, the effects of inanition upon the hypophysis were studied by Guerrini ('04). He found in the hypophysis (anterior lobe) of 4 dogs, 4 rabbits and 4 pigeons, during the first third of the acute inanition period, a slight increase of secretory activity in the cells, as indicated by a more intense reaction to Galeotti's stain. In the remaining period of acute inanition, however, he found a progressive decrease in staining capacity (granules and plasmosomes) with vacuolization of the cytoplasm. The final appearances are described as follows:

"Negli animali morti di fame, uso l'espressione nel senso il più lato, le cellule sono tutte, o presso che tutte, ridotte come in vesicole, quali più e quali meno gonfie, con nucleo, anch'esso, un po' vuoto e rigonfio e il protoplasma ridotto ad un velo, interrotto qua e là di qualche vacuolo e con appena una traccia di granuli o di plasmosomi."

In several dogs and rabbits (both young and adult) subjected to chronic inanition, however, Guerrini found no apparent change in the secretion (specific

staining reactions) of the hypophysis cells. Unfortunately no details are given as to the exact character and extent of the chronic inanition. Possibly his negative results may be due to the comparative mildness of the inanition.

Gans ('15) observed no abnormality in the hypophysis of puppies which were underfed or malnourished on inadequate diets.

The changes in the weight of the hypophysis during inanition have been most extensively studied in the albino rat (Table 4). In adult albino rats subjected to acute inanition (water only) or chronic inanition (underfeeding), with loss of 34-36 per cent in body weight, Jackson ('15) found the corresponding average loss in the weight of the hypophysis was about 26 per cent. In young albino rats held at constant body weight by underfeeding from 3 to 10 weeks of age, the hypophysis increased 18 or 19 per cent in weight (Jackson '15a). Stewart ('18, '18a) found a somewhat greater increase (24-33 per cent) in most cases when the underfeeding began at birth, unless the inanition was prolonged beyond 10 weeks of age, with irregular results.

Stewart ('16) noted practically normal weight of the hypophysis in albino rats refed for 1-4 weeks after underfeeding from 3 to 12 weeks of age. The hypophysis likewise appeared nearly normal in weight in albino rats underfed from birth to 3, 6 or 10 weeks, and then refed to 25, 50 or 75 g. in body weight (Jackson and Stewart '19) (Table 7). In other series of rats, underfed from birth to 3 or 10 weeks, or from 3 to 20 weeks or 1 year, and then refed to maximum (adult) size, Jackson and Stewart ('20) found the hypophysis variable in weight, and slightly subnormal in most groups (Table 8).

Observations on the **pineal body** by Stewart ('18) indicated no appreciable change in weight in young albino rats underfed for various periods. The pineal body was found 6-25 per cent subnormal in weight by Jackson and Stewart ('19) in refed rats, possibly indicating that early inanition (especially when prolonged) may tend to inhibit the later growth of this organ. But in another series, Jackson and Stewart ('20) found the weight of the pineal body in the refed rats more irregular, so no definite conclusions can be drawn.

A more detailed volumetric and histological study of the hypophysis in young and adult albino rats during inanition was made by Jackson ('17), with the following results:

"During inanition, the volume-changes in the lobes are variable. In young rats held at maintenance (constant body weight), the pars anterior is somewhat reduced, the intermedia and nervosa correspondingly larger. In chronic (adult) inanition the partes anterior and intermedia appear reduced, the nervosa increased. In acute (adult) inanition, the pars anterior appears relatively increased, intermedia decreased, and nervosa unchanged in relative volume.

"In young rats refed one-half week, one week, two weeks and four weeks after maintenance, there is some variability, but in general a gradual return to the normal proportions in the lobes of the hypophysis. After a prolonged period of maintenance, however, the relative volume of the lobes may remain permanently abnormal.

"In the pars anterior of the normal newborn rat, the vessels and associated stroma form 6.7 per cent by volume, increasing to 9.6 per cent at three weeks, and

to 10.6 per cent at ten weeks (adult condition). In young animals held at maintenance, the volume of the vascular stroma usually increases to about 13 per cent, and in acute or chronic inanition of adults to about 17 per cent. The parenchyma is, of course, correspondingly reduced in relative volume.

"In the parenchyma of the pars anterior the nuclei form about 34 per cent of the total cell volume in the newborn, decreasing to about 24 per cent at three weeks and to 20 per cent at ten weeks (adult relation). The cytoplasm increases correspondingly in relative volume. During inanition, the loss is usually greater in the cytoplasm, the nuclei thereby increasing to 26-28 per cent of the cell volume in the young held at maintenance, and to 23-26 per cent in adults with chronic or acute inanition.

"According to data obtained by the volumetric method, the (calculated) average diameter of the parenchyma cells of the anterior lobe increases from  $8.4\mu$  in the normal newborn to  $9.3\mu$  at three weeks and  $10.4\mu$  at ten weeks (adult condition). In young rats held at maintenance, the average cell diameter is reduced to  $7.8-8.1\mu$ ; in starved adults to  $8.6-8.7\mu$ . (*Note.* These corrected diameters are slightly smaller than the erroneous data in the original paper.) The nuclear diameter averages  $5.9\mu$  in the normal newborn,  $5.8\mu$  at three weeks, and  $6.0\mu$  at ten weeks. In the young rats at maintenance the nuclear diameter is reduced to  $4.9-5.3\mu$ ; in starved adults to  $5.3-5.5\mu$ . Direct measurements by another method (with filar micrometer) gave similar results for the nuclear diameters, including also those of the pars intermedia.

"The number of mitoses in an entire section of the gland is quite variable. Amitosis was never observed. In the normal newborn pars nervosa, the average number of mitoses is 7 per section; at seven days they are rare, and none occur later. In the pars intermedia, the average number decreases from 9 per section in the newborn to about 1 at three weeks; at ten weeks and later they are rare. In the normal pars anterior the rate likewise decreases, being about 62 at birth, 18 at one week, 7 at three weeks, 2 at ten weeks and rare in adults.

"In young rats held at maintenance from three to ten weeks of age, mitosis has nearly ceased. No mitoses were found in the partes nervosa and intermedia, although in the pars anterior they still occur occasionally, even in rats nearly dead from inanition. No mitoses were observed in the starved adults.

"In the young rats refed after the maintenance period, mitoses reappear promptly in the pars anterior, the average number per section being about 2 after one-half week of refeeding, 7 after one week to two weeks, decreasing to an average of 3 after four weeks of refeeding. Mitoses were observed but rarely in the pars intermedia, and never in the pars nervosa. The rate of mitosis in the hypophysis of the refed rats therefore corresponds roughly to that in younger normal rats of similar body weight.

"In cell structure, the only change noted in the pars nervosa during inanition is a variable degree of hyperchromatism in the nuclei, which rarely may become shrunken and pycnotic. In the pars intermedia, most of the cells usually suffer relatively little change during inanition. The nuclei have a variable tendency to hyperchromatism, occasionally becoming pycnotic, especially in certain atrophic areas. The cytoplasm tends to lose its granular structure, becoming

more homogeneous and often finely vacuolated in appearance. Around pycnotic nuclei it is usually more strongly basophilic, and is much reduced in volume in the atrophic areas above mentioned.

"The colloid which occurs normally in the pars nervosa and in the hypophyseal cavity (residual lumen) appears unaffected by inanition.

"In the pars anterior, the changes during inanition are quite variable. Some areas may remain nearly normal, while others, even in the same gland, show extreme changes of atrophy and degeneration. The cytoplasm is usually reduced in volume (as above shown) and is frequently much vacuolated. The structure becomes sparsely granular and there is a marked tendency to loss of the specific staining reactions, so that the strongly chromophilic cells become weakly chromophilic or even chromophobic. The nuclear changes are likewise variable, but there is a very general tendency to hyperchromatism often reaching a definite pycnosis. Karyorrhexis and karyolysis are rare.

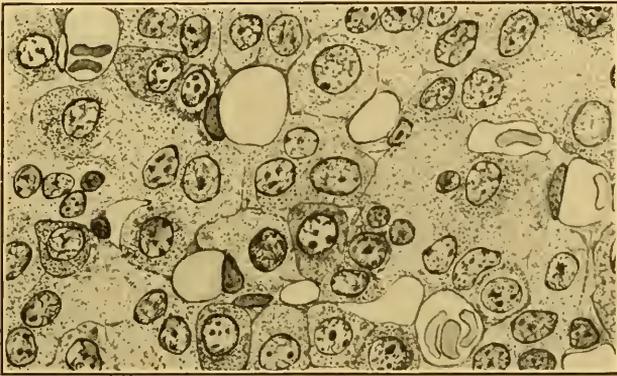


FIG. 115.—A small portion of the pars anterior of the hypophysis in a normal albino rat (J. 1.2) 3 weeks old. Most of the cells are of the faintly basophilic type. Some eosinophilic cells are indicated by darker staining. A few chromophobic cells are shown, a group of four near the left margin. Zenker fixation; hematoxylin-eosin stain. Drawn with the aid of a camera lucida.  $\times 760$ . (Jackson '17.)

"Upon refeeding one-half week after the maintenance period (three to twelve weeks of age), the hypophysis still retains the typical inanition structure, although mitosis and growth have begun. After one week of refeeding, some areas have become nearly normal, and after two weeks the normal structure preponderates. After four weeks, the greater part of the hypophysis appears nearly normal, although atrophic areas may persist for indefinite periods. Recovery is improbable in cells whose nuclei have reached advanced pycnosis."

Some of the characteristic changes in the pars anterior of young albino rats during inanition are shown in Figs. 115-117. Fig. 115 shows the normal structure at three weeks of age; Fig. 117 represents the normal structure at ten weeks; while Fig. 116 shows the atrophic and degenerative changes found in a rat held at constant body weight by underfeeding from three to ten weeks of age.

**Hibernation.**—Some observations on the hypophysis during hibernation are of special interest, since sleep and hibernation have by some authors been ascribed to changes in the hypophysis.

Gemelli ('06, '06a) noted in the marmot (*Arctomys marmota*) evidences of absence or decrease in secretory activity (cyanophile or basophile cells) in the

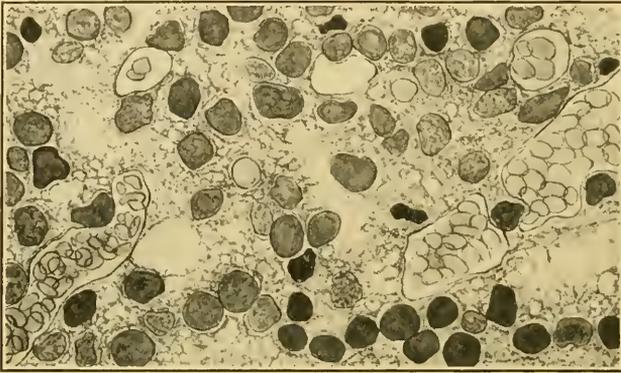


FIG. 116.—A small portion of the pars anterior of an albino rat (S. 5.12) held at constant body weight by underfeeding from 3 to 10 weeks of age. The effect of the inanition is striking, resulting in hyperemia and atrophy of the parenchyma. The cytoplasm is decreased in amount, sparsely granular, and filled with coarse vacuoles which sometimes coalesce to form irregular spaces. The nuclei are hyperchromatic, in various stages of pycnosis.  $\times 760$ . Technique, etc. as in Fig. 115; compare also Fig. 117. (Jackson '17.)



FIG. 117.—A small portion of the pars anterior of the hypophysis in a normal albino rat (St. 47.5) 10 weeks old, body weight 196 g. This represents the typical adult structure. Most of the cells are of the weakly basophilic type. Several eosinophiles are shown (darker color).  $\times 760$ . Technique, etc. as in Fig. 115. (Jackson '17.)

anterior lobe of the hypophysis during hibernation, with the reappearance of mitoses and cyanophile cells upon awakening in the spring. Cushing and Goetsch ('15) found that:

“In a series of hibernating animals (woodchucks) it has been found that during the dormant period histological changes are apparent in many of the ductless glands. The most notable of these changes occur in the pituitary body, as previously observed by Gemelli. The gland not only diminishes in

size, but the cells of the pars anterior in some animals at least completely lose their characteristic staining reactions to acid and basic dyes. At the end of the dormant period the gland swells and as the cells enlarge they again acquire their differential affinity for acid, basic and neutral stains, and at the same time karyokinetic figures may appear."

They emphasized the resemblance of the symptoms of hypopituitarism to those of hibernation, and concluded that "hibernation may be ascribed to a seasonal physiological wave of pluriglandular inactivity," in which the hypophysis plays the essential rôle.

This theory was opposed by Mann ('16) who found definite but inconstant changes in the hypophysis of the hibernating gopher (*Spermophilus tridecemlineatus*). He also pointed out that if such changes are the cause of hibernation, they should appear well-marked at the beginning of hibernation, since later they might be merely a result of the long continued torpid state. Jackson ('17) similarly concluded: "In view of the striking similarity of the cell changes in the two conditions (hibernation and inanition), it seems highly probable that the changes described in the hypophysis during hibernation are simply the effects of the chronic inanition involved."

Rasmussen ('21), however, failed to find the previously described atrophic changes in the pars anterior of the hibernating woodchuck (*Marmota monax*). Material was studied from 32 animals killed at various intervals before, during and after hibernation. He concluded that "Hibernation produces no change in the weight or histological structure of the hypophysis, when compared with the prehibernating gland." During a period of inanition after awakening in the spring, however, the hypophysis in the rutting season undergoes a hypertrophy averaging 33 per cent in volume, affecting proportionately all three parts of the gland. The basophile cells become tripled in number and stain more intensely.

#### (B) EFFECTS OF PARTIAL INANITION

The relatively few observations concerning the effects of partial inanition upon the hypophysis include data in pellagra, rickets, beriberi, scurvy and aqueous inanition (thirst).

In human **pellagra** ("Pellagratyphus"), Rossi ('13) found no histological changes in the hypophysis or in the *pineal* body.

In albino rats with experimental **rickets**, Jackson and Carleton ('23) noted a decrease in the average weight of the hypophysis, varying from 17 to 28 per cent in the various groups (Table 11).

In pigeons with beriberi (vitamin B deficiency), Funk and Douglas ('14) observed definite "signs of degeneration" in the hypophysis and other glands. McCarrison ('19a, '20a, '21) found that in pigeons the hypophysis lost slightly in weight during total inanition, but on autoclaved rice diet remained nearly stationary (Fig. 35) or even gained slightly in males. Congestion and somewhat inconstant histological changes were also observed. Similar findings were recorded for monkeys (*Macacus sinicus*) on variously deficient diets. In the

hypophysis, as in the suprarenal glands, the sex differences in the normal weight of the glands must be considered.

According to van Driel, the hypophysis and suprarenal are exceptional in that they do not atrophy like the other endocrine glands as a result of dietary deficiency of vitamin B. Findlay ('21) found the hypophysis (pituitary) practically unchanged in weight in pigeons and fowls on polished rice diet, with a slight apparent hypertrophy (2.5-6 per cent) during acute and chronic inanition (Table 13).

In guinea pigs on a **scorbutic** diet, Bessesen ('23) found a progressive hypertrophy of the hypophysis, increasing in the various groups from 8 per cent after 5 days to 50.5 per cent at death from scurvy (Table 12).

In adult albino rats during **aqueous inanition** (on dry diet), Kudo ('21) found the weight of the hypophysis practically unchanged in both acute and chronic thirst series, in spite of a loss of 36-52 per cent in body weight (Table 9). In one rat on total inanition the hypophysis apparently increased 8.3 per cent in weight. In young albino rats held at constant body weight by a relatively dry diet for various periods, beginning at about 4 weeks of age, Kudo ('21a) found but slight change in the average weight of the hypophysis in the shorter test periods, but a definite hypertrophy (37.5-43.8 per cent in the longer experiments (Table 10).

# PART III

## CONCLUSIONS, TABLES AND BIBLIOGRAPHY

### CHAPTER XXIX

#### CONCLUSIONS

Having considered the morphological effects of inanition in the various tissues and organs of plants and animals, we may now review briefly some of the more important phases of the subject in conclusion. In part, this review was included in a recent address (Jackson '23).

When the preceding data concerning the effects of inanition upon living organisms are surveyed and compared, many differences are apparent. The results differ more or less according to the type of inanition, the mode of occurrence, the extent and degree of inanition, the complications, the species, the age, the sex, and the individual organism concerned. Apparently variable or contradictory results of inanition are usually due to variation in one or more of these factors.

As to the **type of inanition**, the results in total inanition naturally vary from those in the different forms of partial inanition. The effects of total inanition are usually quite similar (in the same species) to those where water only is given, however, excepting the longer period of duration in the latter case. The peculiar effects in the various types of partial inanition constitute the characteristic syndromes of the corresponding "deficiency diseases," such as pellagra, xerophthalmia, rickets and scurvy. Most frequently the various types of total or partial inanition occur not in pure form but intermixed or associated with other diseases. This is a principle of both theoretical and practical importance in medical diagnosis and therapy.

As to the **mode of occurrence**, we have learned that the cells of the organism may suffer malnutrition from various extrinsic causes, which prevent the necessary nutriment from reaching the cells, or from intrinsic causes, which interfere with the normal cell metabolism. It is probable that the resulting effects in some cases differ according to the mode of occurrence of the inanition, although but little is known as yet concerning these differences.

As to the **extent** and **degree** of inanition, occasional differences have been noted between complete or acute inanition on the one hand, and incomplete or chronic inanition on the other. Some of the atrophic changes require a longer period of time and hence appear more distinctly during incomplete or

chronic inanition. In many chronic disorders, inanition may be an insignificant factor in the earlier stages, but may become increasingly important during the progress of the disease, ultimately constituting the immediate cause of death (Chossat).

**Complications** of various kinds may also modify the results of inanition. This is especially true of the *infections*, which are sometimes characteristic of the later stages (e.g., in xerophthalmia), where the resistance of the organism has been lowered by inanition, either total or partial. Certain phenomena characteristic of *inflammation* often appear, including cell degeneration, vascular exudates, leukocytic or round cell infiltrations and cell proliferation. These may be due to associated infections, or to toxins set free by the atrophic degeneration of the tissues during inanition. Visceral *hyperemia* is characteristic in the later stages of inanition, probably chiefly a passive hyperemia due to cardiac weakness, although Nicolaeff ('23) considers it a hyperemia *a vacuo*, associated with atrophy of the parenchyma.

As to **species**, the effects of inanition are obviously different in plants and animals, between protozoa and metazoa, and between invertebrates and vertebrates. On the whole, the vertebrates appear less plastic and more resistant to inanition, as they are to environmental influences in general. Even among vertebrates, there are often striking differences in the results of inanition in different orders, genera and species. There are also differences according to the age, sex, and even the individual. These differences are due partly to different size and structure of the body, amount of reserve food material, etc., but doubtless depend chiefly upon more fundamental differences in the protoplasmic structure and composition, upon which the rate and character of the metabolism depend.

**Variation in Parts of the Organism.**—It is furthermore clearly apparent that the effects of inanition vary in extent and character in different parts of the same organism. Variable atrophy in different parts of the body may lead to marked abnormalities of form. These variations depend chiefly upon the variable resistance in the constituent organs and tissues. Thus the nervous system and (usually) the skeleton are relatively resistant, while the adipose and lymphoid tissues readily undergo marked atrophy. In general, the ectodermal derivatives appear more resistant than the entodermal, and the mesodermal least resistant. Even in the same tissue, however, the effects may vary greatly in the individual cells. Often scattered groups of cells appear especially affected, perhaps on account of lesser resistance, or of more unfavorable relations to the supply of nutrition.

**Intracellular Variation.**—Within the cell, the different cytoplasmic structures vary notably in the extent and character of change during inanition. Thus metaplastic materials, such as glycogen and ordinary fat, usually soon disappear; while the mitochondria are relatively persistent. The nucleus is relatively more resistant than the cytoplasm, as was noted by Pfitzner ('86), thereby increasing the "nucleus-plasma ratio." *Mitosis* is usually suppressed by inanition, but may continue in certain organs or tissues with persistent growth; and there is sometimes (inflammatory?) cell proliferation, especially

in the connective tissue stroma. Moreschi ('09) and v. Jaworski ('16a) claimed that tumor growth may be repressed by inanition, but this was not confirmed by Rous ('11) for the Flexner-Jobling adenocarcinoma in young rats on a restricted diet.

**Similarity of Effects.**—On the other hand, amidst the diversity of the phenomena resulting from inanition in various plants and animals, and in various tissues and organs, we find certain features in essential agreement. Thus there is always more or less atrophy of the body (rare exceptions being merely apparent), since the vital activities of the organism must continue at the expense of its own substance. The corresponding structural changes in the tissues and cells, though varying in certain respects, also reveal many similarities, some of which have been mentioned. This similarity is to be expected, since these changes are due ultimately to the effects on the cell metabolism, which is essentially the same in all living organisms.

In general, the cells during inanition pass through two stages. The first is a simple atrophy, especially of the cytoplasm, which tends to reduce the cell to a simpler, more embryonal condition. This passes, sooner or later, into the second stage, that of degeneration. Here the cytoplasm typically appears to undergo "cloudy swelling," with subsequent fatty or vacuolar (hydropic) degeneration of varied character. The nucleus, though relatively more resistant, also later undergoes progressive degeneration, usually with pycnosis, and finally karyorrhesis or karyolysis. Ultimately the entire cell may disintegrate and disappear. It is possible that the similar degenerative changes so frequently found in various pathological conditions, and observed by Lewis ('19) in tissue cultures, may also depend ultimately upon an associated state of inanition.

**Recovery from Inanition.**—The possibilities of recovery upon refeeding after inanition will depend chiefly upon the degree of cell injury which has been sustained. Cells which are still in the stage of simple atrophy usually recover rapidly. Those which have undergone extensive cytoplasmic and especially nuclear degeneration are obviously unable to recuperate. As above mentioned, however, there are always great individual differences, even among cells of the same organ or tissue, so that some cells may remain capable of regeneration even though others have degenerated beyond the stage of possible recovery. Although the effects of inanition vary widely in different cases, up to a certain stage of severity perfect recovery is possible in any cell, organ or organism; beyond this only partial recovery (or none at all) is possible. If immediate death is escaped, permanently dwarfed and stunted forms may result. In some cases the structure of the germ plasm may be affected, with results capable of hereditary transmission, at least for a few generations. Ultimately, however, upon adequate diet there is usually an evident tendency to return to the original condition.

**Dystrophic Growth.**—As already stated, the age at the time of inanition is an important factor, there being critical periods at which the various organs are most susceptible to the effects of inanition and other environmental influences. During the developmental period in both plants and animals, inanition (espe-

cially of the chronic type) frequently results not merely in a retardation or cessation of growth, but in an abnormal, disproportional growth, which varies greatly according to species, stage of development, type of inanition and other factors. Some parts may show persistent growth at the expense of others, even during total inanition with continued loss in body weight. Likewise in adult fasting animals, regeneration and healing of wounds proceed, though at a retarded rate; and compensatory hypertrophy occurs after the removal of the greater part of the liver (Rous and McMaster), though apparently not in the remaining kidney after unilateral nephrectomy (Sacerdotti). In some species, there is a seasonal, "physiological inanition," during which the gonads develop at the expense of the remainder of the organism.

The abnormal growth occurring during various types of partial inanition is contrary to Liebig's "*law of the minimum or limiting factor*," according to which (as narrowly interpreted by some authors) growth should cease when any nutritional factor essential for normal growth is exhausted. Thus the mechanism of growth and development is somewhat elastic. Whatever may be the influence correlating the relative growth of the various organs and parts, this correlation may be markedly changed during total or partial inanition and the process of morphogenesis is accordingly subject to experimental control.

**Underlying Causes.**—The question as to why certain cells or organs have a greater resistance to inanition has received various answers. Roux has long held that during inanition those cells persist which happen to require less food in the struggle for existence. This theory was opposed by Schultz and others who claimed that the order of disappearance of the organs (especially in the "reduction" of invertebrates) reverses the order of their appearance during the ontogenetic and phylogenetic development. Another view widely held is the teleologic explanation that during inanition those organs persist longest which are most valuable to the organism or species. Still another (though closely related) view is that the losses of the various tissues and organs are inversely proportional to their functional activity during inanition.

Stefko ('23a) believes that the degeneration cell changes during inanition are useful to the organism, since they set free food material for the surviving cells.

All these theories, however, appear inadequate to explain the facts observed. Runnström (for sea-urchin larvae), Robertson and others have proposed a more rational theory, which would attempt to explain the morphological changes upon the basis of the varying physico-chemical conditions in the starving organism. Cesa-Bianchi ('09) found that the early stages of cell degeneration during inanition correspond to those produced by hypertonic or hypotonic salt solutions, while the later stages resemble those during aseptic autolysis. The characteristic difference in behavior between the lipoidal and the ordinary types of fat is apparently correlated with a fundamental difference in chemical structure. The fatty metamorphosis so frequently observed in cells during inanition may depend upon the exhaustion of the carbohydrates, whose presence facilitates the colloidal protein-fat emulsion in the cytoplasm (Morgulis '23). Robertson ('23a) has recently discussed fully the problem of inanition from the chemical viewpoint. Future investigations along such lines as these will probably give us more satisfactory explanations of the phenomena involved.

The question may also be raised as to why the degenerative changes in the various cells during inanition are so similar, not only in the various types of total and partial inanition, but likewise in many other abnormal conditions such as extremes of temperature, fatigue, toxic or electrical stimuli, etc. Sundwall ('17) emphasized passive congestion (due to cardio-vascular exhaustion) as a common, underlying factor in the various forms of inanition, but this explanation is inadequate for plants and lower animals. A more probable hypothesis is that the effects are similar because all these conditions obstruct the normal cell metabolism, thereby causing similar degenerative cell phenomena (Jackson '16). Ultimately these changes, like the variations in resistance, are doubtless explainable upon a physico-chemical basis. The fundamental similarity in the cellular results of such varied conditions recalls the dictum of Cuénot ('94) that "la plupart des influences de milieu se ramènent en somme à des différences de nutrition."

Nutrition is thus a factor of primary importance for morphology as well as for physiology. The form and structure of all living organisms are clearly dependent in large measure upon the quantity and quality of their nutriment. The effects of inanition of various types apparently account for many of the variations observed among living organisms, under both normal and abnormal conditions. A knowledge of these effects gives a deeper insight into the process of morphogenesis and a means whereby it may be experimentally controlled to a degree hitherto generally unrealized. Furthermore, even though it be contrary to the generally accepted biological doctrine, there is another possibility which must be considered. Not only the somatoplasm, but under certain circumstances even the germ plasm may perhaps be essentially modified by nutritional conditions, a possibility of fundamental significance for heredity and evolution.

## TABLES

TABLE I.—LOSS OF BODY WEIGHT AND LENGTH OF INANITION IN ADULT ANIMALS

Author	No. and species	Average (or range) of percentage loss	Length of fast, etc.
(A) Total inanition (neither food nor water)			
		Per cent	
Asada ('19).....	rabbits	28.0-52.0	11-20 da.
Bourgeois ('70).....	6 rabbits	34.0-40.0	5-8 da.
Bourgeois ('70).....	7 dogs	20.0-51.0	3 <sup>1</sup> -30 da.
Falck ('75).....	2 dogs	48.0-49.0	24-60 da.
Rosenbach ('83).....	8 dogs	30.0-55.0	12-31 da.
Bourgeois ('70).....	7 cats	16.0-48.0	2.5 <sup>1</sup> -17 da.
Bourgeois ('70).....	3 guinea pigs	34.0-39.0	4-7 da.
Chossat ('43).....	5 guinea pigs	33.0	5-8.5 da.
Lazareff ('95).....	10 guinea pigs	35.5	5-8 da.
Coburn ('10).....	swine (fat)	50.0-75.0	43-133 da.
Hantell ('96).....	swine (fat)	75.0	
Valentin ('57).....	3 marmots	35.5	166 da. (hibernation)
Rulot ('01).....	bats	31.2 (males); 35.8 (fem.)	6 mo. (hibernation)
Chossat ('43).....	15 turtle doves	37.9 (22.5-49.5)	25% in young; 46% in old
Chossat ('43).....	1 crow	31.1	3.65 da.
Chossat ('43).....	2 chickens (fat)	52.7	19 da.
Chossat ('43).....	17 pigeons	41.6	5-20 da.
Aducco ('89).....	126 pigeons	35.0-56.0	Greater loss in darkness
Chossat ('43).....	3 lizards	28.7-39.5	90-150 da.
Manca ('95).....	40 <i>Lacerta muralis</i>	29.1-32.9	69-334 da.
Cocco-Pisano ('02)....	49 lizards ( <i>Gongylus</i> )	14.9 (10.0-19.0)	Loss increase to body wt.
Ferralis ('06).....	6 lizards ( <i>Gongylus</i> )	21.6-27.2	cold chamber
Manca ('97).....	13 <i>Cistudo evropa</i>	10.3-36.7	34-110 da.
Manca .....	Same, without carapace	29.5-45.0	{ Larger body wt. gives smaller loss and longer time.
(B) Partial inanition (water only)			
Manassein ('69).....	8 rabbits	39.4%	5-46 da.
Weiske ('74).....	2 rabbits	48.0-49.5	27-32 da.
Rosenbach ('83).....	4 dogs	31.0-43.0	10-20 da.
Luciani ('89).....	2 dogs	44.2-48.5	34-43 da.
Luciani & Bufalini....	1 dog	48.5	43 da.
Daddi ('98).....	3 dogs	43.8-53.1	28-59 da.
Kumagawa & Miura ( '98).....	1 dog	65.0	98 da.
Howe & Hawk ('09)...	1 dog	63.0	117 da. (recovered on refeeding)
Beeli ('08).....	2 cats	28.0-51.0	10-28 da.
Jackson ('15).....	15 albino rats	33.0 (25.0-39.0)	9 (6-12) da.
Kuckein ('82).....	2 chickens	34.0-39.0	9-12 da.
Pellegrin ('01).....	<i>Pelophilus madagascariensis</i>	22.0-26.0 (in last 6-9 mo.)	3-4 yrs.
Chossat ('43).....	1 land tortoise	23.9 (without carapace)	40 da.
Chossat ('43).....	12 frogs	41.4 (33.1-58.6)	6-15 mo.
Blumenthal ('04).....	frogs	67.0	1 yr.
Nalepa ('02).....	Proteus	.....	"Jahrelang"
Chossat ('43).....	3 eels	24.7-41.5	151 da.
Lipschütz ('11).....	Various fishes	28.0-50.0	10-417 da.
Morgulis ('18).....	5 brook trout	1.7-9.3	Killed in 7-28 da.
Morgulis ('15).....	2 flounders	33.0-34.0	Killed in 27-28 da.
Smallwood ('16).....	1 <i>Amia calva</i>	(became emaciated)	20 mo.

<sup>1</sup> Lower figures of Bourgeois refer to young animals.

TABLE 2.—WEIGHT CHANGES IN ORGANS OF ATROPHIC INFANTS

The number of observations in the individual organs varies in general from 30 to 50, about half of which are original Minnesota cases, the others from scattered sources in the literature (Porter's famine cases not included). The maximum body weight (during life) was available in the Minnesota cases only. The percentage change was estimated for each individual separately, using data compiled by Prof. R. E. Scammon as the norm, and the results averaged for each organ. The figures in parenthesis are for the Minnesota cases alone. Further data for the body weight, etc. in these cases are given by Jackson ('22). Data for some of the individuals are given in Table 3

Organ	Average percentage differences when the observed weight is compared with the (estimated) normal for the corresponding			
	Final body weight	Maximum body weight	Body length (height)	Age
Brain.....	+25.9 (+20.5)	+ 1.5	- 7.7 (-7.7)	-12.3 (-19.3)
Kidneys.....	+20.5 (+13.7)	- 5.7	- 1.0 (-7.6)	-19.4 (-18.4)
Lungs <sup>1</sup> .....	+24.5 (+12.8)	- 4.5	-20.6 (-20.6)	-21.2 (-16.7)
Spleen.....	+ 9.5 (-5.6)	-14.9	-20.5 (-20.9)	-31.3 (-18.1)
Heart.....	- 0.9 (-2.4)	-20.9	-14.9 (-21.9)	-28.0 (-32.6)
Whole body.....	0.0	-20.9	-31.6 (-31.0)	-51.5 (-50.6)
Liver.....	- 6.3 (-11.2)	-33.0	-23.2 (-26.3)	-27.1 (-30.3)
Suprarenals.....	-43.3 (-53.1)	-60.5	-56.9 (-56.9)	-38.5 (-41.7)
Thymus.....	-71.8 (-75.8)	-80.7	-80.6 (-80.4)	-82.6 (-84.4)

<sup>1</sup> Pneumonia cases excluded.

TABLE 3.—WEIGHTS OF ORGANS IN ATROPHIC INFANTS. WEIGHTS IN GRAMS. MINNESOTA DATA. FOR CAUSE OF DEATH, ETC., SEE NOTES AT END OF TABLE. CASE NUMBER AT HEAD OF COLUMN

	Norm (Scammon)	M. G. H. 7-17-22	M. G. H. 2-2-22	M. G. H. 3-15-22	S. A. Home	U. H. <sup>5</sup> 17,253	Anat. 10-17-21 <sup>6</sup>
Sex.....		Female	Female	Male	Male	Female	Female
Age, days.....	Newborn	14.0	12.0	13.0	46.0	141.0	164.0
Body wt. max.....	3,500.0	1,800.0	2,800.0	3,005.0	3,005.0	7	5,334.0
Body wt. final.....	50.0	48.0	2,090.0	2,370.0	3,204.0 (2,700.0)	3,580.0 (2,940.0)	5,050.0 (3,972.0)
Height, cm.....	22.5	20.8	50.0	51.0	54.0	55.5	62.0
Index { wt. (gr.) lt. (cm.) <sup>3</sup>	.0254 (Bardeen)	0.0163	0.0168	0.0179	0.0172	0.0172	0.0167
Weights of:							
Heart.....	19.8	11.4	14.0	14.9	16.5 (13.5)	16.7	36.6 (27.7)
Lungs.....	49.0	49.5	81.5	79.0	136.0 (111.0)	54.0	188.0 (142.0)
Spleen.....	9.4	23.8	5.1	4.39	10.7 (9.5)	6.2	9.7 (7.3)
Liver.....	131.0	94.4	85.0	106.0	100.0 (82.0)	137.0	155.0 (117.0)
Thymus.....	13.3	2.6	2.0	2.96	4.7 (3.8)	0.55	5.0 (3.8)
Brain.....	350.0	235.0	400.0	415.0	462.0 (377.0)	516.0	666.0 (503.0)
Kidneys.....	22.5	20.8	20.6	28.9	19.6 (14.4)	37.2	47.6 (36.0)
Suprarenals.....	8.0	2.6	3.4	3.5	2.2 (1.75)	2.5	3.25 (2.5)
Hypophysis.....	0.13	0.071	0.11	0.06	0.055 (0.045)	0.09	0.11 (0.083)
Stomach.....	6.5	8.5	12.2	14.0	12.6 (10.3)	17.4	24.8 (18.7)
Intestines.....	48.0	84.0	75.0	106.0	62.0 (51.0)	84.0	215.0 (162.0)
Pancreas.....	2.8	3.3	3.5	2.0	3.0 (2.5)	5.0	8.5 (6.5)
Ur. bladder.....	.....	3.5	3.5	5.1	4.6 (3.7)	18.4	5.8 (4.4)
Thyroid gland.....	2.44	1.0	3.1	2.5	2.3 (1.9)	1.5	3.6 (2.7)
Testes.....	0.74	.....	.....	0.40	0.62 (0.51)	.....	.....
Epididymides.....	0.21	.....	.....	0.38	0.64 (0.52)	.....	.....
Prostata.....	0.89	.....	.....	.....	0.95 (0.77)	.....	.....
Uterus.....	4.0	1.2	1.9	.....	.....	1.10	1.48 (1.12)
Ovaries.....	0.32	.....	0.45	.....	.....	.....	0.178 (0.135)
Auricles (ear).....	.....	3.8	.....	.....	9.1 (7.4)	.....	12.2 (9.2)
Head.....	800.0	470.0	.....	.....	860.0 (726.0)	.....	1,210.0 (915.0)
Eyeballs.....	3.2	4.1	.....	.....	6.1 (4.9)	6.9	9.0 (6.8)
Integument.....	480.0	136.0	.....	.....	275.0 (224.0)	279.0	316.0 (239.0)
Skeleton (ligamentous)	800.0	345.0	.....	.....	491.0	474.0	625.0
Musculature.....	3.0	307.0	.....	.....	736.0 (601.0)	529.0	666.0 (503.0)
Spinal cord.....	.....	1.7	1.8	.....	4.1 (3.4)	7.55	5.54 (4.2)
Larynx.....	.....	1.3	.....	.....	2.35 (1.9)	.....	4.8 (3.6)
Trachea and bronchi.....	.....	5.3	.....	.....	2.0 (1.6)	.....	2.8 (2.1)
Tongue.....	.....	2.0	9.3	.....	12.2 (10.0)	8.0	16.1 (12.2)
Esophagus.....	1.80	.....	.....	.....	2.4 (1.9)	.....	4.6 (3.5)
Parotid glands.....	.....	.....	.....	.....	3.12 (2.55)	2.15	3.6 (2.7)
Submax. glands.....	0.84	.....	.....	.....	1.47 (1.20)	1.11	2.5 (1.9)
Sublingual glands.....	.....	.....	.....	.....	0.31 (0.25)	.....	1.50 (1.13)
Sucking pads.....	0.42	2.2	.....	.....	1.11 (0.91)	.....	4.4 (3.3)

TABLE 3--(Continued)

	7 Path, 21-462	8 M. G. H. 4-9-22	9 M. G. H. 2-2-22	10 Path, 20-11	11 M. G. H. 3-19-22	12 St. P. 7-3-22	13 Path, 2-447	14 U. H. 20,699	15 Path, 22-170
Sex.....	Female	Male	Female	Male	Male	Female	Male	Female	Male
Age, days.....	33.0	38.0	42.0	120.0	42.0	120.0	255.0	560.0	186.0
Body wt. max.....	2,110.0	1,970.0	2,535.0	2,300.0	2,960.0	3,400(?)	3,645.0(?)	7,718.0	?
Body wt. final.....	1,695.0	1,725.0	1,810.0	1,940.0	2,600.0	2,689.0	3,145.0	5,000.0	5,120.0
Height, cm.....	47.0	47.0	46.0	50.0	56.0	55.0	64.0	70.0	64.0
Index { wt. (g.) (ht. cm.) <sup>3</sup> .....	0.0163	0.0166	0.0186	0.0155	0.0148	0.0155	0.0120	0.0147	0.0195
<i>Weights of:</i>									
Heart.....	9.4	9.0	12.0	13.6	16.0	13.6	20.0	26.9	31.0
Lungs.....	35.3	50.4	40.0	39.8	71.5	48.6	73.2	130.0	127.0
Spleen.....	5.5	5.3	5.6	8.8	28.0	9.6	12.0	19.2	29.0
Liver.....	66.0	65.0	93.0	71.0	149.0	114.0	227.0	230.0	212.0
Thymus.....	0.90	1.5	1.0	.....	3.3	0.1	1.7	.....	5.8
Brain.....	18.8	300.0	350.0	463.0	450.0	.....	511.0	757.0	580.0
Kidneys.....	1.72	11.7	28.7	19.5	20.5	19.7	43.0	51.4	39.0
Suprarenals.....	.....	2.2	2.3	1.6	2.6	2.5	3.4	2.3	4.9
Hypophysis.....	.....	0.10	0.10	.....	0.09	.....	0.06	.....	0.10
Stomach.....	10.0	9.4	11.0	.....	14.1	12.1	24.0	17.3	35.0
Intestines.....	90.0	87.0	53.0	.....	91.0	129.0	175.0	.....	240.0
Pancreas.....	2.25	0.8	2.9	.....	4.9	3.8	7.6	6.7	.....
Ur. bladder.....	2.5	3.8	2.7	.....	4.2	5.3	.....	.....	9.0
Thyroid gland.....	.....	1.2	.....	.....	.....	1.6	1.85	.....	.....
Testes.....	.....	0.4	.....	0.6	0.50	.....	0.90	.....	0.70
Epididymides.....	.....	0.5	.....	0.4	0.70	.....	.....	.....	0.40
Prostata.....	.....	.....	.....	.....	1.3	.....	.....	.....	1.7
Uterus.....	1.75	.....	1.6	.....	.....	1.1	.....	.....	.....
Ovaries.....	0.17	.....	0.20	.....	.....	0.53	.....	.....	.....



## NOTES ON TABLE 3

Case 1. Malnutrition. Congenital syphilis.

Case 2. Malnutrition. Otitis media. Bronchopneumonia. Terminal diarrhea.

Case 3. Malnutrition. Otitis media. Gonorrheal conjunctivitis.

Case 4. Malnutrition. Pylorospasm (?). Bronchopneumonia. Mother gave negative Wassermann. Body weight 3,204 g. *after embalming* by intra-arterial injection of about 500 c.c. of 10 per cent formalin. Assuming this equally distributed over body (skeleton excluded), the corrected weights for the various organs are given (in parenthesis), by deducting 18.4 per cent from the observed weight.

Case 5. Emaciation. Hydrocephalus. Operated spina bifida. Negative luetic history. At autopsy, 640 g. cerebrospinal fluid (deducted from gross body weight of 3,580 g. gives corrected body weight of 2,940 g.).

Case 6. Malnutrition. Multiple boils (healed). Terminal bronchopneumonia. Body weight 3,972 g.; increased to 5,050 g. *after embalming* by intra-arterial injection of 1,078 c.c. of 10 per cent formalin. Assuming this equally distributed over body (skeleton excluded), the corrected weights for the various organs are given (in parenthesis) by deducting 24.4 per cent from the observed weight.

Case 7 (a twin). Malnutrition. Enteritis (?). Bronchopneumonia. Negative Wassermann.

Case 8. Malnutrition. Diarrhea. Otitis media. Mother luetic; infant gave negative Wassermann after mercurial treatment.

Case 9. Malnutrition. Scleroderma neonatorum. Otitis media. Diarrhea.

Case 10. General malnutrition. Premature infant.

Case 11. Malnutrition. Premature. Congenital lues. Bronchopneumonia.

Case 12. Malnutrition ("athreptic"). Hare lip and cleft palate.

Case 13. General malnutrition and inanition.

Case 14. Atrophic. Hydrocephalus. Meningitis (syphilitic) and chronic iritis. Bronchopneumonia.

Case 15. Nutrition "fair." Diarrhea. Bronchitis. Peritonitis. Slight rachitic (?) "rosary."



TABLE 5.—ACTUAL AND RELATIVE (PERCENTAGE) LOSSES IN WEIGHT OF THE BODY AND VARIOUS ORGANS IN THE GUINEA PIG AT VARIOUS STAGES OF TOTAL INANITION. DATA FOR THE AVERAGE OF 10 GUINEA PIGS IN EACH OF THE FIVE GROUPS (TABLE NO. 6 FROM LAZAREFF '95)

Group number	Body weight			Starvation		Lungs			Heart			Liver						
	Degree of loss, Per cent.	Initial	Final	Loss, g.	Length, hrs.	Final temp. (°C.)	Weight		Loss comp. to normal		Weight		Loss comp. to normal					
							g.	Per cent.	g.	Per cent.	g.	Per cent.	g.	Per cent.				
I	0.0	584	...	0	0.0	38.7	3.22	0.56	0.0	0.0	1.86	0.32	0.0	0.0	22.08	3.81	0.00	0.0
II	10.0	584	525	59	30.4	38.7	3.25	0.62	-0.03	-0.93	1.77	0.33	0.09	4.84	18.11	3.45	3.97	17.98
III	20.0	587	469	118	70.0	37.3	3.23	0.69	-0.01	-0.31	1.69	0.36	0.17	9.14	16.89	3.59	5.19	23.51
IV	30.0	580	405	175	121.4	36.6	3.20	0.79	0.02	0.62	1.47	0.37	0.39	20.97	15.24	3.77	6.84	30.98
V	35.5	580	374	206	164.2	29.8	3.06	0.82	0.12	4.97	1.24	0.33	0.62	33.33	14.34	3.83	7.74	35.05

Group number	Body weight			Starvation		Stomach			Intestines			Urinary bladder						
	Degree of loss, Per cent.	Initial	Final	Loss, g.	Length, hrs.	Final temp. (°C.)	Weight		Loss comp. to normal		Weight		Loss comp. to normal					
							g.	Per cent.	g.	Per cent.	g.	Per cent.	g.	Per cent.				
I	0.0	584	...	0	0.0	38.7	2.62	0.45	0.0	0.0	16.32	2.84	0.0	0.0	0.30	0.05	0.0	0.0
II	10.0	584	525	59	30.4	38.7	2.67	0.51	-0.05	-1.91	16.40	3.13	-0.08	-0.49	0.31	0.06	-0.01	-3.33
III	20.0	587	469	118	70.0	37.3	2.45	0.52	0.17	6.49	14.66	3.14	1.66	10.17	0.30	0.07	0.0	0.0
IV	30.0	580	405	175	121.4	36.6	2.45	0.61	0.17	6.49	14.60	3.60	1.72	10.54	0.26	0.07	0.04	13.33
V	35.5	580	374	206	164.2	29.8	2.31	0.62	0.31	11.83	12.11	3.27	4.21	25.80	0.23	0.06	0.07	23.33

TABLE 5.—(Continued)

Group number	Body weight			Starvation		Spleen			Right kidney			Left kidney			Pancreas							
	Degree of loss, Per cent	Initial	Final	Loss, g.	Length, hrs.	Final temp. (°C.)	Weight		Loss comp. to normal		Weight		Loss comp. to normal		Weight		Loss comp. to normal					
							g.	%	g.	%	g.	%	g.	%	g.	%	g.	%				
I	0.0	584	...	0	0.0	38.7	0.48	0.08	0.0	0.0	1.93	0.33	0.0	0.0	1.98	0.34	0.0	0.0	1.50	0.26	0.0	0.0
II	10.0	584	525	59	30.4	38.7	0.48	0.09	0.0	0.0	1.97	0.37	-0.04	-2.07	2.01	0.38	-0.03	-1.52	1.45	0.28	0.05	3.33
III	20.0	587	469	118	70.0	37.3	0.33	0.07	0.15	31.25	1.90	0.41	0.03	1.55	1.91	0.41	0.07	3.54	1.42	0.30	0.08	5.33
IV	30.0	580	495	175	121.4	36.6	0.30	0.08	0.18	37.05	1.73	0.43	0.20	10.36	1.78	0.44	0.29	10.10	1.13	0.28	0.37	24.67
V	35.5	580	374	206	164.2	29.8	0.27	0.07	0.21	43.75	1.72	0.46	0.21	10.88	1.76	0.47	0.22	11.11	0.91	0.24	0.59	39.33

Group number	Body weight			Starvation		Skin			Spinal cord			Brain			Femur bone							
	Degree of loss, Per cent	Initial	Final	Loss, g.	Length, hrs.	Final temp. (°C.)	Weight		Loss comp. to normal		Weight		Loss comp. to normal		Weight		Loss comp. to normal					
							g.	Per cent	g.	Per cent	g.	Per cent	g.	Per cent	g.	Per cent	g.	Per cent				
I	0.0	584	...	0	0.0	38.7	76.76	13.26	0.0	0.0	1.32	0.23	0.0	0.0	3.97	0.69	0.0	0.0	1.41	0.24	0.0	0.0
II	10.0	584	525	59	30.4	38.7	75.76	14.43	1.51	1.97	1.34	0.26	0.02	-1.05	3.91	0.75	0.06	1.51	1.44	0.27	-0.03	-2.13
III	20.0	587	469	118	70.0	37.3	70.49	15.04	6.27	8.17	1.23	0.26	0.09	6.82	3.85	0.82	0.12	3.02	1.44	0.30	-0.03	-2.13
IV	30.0	580	495	175	121.4	36.6	67.00	16.54	9.76	12.71	1.23	0.31	0.09	6.82	3.75	0.93	0.22	5.54	1.36	0.34	0.05	3.55
V	35.5	580	374	206	164.2	29.8	62.99	16.87	13.77	17.94	1.23	0.33	0.09	6.82	3.83	1.01	0.24	6.05	1.37	0.37	0.04	2.84

TABLE 6.—EFFECTS OF HIBERNATION AND SUBSEQUENT INANITION IN THE FROG (*Rana pipiens*)

Average absolute weights of organs and parts in the control group I. Percentage changes in weight for corresponding parts in the various test groups. Changes actually observed for body weight; estimated for the various parts by comparing the observed final weight at autopsy with the weight of the corresponding part in the control group I, which is assumed to be the initial weight (Ott '24)

Organ or part	Group I (controls) grams	Group II (torpid) per cent	Group III (-10) per cent	Group IV (-20) per cent	Group V (-30) per cent	Group VI (-40) per cent	Group VII (-50) per cent	Group VIII (-60) per cent
Males								
Whole body.....	45.5	+ 5.2	-13.7	-20.0	-30.9	-40.9	-50.1	-59.5
Head.....	4.3	+ 3.0	+ 3.0	- 2.0	- 7.0	- 7.0	-16.0	-31.0
Fore-limbs.....	4.3	- 2.0	- 2.0	- 9.0	-28.0	-38.0	-47.0	-65.0
Hind-limbs.....	18.6	- 9.0	-11.0	-21.0	-33.0	-41.0	-53.0	-66.0
Trunk.....	18.3	+20.0	- 9.0	-24.0	-41.0	-45.0	-52.0	-65.0
Integument.....	5.6	± 0.0	- 7.0	-25.0	-38.0	-47.0	-59.0	-72.0
Skeleton (lig.).....	5.0	+ 5.0	+12.0	+ 9.0	- 1.0	+ 3.0	+ 2.0	-12.0
Musculature.....	21.8	-13.0	-19.0	-25.0	-40.0	-52.0	-63.0	-80.0
Brain.....	0.106	- 6.0	- 7.0	- 6.0	- 3.0	-13.0	-15.0	-22.0
Spinal cord.....	0.068	- 4.0	+ 8.0	- 6.0	- 6.0	- 8.0	-14.0	-25.0
Eyeballs.....	0.432	- 3.0	- 3.0	± 0.0	+ 5.0	+ 9.0	+ 7.0	+12.0
Tongue.....	0.397	+ 2.0	+ 6.0	+ 2.0	- 1.0	+17.0	+ 3.0	-13.0
Heart.....	0.137	- 6.0	- 6.0	-15.0	-31.0	-40.0	-54.0	-52.0
Lungs.....	0.317	+18.0	+29.0	+21.0	- 6.0	+ 8.0	-27.0	-29.0
Liver.....	1.53	± 0.0	-30.0	-40.0	-56.0	-74.0	-83.0	-87.0
Spleen.....	0.028	-12.0	-30.0	+30.0	+39.0	+ 5.0	-59.0	-77.0
Stomach-intestines.....	0.78	- 7.0	+11.0	+ 1.0	+ 4.0	+ 1.0	-28.0	-53.0
Fat bodies.....	0.37	-77.0	-86.0	-95.0	-96.0	-98.0	-98.0	-99.0
Kidneys.....	0.168	-15.0	-16.0	-18.0	-25.0	-39.0	-59.0	-69.0
Testes.....	0.058	- 7.0	± 0.0	-33.0	-22.0	-58.0	-83.0	-89.0
"Remainder".....	0.74	+12.0	+ 8.0	- 3.0	-12.0	-27.0	-30.0	-50.0
Females								
Whole body.....	55.3	+ 2.8	-11.5	-20.1	-29.8	-38.8	-50.0	-51.0
Head.....	4.6	- 5.0	- 5.0	- 9.0	± 0.0	-11.0	-11.0	-12.0
Fore-limbs.....	3.3	- 9.0	-15.0	-12.0	-12.0	-41.0	-43.0	-43.0
Hind-limbs.....	19.3	- 9.0	-16.0	-23.0	-21.0	-33.0	-39.0	-39.0
Trunk.....	28.3	+10.0	-23.0	-21.0	-46.0	-57.0	-58.0	-58.0
Integument.....	5.0	+11.0	-16.0	-14.0	-13.0	-36.0	-42.0	-42.0
Skeleton (lig.).....	5.3	± 0.0	+ 6.0	+ 5.0	+ 3.0	+ 4.0	+14.0	+14.0
Musculature.....	21.5	-21.0	-30.0	-30.0	-26.0	-39.0	-41.0	-41.0
Brain.....	0.108	- 8.0	- 5.0	- 7.0	-12.0	- 9.0	- 4.0	- 4.0
Spinal cord.....	0.068	- 8.0	± 0.0	- 4.0	-11.0	- 4.0	- 7.0	- 7.0
Eyeballs.....	0.433	- 2.0	+ 8.0	+ 3.0	+ 2.0	+22.0	+22.0	+22.0
Tongue.....	0.445	- 7.0	+ 9.0	+ 7.0	+ 8.0	- 1.0	+ 2.0	+ 2.0
Heart.....	0.131	- 3.0	-10.0	-11.0	- 7.0	-24.0	-32.0	-32.0
Lungs.....	0.293	+30.0	+12.0	+37.0	+35.0	+14.0	+14.0	+14.0
Liver.....	1.62	-18.0	-52.0	-51.0	-46.0	-65.0	-60.0	-60.0
Spleen.....	0.030	-28.0	-47.0	+ 7.0	-1.0	-20.0	+31.0	+31.0
Stomach-intestines.....	1.20	-27.0	-12.0	- 1.0	-11.0	-28.0	-30.0	-30.0
Fat bodies.....	0.24	-77.0	-96.0	-94.0	-94.0	-97.0	-97.0	-97.0
Kidneys.....	0.180	-11.0	-37.0	-17.0	-22.0	-31.0	-28.0	-28.0
Ovaries.....	7.71	- 7.0	-24.0	- 6.0	-89.0	-95.0	-95.0	-95.0
Oviducts.....	2.18	- 3.0	-23.0	-11.0	-55.0	-77.0	-81.0	-81.0
"Remainder".....	0.61	+14.0	-20.0	+ 2.0	- 4.0	-23.0	-11.0	-11.0

TABLE 7.—DATA FOR VARIOUS PARTS AND ORGANS; AVERAGES FOR GROUPS OF ALBINO RATS, ACCORDING TO TESTS, WITH CORRESPONDING NORMAL CONTROLS AND PERCENTAGE DIFFERENCE (JACKSON AND STEWART '10)

Description	(A.) Underfed from birth to 3 weeks of age and refed to about 25 g. (with controls)			(B.) Underfed from birth to 3 weeks of age and refed to about 50 g. (with controls)			(C.) Underfed from birth to 3 weeks of age and refed to about 75 g. (with controls)		
	Controls	Test rats	Difference	Controls	Test rats	Difference	Controls	Test rats	Difference
Number and sex.....	4M, 4F 21.4	4M, 5F 32.3	.....	4M, 5F 38.2	3M, 6F 51.6	.....	2M, 3F 48.6	5M, 1F 65.5	.....
Age, days.....	.....	.....	.....	.....	.....	.....	.....	.....	.....
Body weight, grams:									
Gross.....	26.1	25.9	- 0.8	51.1	51.0	- 0.2	76.4	76.3	- 0.1
Net.....	24.1	24.1	0.0	47.2	47.5	+ 0.6	70.1	71.6	+ 2.1
Nose-anus length, millimeters.....	90.8	95.9	+ 6.0	120.4	122.8	+ 2.0	138.6	140.5	+ 1.4
Tail length, millimeters.....	60.0	63.0	+ 5.0	95.3	96.7	+ 1.5	116.0	109.0	- 6.0
Head, grams.....	4.84	4.56	- 0.8	6.89	6.50	- 1.7	8.68	8.70	0.0
Fore limbs, grams.....	1.79	1.87	+ 4.5	3.54	3.29	- 7.1	4.96	5.17	+ 3.8
Hind limbs, grams.....	3.39	3.56	+ 5.0	7.54	7.57	+ 0.4	11.50	11.73	+ 2.0
Trunk, grams.....	14.17	14.14	- 0.2	29.00	30.16	+ 4.0	45.20	46.51	+ 2.9
Integument, grams.....	4.89	3.91	- 20.1	8.81	8.49	- 3.6	13.36	13.75	+ 2.9
Skeleton:									
Ligamentous, grams.....	3.77	4.04	+ 7.2	6.34	5.91	- 6.8	7.98	8.24	+ 3.3
Moist cartilage, grams.....	3.04	2.87	- 5.6	5.51	5.00	- 9.3	7.20	7.06	- 1.9
Dry cartilage, grams.....	0.768	0.700	- 8.8	1.80	1.59	- 11.7	2.56	2.41	- 5.9
Musculature, grams.....	6.98	7.31	+ 4.7	16.12	15.94	- 1.1	26.84	27.71	+ 3.2
Visceral group, grams.....	5.39	5.51	+ 2.2	8.88	9.32	+ 5.0	12.71	12.25	- 3.6
Remainder, grams.....	3.18	3.24	+ 1.9	7.05	7.93	+ 12.5	9.42	9.65	+ 2.4
Brain, grams.....	1.331	1.162	- 12.7	1.496	1.252	- 16.3	1.488	1.314	- 11.7
Spinal cord, grams.....	0.181	0.194	+ 5.4	0.279	0.261	- 6.5	0.317	0.311	- 1.3
Eyeballs, grams.....	0.117	0.128	+ 9.5	0.161	0.158	- 1.9	0.177	0.179	+ 1.1
Hypophysis, grams.....	0.024	0.024	0.0	0.031	0.028	- 10.0	0.044	0.039	- 11.4
Pineal body, grams.....	0.0100	0.0094	- 6.0	0.0114	0.0102	- 10.5	0.0108	0.0099	- 6.6
Thyroid gland, grams.....	0.074	0.076	+ 3.8	0.090	0.076	- 15.6	0.111	0.117	+ 7.2
Thymus, grams.....	0.181	0.177	- 2.2	0.152	0.174	+ 14.5	0.263	0.233	- 11.4
Heart, grams.....	0.277	0.281	+ 1.4	0.406	0.285	- 29.8	0.374	0.373	0.0
Lungs, grams.....	1.36	1.35	- 0.7	2.41	2.70	+ 15.8	4.16	3.75	- 9.9
Liver, grams.....	0.994	1.043	+ 52.1	0.219	0.293	+ 33.8	0.452	0.450	0.0
Spleen, grams.....	.....	.....	.....	.....	.....	.....	.....	.....	.....
Stomach and intestines:									
Empty, grams.....	3.24	3.32	+ 2.5	6.57	6.58	+ 0.1	9.75	8.47	- 13.1
Suprenals, grams.....	1.31	1.58	+ 20.6	2.68	3.05	+ 13.8	3.71	3.75	+ 1.1
Kidneys, grams.....	0.091	0.093	+ 2.2	0.148	0.0137	- 91.1	0.0180	0.0178	- 1.1
Testes, grams.....	0.347	0.335	- 3.5	0.561	0.511	- 8.9	0.792	0.736	- 7.0
Epididymides, grams.....	0.120	0.141	+ 17.5	0.375	0.447	+ 19.2	1.047	0.579	- 44.6
Ovaries, grams.....	0.025	0.026	+ 4.0	0.055	0.056	+ 1.8	0.108	0.079	- 26.9
.....	0.0094	0.0115	+ 22.3	0.0108	0.0104	- 3.7	0.0140	0.0162	+ 15.8

TABLE 7. — (Continued)

Description	(D) Underfed from birth to 6 weeks (45 days) of age and referred to about 75 g. (with controls)			(E) Underfed from birth to 10 weeks (66 days) of age and referred to about 50 g. (with controls)			(F) Underfed from birth to 10 weeks (67 days) of age and referred to about 75 g. (with controls)		
	Controls	Test rats	Difference	Controls	Test rats	Difference	Controls	Test rats	Difference
	2M	2M		5F	4F		3F	1F	
Number and sex.....	47.0	92.5	.....	40.0	80.5	.....	49.7	101.0	.....
Age, days.....	.....	.....	.....	.....	.....	.....	.....	.....	.....
Body weight, grams:									
Gross.....	76.5	77.3	+ 1.0	45.7	47.9	+ 4.8	69.2	71.2	+ 2.0
Net.....	72.0	71.3	- 0.1	49.9	51.7	+ 3.0	70.3	75.5	+ 1.2
Nose-anus length, millimeters.....	140.5	134.0	- 4.6	119.6	122.8	+ 2.7	137.3	139.0	+ 1.2
Tail length, millimeters.....	111.0	113.0	+ 1.8	96.0	90.0	- 0.3	118.0	113.0	- 2.9
Head, grams.....	8.75	8.75	0.0	6.80	6.43	- 5.4	8.63	8.40	- 2.7
Fore limbs, grams.....	4.97	4.71	- 5.6	3.45	3.45	0.0	4.95	5.01	+13.3
hind limbs, grams.....	11.61	11.18	- 3.7	7.40	7.08	- 4.3	11.43	10.62	- 7.1
Trunk, grams.....	46.67	46.63	0.0	27.67	30.92	+ 11.8	44.23	46.55	+ 5.2
Integument, grams.....	14.06	14.65	+ 4.2	8.37	9.21	+ 10.0	12.90	17.00	+32.3
Skeleton:									
Ligamentous, grams.....	8.46	7.89	- 6.7	6.15	5.76	- 6.3	7.66	8.07	+ 5.4
Moist cartilage, grams.....	7.19	5.80	-19.3	5.39	3.97	- 26.3	7.23	7.75	+ 7.2
Dry cartilage, grams.....	2.51	1.81	- 27.9	1.89	.....	.....	2.68	.....	.....
Musculature, grams.....	28.08	26.47	- 5.7	15.79	13.36	- 15.4	26.01	24.05	- 7.5
Visceral group, grams.....	13.08	12.04	-12.0	8.84	9.90	+ 12.0	12.07	13.12	+ 8.7
"Remainder," grams.....	7.67	10.22	+ 33.2	6.59	10.39	+ 57.6	10.59	8.89	-10.0
Brain, grams.....	1.500	1.437	- 4.2	1.446	1.120	- 22.5	1.479	1.244	-15.9
Spinal cord, grams.....	0.323	0.321	- 0.6	0.268	0.248	- 7.5	0.313	0.278	- 13.2
Eyeballs, grams.....	0.173	0.266	+ 19.1	0.161	0.170	+ 5.6	0.179	0.194	+ 8.4
Hypophysis, grams.....	0.042	0.048	+ 14.3	0.030	0.034	+ 13.3	0.040	0.041	+ 10.9
Pineal body, grams.....	0.0110	0.0115	+ 4.9	0.0118	0.0098	- 17.0	0.0107	0.0086	- 25.2
Thyroid gland, grams.....	0.0142	0.0149	+ 4.9	0.0076	0.0073	- 4.0	0.0091	0.0097	+ 0.6
Thymus, grams.....	0.275	0.201	- 26.9	0.131	0.109	- 16.8	0.256	0.260	+ 1.1
Heart, grams.....	0.380	0.385	+ 1.3	0.264	0.315	+ 19.3	0.370	0.421	+13.8
Lungs, grams.....	0.475	0.494	+ 4.0	0.363	0.429	+ 18.2	0.485	0.635	+30.9
Liver, grams.....	4.19	4.18	- 0.2	2.51	2.96	+ 17.9	4.14	3.84	- 7.3
Spleen, grams.....	0.337	0.255	- 24.3	0.236	0.500	+ 112.0	0.528	0.468	- 11.4
Stomach and intestines:									
Empty, grams.....	8.60	9.10	+ 5.8	7.07	7.24	+ 2.4	10.52	9.16	-13.0
With contents, grams.....	4.04	3.11	- 23.0	2.89	3.40	+ 17.7	3.49	4.83	+38.4
Suprarenals, grams.....	0.0172	0.0190	+ 10.5	0.0143	0.0144	+ 0.7	0.0185	0.0215	+16.2
Kidneys, grams.....	0.804	0.801	- 0.4	0.530	0.625	+ 17.9	0.784	0.899	+14.7
Testes, grams.....	1.047	0.528	- 49.4	.....	.....	.....	.....	.....	.....
Epididymides, grams.....	0.108	0.090	- 16.7	.....	.....	.....	.....	.....	.....
Ovaries, grams.....	.....	.....	.....	0.0108	0.0086	- 20.4	0.0140	0.0100	- 28.6

TABLE 8.—AVERAGE DATA FOR THE PARTS, SYSTEMS, AND ORGANS IN THE GROUPS OF ALBINO RATS FULLY REFEED TO PERMANENT SIZE (ADULT) AFTER UNDERFEEDING FOR VARIOUS PERIODS. PERCENTAGE DIFFERENCES (+ OR -) BETWEEN THE DATA FOR TEST RATS AND FOR NORMAL CONTROLS OF SIMILAR BODY WEIGHT ARE INDICATED IN PARENTHESES. SEXES ESTIMATED SEPARATELY FOR THE HYPOPHYSIS AND SUPRARENAL GLANDS. SEE NOTE ON THE FOURTH GROUP (JACKSON AND STEWART '20)

	Underfed from birth to 3 weeks and refed	Underfed from birth to 10 weeks and refed	Underfed from 3 weeks to 20 weeks and refed	Underfed from 3 weeks to nearly 1 year and refed
No. of test rats.....	2 males, 3 fem.	1 male, 3 fem.	2 males, 1 fem.	7 males, 8 fem.
No. of controls.....	4 males, 8 fem.	7 males, 9 fem.	5 males, 9 fem.	4 males, 8 fem.
Age of test rats.....	445.0 da. (+18.0)	453.0 da. (+16.1)	340.0 da. (-12.2)	490.0 da. <sup>1</sup>
Body weight, grams.....	180.0 (-0.3)	200.0 (-2.0)	192.0 (+1.1)	129.0 <sup>1</sup>
Body length, millimeters.....	187.0 (-4.5)	190.0 (-5.5)	189.0 (-4.5)	176.0 (-4.0)
Tail length, millimeters.....	159.0 (-8.0)	164.0 (-6.5)	163.0 (-5.9)	147.0 (-6.6)
Head, grams.....	10.7 (-6.2)	18.5 (-1.6)	18.3 (-0.0)	8.0 (+19.4)
Fore-limbs, grams.....	11.7 (+4.5)	13.1 (+6.5)	11.9 (-1.7)	19.7 (-1.5)
Hind-limbs, grams.....	26.5 (-0.4)	29.8 (-1.9)	27.9 (-1.1)	79.2 (-11.1)
Trunk, grams.....	121.0 (+1.7)	127.0 (-5.2)	128.0 (+1.6)	22.5 (-7.8)
Integument, grams.....	30.3 (-5.6)	33.7 (-7.4)	36.8 (+9.8)	16.1 (+5.2)
Skeleton, lig. grams.....	20.1 (-2.4)	19.3 (-11.9)	30.5 (-3.3)	14.1 (-8.6)
Skeleton, cart. grams.....	15.5 (-15.3)	14.6 (-24.7)	17.3 (-7.0)	20.1 (-3.8)
Musculature, grams.....	71.8 (-4.1)	75.8 (-10.3)	83.9 (+5.8)	14.4 (-11.7)
Visceral group, grams.....	26.2 (+9.9)	26.0 (+3.6)	27.5 (+13.2)	1.090 (+2.8)
"Remainder", grams.....	25.2 (+11.0)	33.5 (+26.9)	16.2 (+33.3)	0.514 (-0.9)
Brain, grams.....	1.577 (-8.0)	1.679 (-4.2)	1.726 (-0.6)	0.319 (+18.0)
Spinal cord, grams.....	0.355 (-6.7)	0.605 (-1.3)	0.587 (-2.3)	0.0153 (-13.2)
Eyeballs, grams.....	0.319 (-2.1)	0.332 (+1.2)	0.292 (-10.7)	0.0439 (-7.8)
Thyroid, grams.....	0.0297 (+23.2)	0.0240 (-5.5)	0.0284 (+13.1)	0.0038 (-15.3)
Thymus, grams.....	0.0409 (-29.0)	0.0542 (-12.2)	0.1029 (+85.7)	0.0008 (-5.7)
Hypophysis (m.), grams.....	0.0077 (-7.2)	0.0081 (-10.0)	0.0092 (+8.2)	0.0012 (-)
Hypophysis (f.), grams.....	0.0112 (-2.6)	0.0101 (-18.5)	0.0094 (-24.2)	0.046 (-7.5)
Pituitary body, grams.....	0.0018 (+20.0)	0.0015 (+7.1)	0.0009 (-40.0)	4.94 (+31.4)
Heart, grams.....	0.852 (+8.7)	0.841 (+1.2)	0.934 (+14.9)	5.09 (+8.5)
Lungs, grams.....	3.19 (-11.0)	2.87 (-14.3)	2.96 (-15.2)	1.186 (-0.9)
Liver, grams.....	7.92 (+6.3)	8.27 (+3.4)	9.22 (+19.9)	10.48 (-)
Spleen, grams.....	0.637 (+11.8)	0.647 (+8.2)	0.516 (-12.6)	4.41 (-3.3)
Kidney's, grams.....	1.660 (+3.4)	1.623 (-7.4)	2.060 (+22.5)	0.0362 (+4.5)
Stomach-testestines with contents, grams.....	13.83 (+15.1)	17.42 (+32.2)	14.41 (+14.0)	0.0400 (+17.8)
St.-int., empty.....	7.05 (+17.3)	8.42 (+27.6)	7.09 (+12.7)	0.0355 (-61.5)
Suprarenals (m.), grams.....	0.0374 (-17.6)	0.0370 (-11.1)	0.0479 (+10.6)	1.067 (+17.1)
Suprarenals (f.), grams.....	0.0409 (+1.5)	0.0563 (+12.6)	0.0360 (-20.8)	0.512 (+34.0)
Ovaries, grams.....	0.0451 (-35.5)	0.0306 (-56.8)	0.0482 (-32.0)	0.067 (+17.1)
Testes, grams.....	1.805 (+8.7)	2.232 (+17.6)	2.307 (+30.3)	0.517 (+34.0)
Epididymides, grams.....	0.013 (+22.8)	0.745 (+32.6)	0.637 (+24.4)	

<sup>1</sup> In the fourth group, comparisons between test rats and controls for the organs were made through the Wistar norms by Donaldson's method. For the body parts and systems, the normal was calculated from the data of Jackson and Lowrey.

TABLE 9.—EFFECTS OF THIRST UPON ORGAN WEIGHTS IN ADULT ALBINO RATS (KUDO'21)

The percentage losses are given in three groups and in a regularly descending order of loss for the series subjected to acute thirst. In the series for chronic thirst, and in the one rat total inanition, the losses are entered in the same order as in the acute-thirst series. In the last two series the values do not decrease regularly, but the arrangement facilitates comparison between the several series

	Acute thirst, per cent	Chronic thirst, per cent	Total inanition, per cent
Organs showing a loss in weight greater than that of the entire body			
Loss of weight for entire body.....	36.1	52.4	47.2
Organ or part:			
Thymus.....	-78.1	-90.0	
Remainder.....	-72.7	-88.8	-77.8
Spleen.....	-66.0	-73.3	-62.9
Parotid glands.....	-57.6	-69.7	-67.6
Pancreas.....	-53.1	-52.7	-58.6
Submaxillary glands.....	-47.1	-64.5	-63.3
Lungs.....	-44.0	-51.5	-52.7
Liver.....	-37.0	-55.3	-53.0
Stomach and intestines (filled)....	-36.4	-28.3	-52.4
Organs showing a percentage loss in weight less than that for the entire body—but more than half as great			
Organ or part:			
Musculature.....	-33.1	-61.2	-39.2
Integument.....	-31.9	-47.0	-42.5
Heart.....	-30.6	-46.3	-42.6
Visceral group.....	-30.6	-42.2	-38.7
Epididymides.....	-30.0	-64.8	-55.8
Stomach and intestines (empty)....	-29.1	-31.8	-20.3
Thyroid.....	-23.9	-33.1	-41.7
Kidneys.....	-23.8	-31.4	-30.5
Suprenals.....	-21.3	-27.1	-16.6
Humerus and femur.....	-21.1	-12.1	
Organs showing a percentage loss in weight less than half that for the entire body			
Organ or part:			
Testes.....	-15.1	-59.9	-36.9
Cartilaginous skeleton.....	-11.8	- 5.0	-34.1
Eyeballs.....	-10.2	-13.3	-13.0
Ligamentous skeleton.....	- 4.3	-10.3	
Hypophysis.....	- 1.7	+ 1.7	+ 8.3
Brain.....	+ 0.12	- 4.2	- 7.6
Spinal cord.....	+ 1.80	- 6.7	-16.7

TABLE 10.—EFFECTS OF THIRST UPON ORGAN WEIGHTS IN YOUNG ALBINO RATS (KUDO '21a)  
Average data for controls and test rats, with percentage of change in the various test groups, as compared with normal controls. Weights are given in grams, lengths in centimeters.

		Test rats on dry diet held at constant body weight for periods indicated				
Normal controls (2 m.; 4 f.), Age 25-30 days, average		I-2 weeks (2 m.; 4 f.) Average and percentage difference	3-4 weeks (6 m.; 2 f.) Average and percentage difference	5-6 weeks (3 m.; 3 f.) Average and percentage difference	7-8 weeks (1 m.; 4 f.) Average and percentage difference	9-13 weeks (0 m.; 4 f.) Average and percentage difference
Gross body weight.....	26.2	24.6 (-6.1)	25.3 (-3.4)	27.4 (+4.6)	27.4 (+4.6)	27.8 (+4.6)
Net body weight.....	23.7	22.4 (-5.5)	22.7 (-4.2)	24.0 (+1.3)	24.1 (+3.0)	24.9 (+5.1)
Body length.....	9.8	9.3 (-5.1)	9.8 (0.0)	9.9 (+1.0)	10.1 (+3.1)	10.1 (+3.1)
Tail length.....	7.0	7.4 (+5.7)	8.7 (+24.3)	8.4 (+20.0)	8.4 (+25.7)	9.0 (+28.6)
Weight.....	4.35	3.74 (-14.0)	3.91 (-10.2)	3.48 (-10.0)	3.97 (-8.7)	3.98 (-7.5)
Musculature.....	7.32	6.81 (-7.0)	6.98 (-4.7)	7.38 (+0.8)	6.82 (-6.8)	6.97 (-4.8)
Uterus.....	3.73	4.26 (+14.2)	4.59 (+23.1)	5.09 (+36.5)	5.22 (+40.6)	5.06 (+35.7)
Uterine skeleton.....	2.70	3.80 (+40.2)	3.42 (+22.6)	4.17 (+49.5)	4.29 (+58.4)	4.42 (+63.4)
Cart. skeleton.....	0.3355	0.3850 (+14.9)	0.4026 (+20.0)	0.4540 (+35.3)	0.4152 (+23.7)	0.4439 (+32.3)
Humeral and femurs.....	5.1012	5.3501 (+3.1)	5.4883 (+5.7)	5.6224 (+8.3)	6.1769 (+19.0)	6.2578 (+20.6)
Visceral group.....	1.10	0.51 (-37.3)	0.58 (-47.3)	0.64 (-41.9)	0.59 (-46.4)	0.54 (-50.9)
Remainder.....	1.2424	1.1894 (-4.3)	1.3088 (+5.4)	1.2583 (+1.3)	1.2636 (+8.6)	1.3493 (+8.6)
Brain.....	0.1565	0.1801 (+20.8)	0.2107 (+34.6)	0.2165 (+38.2)	0.2389 (+52.5)	0.2398 (+53.1)
Spinal cord.....	0.0687	0.0900 (+3.5)	0.0110 (+36.8)	0.0111 (+27.6)	0.0123 (+41.4)	0.0129 (+48.3)
n. ischiadici.....	0.1054	0.1152 (+9.3)	0.1456 (+3.8)	0.1448 (-37.5)	0.1710 (+63.3)	0.1707 (+70.8)
Eyeballs.....	0.1696	0.1527 (-8.2)	0.1527 (-8.8)	0.1527 (-8.8)	0.1695 (+15.8)	0.1873 (+10.4)
Heart.....	0.0838	0.0432 (-48.4)	0.474 (-43.5)	0.0436 (-48.0)	0.0762 (-9.1)	0.1136 (+36.6)
Spleen.....	0.2369	0.2145 (-9.5)	0.2310 (-2.5)	0.2452 (+3.5)	0.2363 (-0.25)	0.0523 (-37.6)
Lungs.....	0.0284	0.0149 (-47.6)	0.0152 (-46.5)	0.0115 (-59.6)	0.0106 (-43.7)	0.0115 (-45.4)
Parotid glands.....	0.1014	0.0750 (-24.0)	0.0573 (-43.4)	0.0415 (-59.0)	0.0512 (-49.3)	0.0508 (-40.8)
Submaxillary glands.....	1.1636	1.3211 (+13.8)	1.2313 (+5.8)	1.3045 (+12.1)	1.2363 (+6.3)	1.5522 (+33.5)
Liver.....	0.1389	0.1610 (+15.9)	0.1705 (+9.2)	0.1722 (+24.0)	0.1846 (+32.0)	0.2032 (+46.3)
Pancreas.....	3.00	3.65 (+21.4)	3.91 (+9.4)	4.00 (+11.1)	4.65 (+29.2)	4.70 (+30.6)
Stomach-intestines (with contents).....	1.3688	1.38 (+6.2)	1.36 (+4.6)	1.44 (+10.8)	1.68 (+20.3)	1.75 (+24.6)
Stomach-intestines (empty).....	0.2988	0.3034 (+15.0)	0.4451 (+48.4)	0.4797 (+60.5)	0.4949 (+65.3)	0.4435 (+48.4)
Kidneys.....	0.1427	0.0623 (-32.5)	0.0738 (-47.5)	0.1005 (-29.5)	0.0450 (-68.3)	0.0450 (-68.3)
Testes.....	0.0190	0.0144 (-32.5)	0.0147 (-22.6)	0.0138 (-30.5)	0.0132 (-30.5)	0.0038 (-66.7)
Epididymides.....	0.0164	0.0077 (-32.5)	0.0061 (-46.5)	0.0041 (-64.0)	0.0043 (-62.3)	0.0217 (+34.8)
Ovaries.....	0.0164	0.0138 (-32.5)	0.0174 (+8.1)	0.0136 (-15.5)	0.0204 (+26.7)	0.0039 (+2.6)
Uterus.....	0.0638	0.0933 (+43.1)	0.0935 (-7.0)	0.0932 (-15.8)	0.0928 (-26.3)	0.0067 (-91.3)
Thyroid.....	0.0771	0.0240 (-68.9)	0.0094 (-87.8)	0.0134 (-82.6)	0.0109 (-85.9)	0.0037 (-91.3)
Suprarenals (m.).....	0.0077	0.0124 (+61.0)	0.0132 (+71.4)	0.0132 (+71.4)	0.0132 (+71.4)	0.0038 (-66.7)
Suprarenals (f.).....	0.0016	0.0106 (+37.7)	0.0017 (+6.3)	0.0023 (+43.8)	0.0023 (+43.8)	0.0039 (+2.6)
Hypophysis (m.).....		0.0017 (+6.3)	0.0015 (-6.3)	0.0023 (+43.8)	0.0023 (+43.8)	0.0039 (+2.6)
Hypophysis (f.).....		0.0016	0.0015 (-6.3)	0.0023 (+43.8)	0.0023 (+43.8)	0.0039 (+2.6)

TABLE 11.—RATS WITH EXPERIMENTAL RICKETS AND CONTROLS. AVERAGE PERCENTAGE DEVIATION FROM NORM FOR ORGAN WEIGHTS  
The corrected data (in parenthesis) for the test rats were obtained by subtracting the average deviation in the corresponding controls  
(Jackson and Carleton '23)

	37 <sup>1</sup> normal controls, per cent	Test rats on experimental diets			
		27 <sup>1</sup> apparently normal, per cent	19 <sup>1</sup> slight rickets, per cent	19 <sup>1</sup> moderate rickets, per cent	16 <sup>1</sup> severe rickets, per cent
Body weight.....	+ 8.9	+ 9.8 (+0.9)	+ 8.3 (-0.6)	+ 12.4 (+3.5)	+ 4.6 (-4.3)
Tail length.....	- 5.3	0.0 (+5.3)	- 4.6 (-0.7)	+ 3.3 (+8.6)	+ 4.4 (+9.7)
Head weight.....	- 2.5	+ 1.9 (+4.4)	+ 4.7 (+7.2)	+ 8.5 (+11.0)	+ 2.5 (+5.0)
Integument.....	- 10.0	- 2.2 (+7.8)	- 30.0 (-20.0)	- 24.1 (-14.1)	- 22.1 (-12.1)
Lig. skeleton.....	- 13.2	+ 5.9 (+19.1)	- 13.2 (0.0)	+ 1.8 (+15.0)	+ 2.6 (+15.8)
Cart. skeleton.....	+ 24.3	+ 3.8 (-20.5)	+ 22.6 (-1.7)	+ 21.0 (-3.3)	+ 17.0 (-7.3)
Cart. skeleton (dry).....	.....	+ 27.3	- 7.3	- 19.1	- 18.5
Musculature.....	+ 4.4	+ 7.4 (+3.0)	+ 3.2 (-1.2)	- 3.4 (-7.8)	- 7.8 (-12.2)
Submaxillary glands.....	+ 43.3	+ 21.9 (-21.4)	+ 58.3 (+15.0)	+ 95.2 (+51.9)	+ 92.3 (+49.0)
Brain.....	+ 1.8	- 2.1 (-3.9)	- 2.3 (-4.1)	- 1.1 (-2.9)	- 2.6 (-4.4)
Eyeballs.....	+ 14.5	+ 15.5 (+1.0)	+ 19.6 (+5.1)	+ 28.8 (+14.3)	+ 40.6 (+26.1)
Thymus.....	+ 3.4	- 30.1 (-33.5)	- 33.3 (-36.7)	- 52.8 (-56.2)	- 66.5 (-69.9)
Heart.....	+ 8.7	+ 23.5 (+14.8)	+ 17.1 (+8.4)	+ 28.8 (+20.1)	+ 26.3 (+17.6)
Lungs.....	+ 7.9	+ 13.4 (+5.5)	- 0.0 (-7.9)	+ 16.8 (+7.9)	+ 6.1 (-1.8)
Liver.....	- 22.0	- 2.1 (+20.9)	+ 14.1 (+36.1)	- 8.9 (+13.1)	- 27.7 (-5.7)
Spleen.....	+ 53.2	+ 13.7 (-39.5)	+ 27.7 (-25.5)	+ 61.9 (+8.7)	+ 37.7 (-15.5)
Stomach—intestines (empty).....	- 25.0	- 43.0 (-18.0)	- 34.0 (-9.0)	- 7.7 (+17.3)	- 48.7 (-23.7)
Stomach—intestines (+ contents)	- 0.1	+ 12.9 (+13.0)	+ 33.4 (+33.5)	+ 14.7 (+14.8)	+ 25.6 (+25.7)
Suprarenals.....	+ 2.3	+ 42.4 (+44.7)	+ 42.0 (+44.3)	+ 45.8 (+48.1)	+ 62.0 (+64.3)
Kidneys.....	+ 9.5	+ 42.8 (+33.3)	+ 54.5 (+45.0)	+ 57.6 (+48.1)	+ 51.2 (+41.7)
Ovaries.....	+ 13.2	+ 12.5 (-0.7)	+ 36.8 (+23.6)	+ 41.3 (+28.1)	+ 4.7 (-8.5)
Testes.....	+ 15.8	+ 55.8 (+40.0)	- 1.7 (-17.5)	+ 4.0 (-11.8)	+ 21.2 (+5.4)
Epididymides.....	+ 11.8	+ 35.1 (+23.3)	+ 5.4 (-6.4)	+ 44.1 (+32.3)	+ 30.6 (+18.8)
Hypophysis.....	+ 15.8	- 10.9 (-26.7)	- 12.2 (-28.0)	- 8.4 (-24.2)	- 1.4 (-17.2)

<sup>1</sup> In the case of the integument, skeleton, musculature, empty stomach-intestines, submaxillary glands, and gonads, the number of observations is considerably less, as explained in the text.

TABLE 12.—EFFECTS OF EXPERIMENTAL SCURVY UPON THE WEIGHTS OF THE VARIOUS ORGANS IN GUINEA PIGS (TABLE 3 FROM BESSESEN '23)

Average percentage differences of organ weights compared with the normal. Final body weights compared with the initial weight; organs compared with normal for corresponding final body weight

Parts	5 day test, per cent	10 day test, per cent	15 day test, per cent	Begin-ning scurvy (19 days), per cent	Death from scurvy (21-54 days), per cent
Body weight.....	- 5.8	- 3.6	- 4.5	-16.3	-37.0
Suprenals.....	+ 8.1	- 7.4	+ 9.0	+78.8	+270.1
Brain.....	+ 2.8	+ 0.3	- 0.4	+12.4	+10.4
Spinal cord.....	+30.6	+40.6	+28.0	+62.0	+69.8
Eyeballs.....	+ 8.9	+ 6.8	+ 7.0	+20.8	+ 27.5
Thyroid.....	+14.3	+17.5	+ 6.4	+68.8	+ 21.2
Heart.....	+ 2.5	+ 2.4	- 0.6	+11.1	+ 8.6
Lungs.....	- 9.8	- 5.8	+12.7	+ 4.8	+ 60.3
Liver.....	-25.0	-24.7	-18.0	+ 9.7	- 1.0
Spleen.....	-20.8	-38.6	-18.2	+56.3	+ 35.0
Stomach-intestines (filled).....	- 7.0	+41.3	+23.2	- 1.3	+ 7.1
Stomach-intestines (empty).....	-25.2	-19.9	- 8.4	+ 3.9	+ 36.3
Stomach.....	- 3.5	-15.3	-10.7	+20.7	+ 7.9
Pancreas.....	+14.3	-13.7	- 1.0	+29.6	- 1.2
Kidneys.....	+ 9.9	+22.0	+ 7.0	+38.0	+ 57.7
Testes.....	+41.7	+31.1	+35.6	+76.4	+ 4.8
Epididymides.....	+47.2	+42.2	+45.4	+71.4	+ 75.2
Ovaries.....	.....	.....	.....	- 7.6	- 19.8
Bladder (urinary).....	+37.3	+12.6	+ 9.7	+29.7	+ 44.7
Hypophysis.....	+ 8.0	+ 9.2	+12.9	+12.8	+ 50.5
Integument.....	-11.3	-19.4	-16.8	-13.0	- 1.8

TABLE 13.—LOSSES OF ORGAN WEIGHTS IN AVIAN BERIBERI AND SIMPLE INANITION

Showing average percentage loss (gain in the adrenal) in organs of young adult pigeons and fowls (34 grown) fed on polished rice or subjected to simple inanition; calculated as percentages of weights per kilo of control birds. Sexes combined (excepting adrenals). From Findlay ('21), chiefly from his Table 3

Organs	Pigeons (15 m., 18 f.)		Fowls (23 m., 16 f.)	
	Rice-fed	Chronic inanition	Rice-fed	Acute inanition
Whole body.....	29.0	.....	26.5	38.7
Thymus.....	100.0	100.0	100.0	100.0
Testis.....	82.0	85.0	61.0	60.0
Spleen.....	67.0	71.0	65.0	60.0
Ovary.....	67.0	69.0	37.0	
Pancreas.....	35.0	37.0	28.0	28.0
Stomach.....	23.0	27.0	19.0	20.0
Heart.....	17.0	19.0	15.0	14.0
Liver.....	12.0	13.0	12.0	14.0
Thyroid.....	8.5	10.9	8.0	11.0
Kidneys.....	3.0	2.0	6.0	7.0
Brain.....	0.6	0.3	5.0	3.0
Pituitary (hypophysis).....	0.0	2.5	3.0	6.0
Adrenal (Suprarenal), male.....	+37.0	+18.0	+53.0	+10.0
Adrenal (Suprarenal), female.....	+86.0	+54.0	+70.0	

## BIBLIOGRAPHY

Except where otherwise indicated, the references were verified from the original. In cases where the original was not consulted, the paging, etc. were verified, where possible, in the *Index Medicus*. The abbreviations for the periodicals in general follow (with slight modifications) those used by the *Index Medicus* and the *Index Catalogue of the Army Medical (Surgeon General's) Library, Washington*. The number preceding a colon indicates the volume; the numbers following, the inclusive paging. The final (bold-face) figures indicate the text pages on which the corresponding article is mentioned, thus constituting an author index.

- Abderhalden, E. 1900. Die Beziehungen des Eisens zur Blutbildung. *Ztschr. f. Biol.*, 39: 483-523. **256**.
- . 1919. Studien über den Einfluss der Art der Nahrung auf das Wohlbefinden des einzelnen Individuums, seine Lebensdauer, seine Fortpflanzungsfähigkeit und das Schicksal der Nachkommenschaft. *Arch. f. d. ges. Physiol.*, 175: 187-326. **112, 129, 413**.
- . 1922. Neuere Untersuchungen über das Wesen und die Bedeutung der Nutramine (Vitamine). *Klin. Wchnschr.*, 1: 160. **111**.
- Abel, G. 1918. Amenorrhöe und Krieg. *Ztschr. f. ärztl. Fortbild.*, 15: 624-626. (Ref. in *Index Med.*) **391**.
- . 1923. Von Hungersnot und Seuchen in Russland. *Münch. med. Wchnschr.*, 70: 485-487. **71, 139, 255, 391, 405**.
- Ackerknecht, E. 1912. Beiträge zur Kenntnis des Markes der Röhrenknochen beim Pferde. *Arch. f. path. Anat. u. allg. Path.*, 208: 396-414. (Also *vet. med. Dissert., Zürich.*) **136**.
- Ackermann. 1804. Brief an Brüninghausen. (Cited by Reeb '05.) **78**.
- Adami, J. G. 1908. The principles of pathology. Vol. 1. General pathology. Phila. & N. Y. **379**.
- Addams, J. & Hamilton, A. 1919. A visit to Germany. *Brit. J. Child. Dis.*, 16: 129-139. **84**.
- Adler, L. 1914. Die Wirkungsweise des Milieus auf die Gestaltung der Organismen. Beiträge zur Lehre von der inneren Sekretion. *Berl. klin. Wchnschr.*, No. 26. (Cited by O. Hertwig '20.) **441**.
- . 1920. Schilddrüse und Wärmeregulation. (Untersuchungen an Winterschläfern.) *Arch. f. exp. Path. u. Pharmakol.*, 86: 159-224. 3 Taf. 9 Textfig. **441**.
- Aducco, V. 1889. Action de la lumière sur la durée de la vie, la perte de poids, la température et la quantité de glycogène hépatique et musculaire chez les pigeons soumis au jeune. *Arch. ital. de biol.*, 12: 208. **333, 462**.
- Aeby, C. 1875. Ueber den Einfluss des Winterschlafes auf die Zusammensetzung der verschiedenen Organe des Thierkörpers. *Arch. f. exp. Path. u. Pharmakol.*, 3: 180-184. **170, 186, 280**.
- Afanassiew, B. 1877. Weitere Untersuchungen über den Bau und die Entwicklung der Thymus und der Winterschlagdrüse der Säugethiere. *Arch. f. mikr. Anat.*, 14: 343-390. 1 Taf. **126**.
- M. 1883. Ueber anatomische Veränderungen der Leber während verschiedener Tätigkeitszustände. *Arch. f. d. ges. Physiol.*, 30: 385-436. 2 Taf. **332**.
- Agostini, C. 1892. Delle cause della pellagra. *Riv. sper. di freniat.* (Cited by Raubitschek '15.) **442**.

- . 1902. Infantilismo distrofico da eredopellagra. Riv. di pat. nerv. e ment., 7: 68-79. **442.**
- e Rossi, U. 1907. Sulle alterazioni della sostanza reticolo-fibrillare delle cellule nervose in alcune malattie mentali. Ann. del Manicomio prov. di Perugia, fasc. 1-2, pp. 4-21. 46 Fig. **181.**
- Aimé, P. 1912. L'évolution périodique du thymus des chéloniens. Compt. rend. Soc. de biol., Par., 72: 115-116. (Cited by Hammar '21.) **297.**
- . 1912a. Note sur le thymus chez les chéloniens. *Ibid.*, 72: 889-890. **297.**
- Alagna, G. 1908. Cisti paratiroidée. Anat. Anz., 33: 406-417. 2 Fig. **446.**
- Albarel, P. 1905. L'atrophie infantile au xvie siècle. Ann. d. med. et chir. inf., Par., 9: 1-2. **81.**
- Albitzki, P. 1884. Ueber den Einfluss des Sauerstoffhungerns auf den Stickstoffumsatz im tierischen Organismus. Dissert., St. Petersburg., 119 pp. (Cited by Mühlmann '99 and Beeli '68.) **256.**
- Albrecht. 1913. Die Geburtshilfe beim Pferd. Braunmüller, Wien u. Lpz., 231 pp. (Cited by Bondi '13.) **102, 142.**
- Albu, A. u. Neuberg, C. 1910. Physiologie und Pathologie des Mineralstoffwechsels. Berl. (Cited by Osborne and Mendel '18.)
- Aldehoff, G. 1889. Ueber den Einfluss der Carenz auf den Glykogenbestand von Muskel und Leber. Ztschr. f. Biol., 25: 137-162. **170, 333.**
- Alessandrolo. 1902. Sull' atrepsia del Parrot, e sul sue meccanismo di produzione. *Pediatria*, 10: 1-22. **318.**
- Alexandre, R. 1888. L'hibernation humaine. Rev. scient., Par., 42: 738-741. Also in *Practicien*, Par., Anno 12, T. 11, p. 1; 13. **70.**
- Alezias, H. et Mattéi, C. 1913. L'atrophie thyroïdienne chez les athrepsiques. Réunion biol. de Marseille, 16 déc. 1913. Compt. rend. Soc. de biol., Par., 75: 667-669. **437.**
- Allen, E. 1919. Degeneration in the albino rat testis due to a diet deficient in the water-soluble vitamins, with a comparison of similar degeneration in rats differently treated, and a consideration of the Sertoli tissue. *Anat. Rec.*, 16: 93-117. 17 Figs. **414.**
- Allescher, M. 1912. Ueber den Einfluss der Gestalt des Kernes auf die Grössenabnahme hungernder Infusorien. *Arch. f. Protistenk.*, 27: 129-171. **15, 19, 20.**
- Altmann, R. 1890. Die Elementarorganismus und ihre Beziehungen zu den Zellen. Lpz., 145 pp. 21 Taf. **334, 341.**
- Alwens. 1919. Ueber die Beziehung der Unterernährung zur Osteoporose und Osteomalazie. *Münch. med. Wchnschr.*, 66: 1071-1075. **140, 141, 256.**
- Anderson, P. V. & Spiller, W. G. 1911. Pellagra, with a report of two cases with necropsy. *Am. J. Med. Sc.*, 141: 94-106. 5 Figs. **200.**
- Andreesen, A. 1883. Ueber die Ursachen der Schwankungen im Verhältniss der rothen Blutkörperchen zum Plasma. Dissert., Dorpat, 55 pp. **242.**
- Andrews, V. L. 1912. Infantile beriberi. *Philip. J. Sc.*, Ser. B, 7: 67-90. 3 pl. **207, 233, 283, 298, 312, 343, 367, 385, 432, 444, 447.**
- Arapow, A. B. 1898. (On the question of double nuclei of the liver cells. Russian.) *Dissert.*, St. Petersburg., 78 pp. **335.**
- . 1901. Contribution a l'étude des cellules hépatiques binucléaires. *Arch. d. sc. biol.*, St. Petersburg., 8: 184-209. **335.**
- Arcangeli, A. 1906. I cambiamenti dell'epitelio intestinale del *Box salpa* L. durante l'assorbimento. *Arch. ital. di anat. e di embriol.*, 5: 150-176. **321.**
- Argaud, R. et Billard, G. 1911. Inversion de la formule leucocytaire sous l'influence de l'inanition. *Compt. rend. Soc. de biol.*, Par., 70: 746-747. **252, 253.**
- Arkle, A. S. 1908. The correlation of physical and mental development. *J. Roy. Inst. Public Health, Lond.*, 16: 741-748.
- Armsby, H. F. 1906. The principles of animal nutrition. 2nd ed. N. Y.
- Arneht, J. 1905. Die Leukocytose in der Schwangerschaft, während und nach der Geburt, und die Leukocytose der Neugeborenen. *Arch. f. Gyn.*, 74: 145-188. **247.**

- Arnold, J. 1914. Ueber Plasmastrukturen und ihre funktionelle Bedeutung. G. Fischer, Jena, 471 pp. 4 Taf. **321, 338, 384, 388.**
- Aron, H. 1910. Wachstum und Ernährung. *Biochem. Ztschr.*, 30: 207-226. **89, 95, 119, 135, 140, 165.**
- . 1911. Nutrition and growth. *Philip. J. Sc.*, Ser. B, 6: 1-51. 6 pl. **75, 89, 95, 119, 135, 136, 140, 165, 180.**
- . 1913. Weitere Untersuchungen über die Beeinflussung des Wachstums durch die Ernährung. Verh. d. 29 Versammlung d. Ges. f. Kinderh. in der Abt. f. Kinderh. d. 84. Versammlung d. Ges. deut. Naturf. u. Aerzte in Münster, 1912, pp. 99-106. 2 Taf. **89, 135, 136, 140.**
- . 1913a. Biochemie des Wachstums des Menschen und der höheren Tiere. In Oppenheimer's Handb. d. Biochemie d. Menschen u. d. höheren Tiere, Ergänzungsbd. G. Fischer, Jena, p. 661 ff. **89, 140.**
- . 1914. Untersuchungen über die Beeinflussung des Wachstums durch die Ernährung. *Berl. klin. Wchnschr.*, 51: 972-977. (Also in Tr. 15. Internat. Congr. Hyg. and Dem., 2: 451 ff.) **91, 95.**
- . 1918. Ueber akzessorische Nährstoffe und ihre Bedeutung für die Ernährung des Kindes. *Berl. klin. Wchnschr.*, 55: 546-550.
- . 1920. Nährstoffmangel als Krankheitsursache. *Berl. klin. Wchnschr.*, No. 33, pp. 773-777. (Ref. in *Ber. d. ges. Physiol.*, 1920, 4: 60.) **71, 110.**
- u. Sebauer, 1908. Untersuchungen über die Bedeutung der Kalksalze für den wachsenden Organismus. *Biochem. Ztschr.*, 8: 1-28. **147, 171.**
- Asada, H. 1919. Acidosis during starvation. *Am. J. Physiol.*, 50: 1-8. **185, 280, 340, 366, 381, 462.**
- Aschner, B. 1914. Ueber Morphologie und Funktion des Ovariums unter normalen und pathologischen Verhältnissen. *Arch. f. Gyn.*, 102: 446-510. 2 Taf. **395, 398.**
- Aschoff, L. 1909. Zur Morphologie der lipoiden Substanzen. Ein Beitrag zur Verfettungsfrage. *Beitr. z. path. Anat. u. z. allg. Path.*, 47: 1-50. **124.**
- . 1913. *Pathologische Anatomie*, 3. Aufl., 2. Bd. (5. Aufl., 1921.) Jena. **271, 316.**
- und Koch, W. 1919. Zur Epidemiologie des Skorbut. Eine pathologisch-anatomische Studie. G. Fischer, Jena, 122 pp. 13 Taf. u. 16 Textabb. **132, 151, 160, 171, 208, 234, 258, 268, 284, 299, 323, 343, 355, 386, 433, 445.**
- Ash, J. E. 1914. The blood in inanition. *Arch. Int. Med.*, 14: 8-32. **241, 244.**
- . 1915. Chapter on "The blood" in Benedict's "A study of prolonged fasting." *Carnegie Inst. Washington, Publ. No. 203*, pp. 124-157. **241, 242, 244, 245, 246.**
- Asher, L. 1908. Das Verhalten des Darmepithels bei verschiedenen funktionellen Zuständen. 1. *Mitt. Ztschr. f. Biol.*, 51: 115-126. 1 Taf. **321.**
- . 1921. Der jetzige Stand der Lehre von den Vitaminen. *Deut. med. Wchnschr.*, 47: 510-511.
- Askanazy, M. 1913. Die Störungen der Nahrungszufuhr zum Organismus. In Aschoff's *Pathologische Anatomie*, 3. Aufl., 1: 41-46. **224, 256.**
- Asp, G. 1873. Zur Anatomie und Physiologie der Leber. *Ber. d. k. sächs. Ges. d. Wiss., Math.-Physik. Kl.*, 25: 470-504. 3 Fig. u. 1 Taf.
- Athanasii, J. 1899. Ueber den Gehalt des Froschkörpers an Glykogen in den verschiedenen Jahreszeiten. *Arch. f. d. ges. Physiol.*, 74: 561-569.
- et Dragoin, I. 1908. La distribution de la graisse dans le corps de la grenouille pendant l'hiver. Infiltration graisseuse normale. *Compt. rend. Soc. de biol., Par.*, 64: 191-193. **168, 341, 412.**
- Auboyer, M. L. 1881. De la croissance et de ses rapports avec les maladies aiguës fébriles. Thèse, Lyon, No. 100, 115 pp. **90.**
- Auerbach, M. 1902. Das braune Fettgewebe bei schweizerischen und deutschen Nagern und Insektivoren. *Arch. f. mikr. Anat.*, 60: 291-338. (Also *Dissert.*, Basel.) **126.**
- Awrorow (Avrorov), P. 1900. (Metabolism of matter and energy in the organism during complete inanition.) *Russian dissert.*, St. Petersburg. (Cited by Morgulis '23.)

———. (Tables of fasting in dogs. According to Benedict, manuscript copies are filed in the Surgeon General's Library, Washington; Carnegie Nutrition Laboratory, Boston; N. Y. Public Library and John Crerar Library, Chicago.)

Azzi, A. 1916. Sul comportamento dei condriosomi del rene nel digiuno e sotto determinati stimoli e in animali trattati con lecitina. *Arch. per le sc. med.*, Torino, 40: 22-36. **384.**

Babák, E. 1906. Experimentelle Untersuchungen über die Variabilität der Verdauungsröhre. *Arch. f. Entw. d. Org.*, 21: 611-702. **318.**

Babcock, S. M. 1905. The addition of salt to the ration of dairy cows. 22nd Ann. Rep. Wisc. Exp. Sta., pp. 129-156. **105, 131.**

Babes, V. 1907. Observations sur la graisse surrénale. *Compt. rend. Acad. des sc., Par.*, 144: 766-768.

——— et Jonesco, V. 1908. Études sur la diminution de la graisse surrénale dans les états pathologiques. *Compt. rend. Soc. de biol., Par.*, 65: 267-269. **418, 423.**

——— u. Sion, V. 1900. Ueber Veränderungen im Nervensystem bei Pellagra. *Verh. d. deut. path. Ges., Berl.*, pp. 310-319. **187, 199, 206, 281.**

——— ————. 1901. Die Pellagra. In Nothnagel's *Handb. d. spez. Pathologie u. Therapie*, Wien. (Cited by Raubitschek '15.) **130.**

Baelz, 1882. Ueber das Verhältniss der multiplen peripherischen Neuritis zur Beriberi (Panneuritis endemica). *Ztschr. f. klin. Med.*, 4: 616-617. **171, 206.**

Baginsky, A. 1884. Ueber atypische Epithelwucherungen im kindlichen Darmkanal. *Deut. med. Wchnschr.*, pp. 444-445. **20, 263, 304, 314.**

———. 1884a. Die Verdauungskrankheiten der Kinder bei Laupp. Tübingen. (Cited by Tugendreich '04.) **263, 304, 314.**

Bahrdt, H. u. Edelstein, F. 1913. Organanalysen bei Morbus Barlow. *Verh. d. 29. Versamml. d. Ges. f. Kinderh. in Münster (1912)*, pp. 38-43. **153.**

Bailey, H. C. & Murlin, J. R. 1915. The energy requirements of the newborn. *Am. J. Obst.*, 71: 526-547. **81.**

Baker, J. S. 1918. Improper feeding among New York school children. *City School Circ. No. 1, Bureau Educ., Dep't. of the Interior.* (Also abstr. in *School and Soc.*, 7: 312.) **84.**

———. 1918a. Malnutrition among school children. *Weekly Bull. Dep't. of Health, City of N. Y., N. S.*, 7: 75-77. **84.**

———. 1918b. The relation of war to the nourishment of children. *N. Y. Med. J.*, 107: 289-ff. (Cited by Roberts '23.) **84.**

Baldwin, B. T. 1924. The use and abuse of weight-height-age tables as indexes of health and nutrition. *J. Am. M. A.*, 82: 1-4. **87.**

Balestre, A. 1875. Du rôle de l'inanition dans la pathologie. *Thèse, Par. (Ind. Cat. S. G. L.)*

Balli, R. 1907. I centri nervosi di mammiferi adulti di fronte all'azione combinata dell'inanizione e dell'autointossicazione per tiro-paratiroidectomia. *Mem. d.r. Accad. di sc., lett. ed arti di Modena*, ser. 3, vol. 8, 12 pp. 1 pl. (Cited by Legendre '09.) **184.**

Ballowitz, E. 1891. Ueber das Vorkommen der Ehrlich'schen granulierten Zellen (Mastzellen) bei winterschlafenden Säugetieren. *Anat. Anz.*, 6: 135-142. **322.**

Bandelocque. 1820. *L'art des accouchements.* (Cited by Reeb '05.) **78.**

Banu, G. 1921. La myopathie rachitique. *Nourrisson*, 9: 229-238. 5 figs. **170.**

Barbacci, O. 1899. Die Nervenzelle in ihren anatomischen, physiologischen und pathologischen Beziehungen nach den neuesten Untersuchungen. *Centralbl. f. allg. Path. u. path. Anat.*, 10: 757-823; 865-936. **185, 196.**

Barbèra, A. G. 1900. La secrezione e la composizione chimica del latte nel digiuno prolungato e nella rialimentazione. *Ricerca sperimentale. Bull. d. Soc. med.-chir. e d. Scuola med. di Bologna*, Anno 71, ser. 7, 11: 758-760. (Cf. also *Annali di farmacoterapia*, etc., 1900, p. 456.) **128.**

———. 1902. Contributo alla conoscenza della modificazioni che il digiuno apporta negli elementi anatomici dei vari organi e tessuti dell'economia animale: glandola tiroide. *Bull. d. sc. med., Bologna*, Anno 73, ser. 8, 2: 223-231. **437.**

——— e Bicci, D. 1900. Contributo istologico alla conoscenza delle modificazioni che il digiuno apporta negli elementi anatomici dei vari organi e tessuti dell'economia animale. Prima nota: capsule soprarrenali. *Bull. d. sc. med.*, Bologna, Anno 71, ser. 7, 2: 679-682. 422.

——— . 1903. Contribution à la connaissance des modifications que le jeûne apporte dans les éléments anatomiques des différents organes et tissus de l'économie animale: glande thyroïde. *Arch. ital. de biol.*, 39: 56-62. 437.

Bardeen, C. R. 1920. The height-weight index of build in relation to linear and volumetric proportions and surface area of the body during postnatal development. *Carnegie Inst. of Washington, Contrib. to Embryol.*, No. 46 (Publ. 272), pp. 483-554. 11 charts and 2 textfigs. Also abstr. in *Am. J. Phys. Anthropol.*, 3: 263-265. 85, 86.

——— . 1921. The von Pirquet standard of normal body weight as compared with other standards. *J. Am. M. A.*, 77: 1988-1990. 85.

——— . 1923. General relations of sitting height to stature and of sitting height and stature to weight. *Am. J. Phys. Anthropol.*, 6: 355-388. 85.

Bardier, E. 1904. Inanition aqueuse et inanition minérale. *Arch. méd. de Toulouse*, 10: 372-376.

——— . 1913. Inanition. In *Richet's Dict. de physiol.*, Par., 9: 58-131. 69, 185, 242, 395, 409, 436.

Bardin, J. C. 1913. *Am. J. Insan.* July. (Cited by Huck '23.) 255.

Barfurth, D. 1885. Vergleichend histochemische Untersuchungen über das Glycogen. *Arch. f. mikr. Anat.*, 25: 259-404. 332.

——— . 1886. Versuche über die Verwandlung der Froschlaven. *Anat. Anz.*, 1: 314-317. 77.

——— . 1886a. Biologische Untersuchungen über die Bachforelle. *Arch. f. mikr. Anat.*, 27: 128-179. 77.

——— . 1886b. Experimentelle Untersuchungen über die Verwandlung der Froschlaven. *Biol. Centralbl.*, 6: 609-613.

——— . 1887. 1. Versuche über die Verwandlung der Froschlaven. 2. Der Hunger als förderndes Princip in der Natur. *Arch. f. mikr. Anat.*, 29: 1-34. 77.

——— . 1887a. Die Rückbildung des Froschlavenschwanzes und die sogenannte Sarcoplasten. *Ibid.*, 29: 35-60. 2 Taf.

——— . 1893. Regeneration und Involution. *Ergeb. d. Anat. u. Entw.*, Bd. 3, p. 198.

Barker, L. F. 1916. The clinical diagnosis of internal diseases. Vol. 4, p. 769. *Appleton & Co.*, N. Y. & Lond.

Barlow, T. 1883. On cases described as acute rickets, which are probably a combination of scurvy and rickets. *Trans. Roy. Med.-Chir. Soc.*, 66: 159-ff. (Also in *Med. Times & Gaz.*, Apr. 7, and *Lancet*, Mar. 31, 1883.) (Cited by Hess '20.) 151.

——— . 1894. Infantile scurvy and its relation to rickets. *Lancet*, Lond., 2: 1075-1080. 151.

Baroncini, L. e. Beretta, A. 1900. Ricerche istologiche sulle modificazioni degli organi nei mammiferi ibernanti. 1. Sistema nervoso centrale. 2. Reni. Nota preventiva. *Rif. med.*, Anno 16, 3: 206-210; 218-220. (Also abstr. in *Arch. ital. de biol.*, 34: 458-459.) 185, 197, 198, 231, 383.

——— . 1901. Ricerche istologiche sulle modificazioni degli organi nei mammiferi ibernanti. 3. Cuore. *Rif. med.*, Anno 16, 3: 136-137; 147-149 (Also abstr. in *Arch. ital. de biol.*, 39: 346-347.) 231, 253.

——— . 1901a. Ricerche istologiche sulle modificazioni degli organi nei mammiferi ibernanti. 4. Capsule surrenali. (Nota preventiva.) *Rif. med.*, Anno 16, 3: 162-163; Anno 17, 1: 76-78. 430.

Barrows, F. W. 1898. The effect of inanition on the structure of nerve cells. *Proc. Am. Physiol. Soc.*, Boston, 1898, Suppl. to *Am. J. Physiol.*, 1: xiv-xv. 195, 204.

Barry, L. W. 1920. The effects of inanition in the pregnant albino rat, with special reference to the changes in the relative weights of the various parts, systems and organs of the offspring. *Carnegie Inst. of Washington, Contrib. to Embryol.*, No. 53, pp. 91-136. Also, 1921, in *Papers from the Mayo Foundation for Medical Education and Research* and the

Medical School, Univ. of Minnesota, 1: 590-640. W. B. Saunders Co., Phila. & Lond. (Also, abstr., 1920, Anat. Rec., 18: 221.) 78, 89, 119, 135, 165, 180, 193, 212, 228, 276, 297, 307, 339, 353, 366, 380, 395, 401, 409, 429, 438, 467.

Bartenstein. 1905. Beiträge zur Frage des künstlichen Morbus Barlow bei Tieren. Jahrb. f. Kinderh., 61: 6-35. 153.

Bassett-Smith. 1920. Scurvy: with special reference to prophylaxis in the Royal Navy. Proc. Roy. Soc. Med., No. 9, XIII, No. 9 (War Sect.), pp. 51-70. 433.

Bataillon, E. 1891. Recherches anatomiques et expérimentales sur la métamorphose des amphibiens anoures. Thèse de Par. 77.

Batkin, S. 1915. Die Dicke des Fettpolsters bei gesunden und kranken Kindern. Jahrb. f. Kinderh., 82: 103-122. 122.

Baudelot. 1869. (Cited by Kleinenberg '72 from Grenacher's Bericht for 1869.) 35.

Baudrand, J. M. 1911. L'accroissement: ses caractères normaux et anormaux chez le nourrisson; ses rapports avec l'hérédité, plus spécialement dans les états morbides (syphilis, alcoolisme et tuberculose). Essai de théorie ontogénétique. Preface de G. Variot. O. Doin et fils, Par., 648 pp. Also Thèse med., Par., 1910-11, No. 217. 91, 97.

Bauereisen, A. 1919. Geburtshilfliche Fragen. Jahreskurse f. ärztl. Fortbildung, 10: 7-8. 391, 392, 400.

Baumberger, J. P. 1919. A nutritional study of insects, with special reference to micro-organisms and their substrata. J. Exp. Zool., 28: 1-81. 32, 60, 62.

Baur, E. 1911. Einführung in die experimentelle Vererbungslehre. Berl. (Cited by Stieve '18.)

———. 1914. Bemerkungen zu Kammerer's Abhandlung: Vererbung erzwungener Färbeveränderungen, IV. Arch. f. Entw. d. Org., 38: 682-684.

Bayard, O. 1923. Ueber das Kropfproblem. Schweiz. med. Wchnschr., 53: 703-707; 732-736. 444.

Bayle, F. A. 1816. Considérations physiologiques et pathologiques sur la faim. Thèse, Par. No. 85.

Beach, J. R. 1923. "Vitamin A" deficiency in poultry. Science, N. S., 58: 542. 218, 302, 367, 385.

Beale, 1860. Arch. Med., No. 41, Also Canstatt's Jahresber., Bd. 3. (Cited by Ochotin '86 and Statkewitsch '94.) 331.

Bean, C. H. 1909-10. Starvation and mental development. Psychol. Clinic, Phila., 3: 78-85.

——— R. B. 1914. The eruption of the teeth as a physiological standard for testing development. Ped. Seminar, 21: 596-614. 157.

——— & Baker, W. 1919. The weights of human organs (preliminary report). Proc. Am. Assn. Anat. 35th session. Anat. Rec., 16: 142-143. (Tabulated data presented at meeting, but not published with the abstract.) 224, 225, 272, 326, 372.

von Bechterew, W. 1895. Ueber den Einfluss des Hungerns auf die neugeborenen Tiere, insbesondere auf das Gewicht und die Entwicklung des Gehirns. Neurol. Centralbl., 14: 810-817. Also in Neurol. Vestnik, Kazan, 1895, 3: 85-96. (Index med.) 74, 179, 185, 193, 214, 228, 275, 334, 365.

Beccquerel, P. 1904. Sur la germination des spores d'*A'trichium undulatum* et d'*Hypnum velutinum* et sur la nutrition de leurs protonémas dans des milieux stérilisés. Compt. rend. Acad. des sc., Par., 139: 745-747. 10.

Bedson, S. P. 1921. The blood picture in scurvy, with particular reference to the platelets. Brit. Med. J., 2: 792-793. 259.

——— & Zilva, S. S. 1923. The influence of vitamin A on blood platelets of the rat. Brit. J. Exp. Path., 4: 5-12. 257.

——— ————. 1923a. Platelet count in rats suffering from vitamin A deficiency. *Ibid.*, 4: 305-309. 257.

Beeli (Beyeli), S. S. 1908. (Atrophic changes in acute starvation. Russian.) Kiev, 60 pp. (Bound with Univ. Izviestiya, Kiev, 1908, vol. 48.) 69, 99, 168, 184, 228, 231, 252, 275, 278, 336, 366, 379, 408, 423, 462.

- Béguin, F. 1902. Contribution à l'étude histologique du tube digestif des reptiles. Rev. suisse de zool., 10: 251-397. 6 pl. Also Dissert., Lausanne, 1902. (Jahresber. f. Anat. u. Entw., 1902.) 310.
- . 1904. L'intestin pendant le jeûne et l'intestin pendant la digestion. Études faites sur le crapaud des joncs et le lézard des murailles. Arch. d'anat. micr., 6: 385-454. 4 pl. 321.
- Behr, 1892. Zee, vol. 4, no. 4, Jan. 12. (Cited by Nussbaum '98.) 29, 61.
- Beitzke, H. 1921. Atmungsorgane. In Aschoff's Pathologische Anatomie, 5te Aufl., 2: 293. G. Fischer, Jena. 362.
- Bekhtereff—see von Bechterew.
- Bell, E. T. 1909. I. On the occurrence of fat in the epithelium, cartilage and muscle fibers of the ox. II. On the histogenesis of the adipose tissue in the ox. Am. J. Anat., 9: 401-438. 2 pl. 137, 168.
- . 1910. The staining of fats in epithelium and muscle fibers. Anat. Rec., 4: 199-212. 168.
- . 1911. The interstitial granules of striated muscle and their relation to nutrition. Internat. Monatschr. f. Anat. u. Physiol., 28: 297-347. 1 Taf. 168, 231.
- . 1912. The interstitial granules (liposomes) in fatty metamorphosis of striated muscle. J. Path. & Bact., 17: 147-159. 1 pl. 168.
- Bellion, M. 1909. Contribution à l'étude de l'hibernation chez les invertébrés. Recherches expérimentales sur l'hibernation de l'escargot (*Helix pomatia*, L.). Thèse sc., Lyon, 141 pp. (Inaccessible.) 54.
- Belmondo. 1889. Le alterazioni anatomiche del midollo spinale nella pellagra e loro rapporto coi fatti clinici. Riv. sperim. di freniat., 15: 266-294, 394-443; 16: 107-146. Also in Rif. med., 1889, p. 1533. (Cited by Harris '19.) 199.
- Bendix, B. 1916. Ueber die "Kriegsneugeborenen." Ztschr. f. Säuglingsschutz, 6: 335-343. 79.
- Benedict, F. G. 1907. The influence of inanition on metabolism. Carnegie Inst. of Washington, Publ. No. 77, 542 pp. 243.
- . 1908. Metabolism during inanition. The Harvey Lectures, ser. XII, pp. 170-199. J. B. Lippincott Co., Phila. & Lond. 243.
- . 1915. A study of prolonged fasting. Carnegie Inst. of Washington, Publ. No. 203, 416 pp. 72.
- Miles, Roth & Smith. 1919. Human vitality and efficiency under prolonged restricted diet. *Ibid.*, Publ., No. 280. 405.
- & Ritzmann, E. G. 1923. Undernutrition in steers; its relation to metabolism, digestion and subsequent realimentation. *Ibid.*, Publ. No. 324, 333 pp. 93.
- Beneke. (date?) Die Teichwirtschaft. (Cited by Stieve '18.) 393.
- . 1894. Pathologische Anatomie der Nebenniere in Zülzer's Handb. d. Harn- und Sexualorgane. (Cited by Ewald '02.) 418, 420, 423.
- R. 1905. Ueber physiologisches und pathologisches Wachstum. Berl. klin. Wchnschr., 42: 1133-1137; 1186-1188. 123.
- Benestad, G. 1914. Wo liegt die Ursache zur "physiologischen" Gewichtsabnahme neugeborener Kinder? Jahrb. f. Kinderh., 80: 21-41. 80, 81.
- Beninde, Dr. 1919. Die Aushungerung Deutschlands. Vortr. a. d. ausserord. Sitz. d. ver. arztl. Ges. am 18. Dez., 1918. Berl. klin. Wchnschr., 56: 7-8. 79, 84, 391, 400.
- Benjamin, J. 1908. Das Blut bei den Ernährungsstörungen des Säuglings. 80 Versamml. deut. Naturf. u. Aerzte, Köln, Abt. Kinderh., p. 346. 248.
- Bensley, R. R. 1911. Studies on the pancreas of the guinea pig. Am. J. Anat., 12: 297-388. 15 Figs. 345, 352.
- Bentkowsky, K. 1876. Beiträge zur Histologie der Schleimhaut des Magens und des Duodenum. Med. Zeitung, No. 14, 15, 17, 18. (Polish.) Abstr. in Protokollen d. Sect.-Sitz. d. V. Versamml. russ. Naturf. u. Aerzte in Warschau, 1876. (Russian.) Abstr. by Hoyer in Jahresb. d. Anat. etc., 1876, p. 298. 309.
- Beretta, A. 1902. La moltiplicazione cellulare nel midollo delle ossa del riccio durante l'ibernazione. Monit. zool. ital., 13: 212-215. 137.

- Berg, F. 1907. Pädatrophie. Dissert., Zürich, 20 pp.
- . W. 1912. Ueber spezifische, in den Leberzellen nach Eiweissfütterung auftretende Gebilde. *Anat. Anz.*, 42: 251-262. 11 Fig. 338.
- . 1913. Zur Histologie der Leberfunktionen. Verh. d. naturw. med. Vereins zu Strassburg. Münch. med. Wchnschr., Bd. 60, 1: 105-106. (Cf. also *ibid.*, 1914, No. 19, pp. 1043-1044.) 338.
- . 1914. Ueber den mikroskopischen Nachweis der Eiweiss-speicherung in der Leber. *Biochem. Ztschr.*, 61: 428-433. 2 Taf. 338.
- . 1914a. Ueber periodische Veränderungen der Salamanderleber mit besonderer Berücksichtigung der Pigmentzellen. *Ztschr. f. Morph. u. Anthropol.* (Festschr. f. G. A. Schwalbe.) 18: 579-608. 1 Taf. 338, 341.
- . 1920. Ueber funktionelle Leberzellstrukturen. I. Die Leberzelle von *Salamandra maculata* während des Zustandes der guten Ernährung und des Hungerns. Die Einwirkung von Fütterung und von der Beförderung der Gallenabsonderung bei Hungertieren. *Arch. f. mikr. Anat.*, 94: 518-567. 3 Taf. 338.
- . 1922. Ueber funktionelle Leberzellstrukturen II. Das Verhalten des Fettes in der Leber von *Salamandra maculata* unter verschiedenen Bedingungen der Jahreszeit und der Ernährung. *Ibid.*, 96: 54-76. 1 Taf. 338, 341.
- Bergel, S. 1919. Beiträge zur Biologie der Lymphozyten. *Berl. klin. Wchnschr.*, 56: 915-919. 248.
- . 1921. Die Lymphocytose; ihre experimentelle Begründung und biologisch-klinische Bedeutung. Verlag J. Springer, Berl., 140 pp. 36 Textabb. Repr. from *Ergeb. d. inn. Med. u. Kinderh.*, Bd. 20. 248.
- Bernard, C. 1870-78. Phénomènes de la vie communs aux animaux et aux végétaux. 2 vols. 240.
- . L. et Leoderich. 1908. Sur l'état clair des cellules hépatiques. *Presse méd.*, Par., pp. 451-452. 336.
- Berninger, J. 1910. Ueber die Einwirkung des Hungers auf Hydra. *Zool. Anz.*, 36: 271-279. 18 Fig. 28, 34, 36, 38.
- . 1911. Ueber die Einwirkung des Hungers auf Planarien. *Zool. Jahrb., Abt. allg. Zool.*, 30: 181-216. (Abstr. in *Jahresber. f. Anat.*, 1911, T. 2, pp. 224, 266.) 44, 204.
- Bessesen, A. N. & Carlson, H. A. 1923. Postnatal growth in weight of the body and of the various organs in the guinea pig. *Am. J. Anat.*, 31: 483-521. 25 charts. 80.
- . D. H. 1923. Changes in organ weights of the guinea pig during experimental scurvy. *Am. J. Physiol.*, 63: 245-256. 113, 114, 132, 189, 202, 221, 234, 284, 312, 343, 355, 368, 386, 399, 415, 434, 445, 456, 477.
- von Betlingk (Böhrling), R. R. 1896-7. (On changes in the chemical composition of the organism in starvation. Russian.) *Arch. biol. nauk.*, St. Petersburg., 5: 387-408. Also French transl., *Arch. d. sc. biol.*, St. Petersburg., 1897, 6: 395-416. (Abstr. in *Physiol. Jahresber.*, 1896; also by Mühlmann '99.)
- . 1901-2. Contribution à l'étude des variations du poids de certains organes au cours de l'inanition complète. *Arch. d. sc. biol.*, St. Petersburg., 9: 397-409.
- Betta, A. 1910. Des pesées dans la première enfance au point de vue physiologique et pathologique. Thèse, Montpellier, No. 67, 45 pp.
- Beyeli—See Beeli.
- Beyermann, W. 1919. (Edema disease in the Netherlands.) *Nederl. Tijdschr. v. Genesek.*, 1: 2265-ff. (Abstr. in *J. Am. M. A.*, 1919, 73: 1172.) 71.
- Beylard, E. 1852. Du rachitis, de la fragilité des os, de l'osteomalacie. Thèse de Par., 288 pp. 8 pl. 108, 142, 145.
- Bezançon, F. et Labbé, M. 1904. *Traité d'hématologie*, Par., 959 pp. 242.
- Bezzola, C. 1904. Contributo alla conoscenza dell'assorbimento intestinale. *Boll. d. Soc. med.-chir. di Pavia*, pp. 260-272. 1 pl. 321.
- Bialasewicz, K. 1919. Études comparées sur le métabolisme chimique et énergétique. I. L'inanition et la nutrition chez les Hirudinees. *Trav. de la Soc. des Sc. de Varsovie*, III, Nr. 32. (Cited by Kopeć '24.) 47.

- von Bibra, E. 1844. Chemische Untersuchungen über die Knochen und Zähne des Menschen und der Wiebelthiere, etc. Schweinfurt, 435 pp. 5 Taf. (Cited by Schabad '10.)
- . 1854. Vergleichende Untersuchung über das Gehirn des Menschen und der Wirbelthiere. Mannheim, 133 pp. (Cited by Voit '66 and Falck '75.) 178.
- Bich, I. A. 1895. (Pathological-anatomical changes in the retina of the dog's eye during starvation. Russian.) Med. Dissert., St. Petersburg, 722 pp. 1 pl. 120, 183, 213, 214, 365.
- Bichat, X. 1801. Anatomie générale, Par., 3: 116. 124.
- . 1812. Anatomie générale, nouv. ed., Par., 1: 60. 124.
- Bidault, C. 1904. Les leucocytes du sang du cheval. Bull. Soc. centr. méd. vétér., Par., 58: 671-687. (Cited by Schwarz '14.) 254.
- . 1904a. Recherches sur les leucocytes du sang du cheval, et sur certaines leucocytoses expérimentales. Arch. d. méd. exp., 16: 355-374. (Cited by Schwarz '14.) 254.
- Bidder, F. u. Schmidt, C. 1852. Die Verdauungssäfte und der Stoffwechsel. Mitau u. Lpz., 413 pp. 122, 134, 164, 178, 213, 227, 235, 249, 274, 305, 331, 348, 356, 364, 376.
- Biedermann, W. 1898. Beiträge zur vergleichenden Physiologie der Verdauung. I. Die Verdauung der Larve von *Tenebrio molitor*. Arch. f. d. ges. Physiol., 72: 105-162. 2 Taf. 64.
- . 1910. Inanitionserscheinungen. (Infusoria.) Winterstein's Handb. d. vergl. Physiol., 3 Lief., Bd. 2, 1. Halfte. Die Aufnahme, Verarbeitung und Assimilation der Nahrung, pp. 382-384. G. Fischer, Jena.
- Biedl, A. 1916. Innere Sekretion. 3. Aufl. Urban & Schwarzenberg, Berl. u. Wien. Also 4. Aufl., 1922. 286.
- Bierrich, R. 1919. Ueber Skorbut. Deut. Arch. f. klin. Med., 130: 151-171. 132, 151, 160, 221, 237, 258, 299, 302, 433.
- Bigland, A. D. 1920. Oedema as a symptom in so-called food-deficiency diseases. Lancet, 1: 243-247. 71, 431.
- Billard, G. 1922. Les têtards de grenouille, réactifs biologiques pour l'étude des vitamines de croissance. Jour. de physiol. et de pathol. gén., 20: 182-188. 110.
- Bing, R. 1907. Ueber atonische Zustände der kindlichen Muskulatur. Vorl. Mitt. I. Rachitische Myopathie. Med. Klin., 3: 10-14. (Cited by Banu '21.) 170.
- . 1908. Myopathia rachitica. Jahrb. f. Kinderh., 2: 649-667. (Cited by Banu '21.)
- Birch-Hirschfeld, F. V. 1883. Lehrbuch der pathologischen Anatomie, 2. Aufl., 2: 166. (Cited by Coen '90.)
- . 1892. Allgemeine Pathologie. (Cited by Pernice e Scagliosi '95.) 69.
- Birk, W. 1911. Unterernährung und Längenwachstum beim neugeborenen Kinde. Berl. klin. Wchnschr., Jahrg. 48, 2: 1227-1231. 91, 120, 135.
- von Bischoff, T. 1864. Das Hirngewicht des Menschen. Sitzungsber. d. k. bayr. Akad. d. Wiss. (Cited by Sawidowitsch '14.) 174.
- Biscossi, A. 1908. Sui cambiamenti dell'epitelio dei villi intestinali ai vari stadi assorbimento. Arch. ital. di anat. e embr., 7: 244-263. 2 pl. 321.
- Bitôt. 1863. Gaz. méd. de Paris, 1/5, p. 435. (Cited by Blegvad '24.) 216.
- Bitsch—see Bich.
- Bizzozero, G. 1869. Sul midollo delle ossa. Morgagni, 11: 465-481; 617-646. 125.
- . 1889. Nouvelles recherches sur la structure de la moelle des os chez les oiseaux. Arch. ital. de biol., 14: 293-332. 127.
- . 1889a. Ueber die Atrophie der Fettzellen des Knochenmarkes. Arch. f. mikr. Anat., 33: 247-254. 1 Taf. 127.
- e Torre, A. A. 1881. Ueber die Entstehung und Entwicklung der rothen Blutkörperchen bei Vögeln. Moleschott's Unters., z. Naturlehre, Bd. 12. Also in Arch. per le sc. med., vol. 4, n. 18. 127.
- e Vassale, G. 1887. Sulla produzione e sulla rigenerazione fisiologica degli elementi ghiandolari. Arch. per le sc. med., 11: 195-254. 306.
- Blake, E. M. 1921. Ocular changes in infantile scurvy. Am. J. Ophth., 4: 736-739. 221.

- Blanton, S. 1919. Mental and nervous changes in the school children of the Volksschulen of Trier, Germany, caused by malnutrition. *Mental Hyg.*, 3: 343-386. 204.
- Blaschko, A. 1883. Mittheilung über eine Erkrankung der sympathischen Geflecht der Darmwand. *Arch. f. path. Anat. u. allg. Path.*, 94: 136-147. 204, 314.
- Blegvad, O. 1924. Xerophthalmia, keratomalacia and xerosis conjunctivae. *Am. J. Ophth.*, 7: 89-117. (Also in *Acta Ophth.*, 1923, 1: 172-176.) 211, 220.
- Blessig. 1866. *Petersburger med. Ztschr.* (Cited by Blegvad '24 from *Centralbl. f. d. med. Wiss.*, 1867, p. 424.) 211, 216.
- Blix, G. 1916. Ueber den Wassergehalt des Blutes. *Biochem. Ztschr.*, 74: 302-311. 260.
- Bloch, C. E. 1903. Studien über Magendarmkatarrh bei Säuglingen. *Jahrb. f. Kinderh.* 58: 733-794. 7 Fig. 315.
- . 1904. Die Säuglings-Atrophie und die Paneth'schen Zellen. *Jahrb. f. Kinderh.*, 59: 1-29. 315.
- . 1905. (Researches on the atrophy of children.) *Hosp.-Tid.*, Kopenh., 13: 345; 369, 2 pl. (Abstr. in *Centralbl. f. allg. Path. etc.*, 1905, 16: 634.) 315, 347.
- . 1905a. Die Säuglingsatrophie und die Paneth'schen Zellen. *Beitr. z. Path. d. Verdauungsorg.* . . . *med. Klin. in Kopenh., Berl.*, 1: 203-232. (Index med.) 315.
- . 1906. Untersuchungen über die Pädatrie. *Jahrb. f. Kinderh.*, 63: 421-445. 4 Fig. 315, 347.
- . 1918. (Xerophthalmia and dystrophy in infants.) *Ugesk. f. Laeger.*, 80: 815-ff. (Abstr. *J. Am. M. A.*, 71: 322.) 220.
- . 1919. Klinische Untersuchungen über Dystrophie und Xerophthalmie bei jungen Kindern. *Jahrb. f. Kinderheilk.*, 89: 405-441. 220.
- . 1921. Clinical investigation on xerophthalmia and dystrophy in infants and young children (xerophthalmia et dystrophia alipogenetica). *Jour. Hyg.*, 19: 283-304. 3 pl. 220.
- . 1924. Blindness and other diseases in children arising from deficient nutrition (lack of fat-soluble A factor). *Am. J. Dis. Child.*, 27: 139-148. 8 figs. 220.
- Bloor, W. R. 1914. Studies on blood fat. I. Variations in the fat content of the blood under approximately normal conditions. *J. Biol. Chem.*, 19: 1-24. 241.
- Blumenthal, R. 1904. Recherches expérimentales sur la genèse des cellules sanguines et les modifications fonctionnelles des organes hématopoiétiques. *Soc. roy. d. sc. méd. et. nat. (Bruxelles)*, 1. fév., 356 pp. 3 pl. 276, 278, 394, 407, 462.
- Boas, F. 1897. The growth of children. *Science, N. S.*, 5: 570-572. 83.
- . 1912. The growth of children. *Ibid.*, 36: 815-818.
- . 1923. The growth of children as influenced by environmental and hereditary conditions. *School & Soc.*, 17: 305-308. 157.
- Bodine, J. H. 1921. Factors influencing the water content and the rate of metabolism of certain orthoptera. *J. Exp. Zool.*, 32: 137-164. 60.
- Boehm, A. u. Davidoff, M. V. 1894. *Lehrbuch der Histologie des Menschen.* (Also 2. Aufl., 1898, and Engl. transl. by Huber, Saunders Co., Phila., 1904.) 334.
- . J. 1875. Ueber den vegetabilischen Nährwerth der Kalksalze. *Sitzungsber. d. k. Akad. d. Wissensch.*, Wien, 71: 287-304. (Cited by Reel '07.) 8.
- . P. 1908. Ueber den feineren Bau der Leberzellen bei verschiedenen Ernährungszuständen; zugleich ein Beitrag zur Physiologie der Leber. *Ztschr. f. Biol.*, 51: 409-434. 1 Taf. 337.
- Boehme, A. 1919. Gehäuft auftretende Knochenerkrankungen infolge von Unterernährung. *Deut. med. Wchnschr.* 45: 1160-1162. 145.
- Boetlingk or Boetlingk—see Betlingk.
- Bohn, G. 1904. Influence de l'inanition sur les métamorphoses. *Compt. rend. Soc. de biol., Par.*, 56: 661-663. 77.
- . 1904a. De la lumière, de l'aliment, e de la chlorophylle comme modifications du développement des amphibiens. *Compt. rend. Acad. des sc., Par.*, 138: 1244-1245. 77.
- Bokorny, T. 1892. Einige Beobachtungen über den Einfluss der Ernährung auf die Beschaffenheit der Pflanzenzelle. *Biol. Centralbl.*, 12: 321-330. 4, 8.

- . 1895. Ueber den Einfluss des Calciums und Magnesiums auf die Ausbildung der Zellorgane. Bot. Centralbl., 62: 1-4. **8, 9.**
- Bondi, J. 1913. Das Gewicht des Neugeborenen und die Ernährung der Mutter. Wien. klin. Wchnschr., 26: 1026-1028. **79.**
- Bonnamour, S. 1905. Étude histologique des phénomènes de sécrétion de la capsule surrénale chez les mammifères. Thèse, Lyon, 112 pp. 1 pl. **423, 430.**
- . 1905a. Modifications histologiques de la capsule surrénale dans certains états physiologiques (hibernation, inanition) et pathologiques expérimentaux (diphthérie, rage). Compt. rend. Assoc. d. Anat., Internat. Congr. Anat., Geneva, 1905, 7: 87-93. 4 figs. **423, 430.**
- Bonne, M. C. 1901. Sur les gouttelettes de graisse à existence temporaire des ganglions spinaux de la grenouille. Compt. rend. Soc. de biol., Par., 53: 474-476. **204.**
- Borberg, N. C. 1912. Das chromaffine Gewebe. Nebennierenuntersuchungen II. Skand. Arch. f. Physiol., 28: 91-163. **427.**
- Borchers, E. 1914. Die Rolle der Fettphanerose bei der krankhaften Verfettung der Herzmuskulatur. Arch. f. path. Anat. u. allg. Path., 218: 37-47. 1 Taf. **229.**
- Bornhardt, A. 1886. Die Körperwägungen der Einberufenen als Mittel zur Bestimmung der Tauglichkeit zum Militärdienst. Petersburger med. Wchnschr., pp. 108-ff; 196-ff. (Cited by Guttman '22.) **86.**
- Borowsky, W. M. 1910. Untersuchungen über *Actinosphaerium eichhorni*. Arch. f. Protistenk., 19: 255-288. 2 Taf. **18.**
- Borrino, A. 1917. (Physiologic loss of weight in the newborn.) *Pediatrics*, 25: 413-ff. (Cited by Pearce in *Am. J. Dis. Child.*, 1919, 19: 363.)
- Bottomley, W. B. 1914. Some accessory factors in plant growth and nutrition. *Proc. Roy. Soc. Lond.*, Ser. B, 88: 237-247. (Cf. also 1915-17, 89: 102; 481.) **3, 14.**
- . 1914a. The significance of certain food substances for plant growth. *Ann. Bot.*, 28: 531-540. 2 figs. (Abstr. by Funk '22.) **3, 14.**
- Bouchardat. 1852 (?). De l'alimentation insuffisante. Thèse, Par., 111 pp. (Cited by Bardier '13.)
- Bouchaud, J. B. 1864. De la mort par inanition et études expérimentales sur la nutrition chez la nouveau-né. Thèse de Par. **82, 135.**
- Bouci. (Cited by Deflandre '03.)
- Bourgeois. 1855. (Cited by Falck '81; abstr. in *Canstatt's Jahresb.*, 1855, II, p. 101-102.) **120.**
- . L. 1870. Étude de physiologie expérimentale de la mort par inanition. Thèse no. 186, Par. **70, 99, 134, 139, 164, 179, 211, 213, 227, 249, 264, 274, 303, 306, 316, 331, 348, 364, 376, 406, 462.**
- Bovaird, D. & Nicoll, M. 1906. The weights of the viscera in infancy and childhood with special reference to the weight of the thymus gland. *Arch. Pediat.*, 23: 641-668. **226, 273, 289, 328, 374.**
- Bowin, M. 1880. (Beiträge zur Frage über die Trockenernährung. Russian.) *Dissert. St. Petersburg*, 37 pp. (Cited by Mühlmann '09 and Bardier '13.) **115, 132, 190, 234, 259, 284, 368, 387.**
- Box, C. R. 1913. Fatal pellagra in two English boys. *Brit. Med. J.*, 2: 2-4.
- Boycott, A. E. & Chisholm, R. A. 1911. The influence of underfeeding on the blood. *J. Path. & Bact.*, 16: 262-268. **254.**
- Boyd, F. D. 1920. Pellagra. *Edinb. Med. J.*, 24: 366-371. Also cf. Report on pellagra among Turkish prisoners of war, Alexandria, Dec. 31, 1918. (Cited by McCarrison '21.) **103, 311, 431.**
- Bracco, J. J. 1923. Alterations dentaires chez des rats par régimes déficients. *Compt. rend. Soc. de biol., Par.*, 89: 453. **161.**
- Braitmaier, H. 1904. Ein Beitrag zur Physiologie und Histologie der Verdauungsorgane bei Vögeln. *Med. Dissert.*, Tübingen, 40 pp. 1 Taf. (Abstr. in *Jahresb. d. Anat.*, 1904, T. 3, p. 381; 429.) **352.**

- Brandt, H. 1919. Blutuntersuchungen bei Barlow'scher Krankheit. Arch. f. Kinderh., 67: 395-413. (Also in Monatschr. f. Kinderh., 1920, Bd. 18, Nr. 2.) 258.
- Brasch, F. 1898. Ueber den Einfluss der Wasserentziehung auf die Nervenzelle. Fortschr. d. Med., 16: 803-817. 1 Taf. 202, 209.
- . M. 1912. Studien zur Verdauungsleukocytose beim Kaninchen und beim Hund. Ztschr. f. exp. Path. u. Therap., 10: 380-411. 252.
- Brass, A. 1883. Die chromatische Substanz in der thierischen Zelle. Zool. Anz., 6: 681-683. 17.
- Breaudat, L. 1910. Sur les urines et sur le sang des beriberiques. Bull. d. Soc. path. exot., Par., 3: 620-624. (Cited by Hoffman '22.) 257.
- Brehm. 1896. Das Leben der Säugetiere. (Cited by Reeb '05.)
- . 1912. Tierleben. 4 Aufl., 4: 146-155; also Bd. 3, 1915. 76.
- Brettauert, J. u. Steinach, E. 1857. Untersuchungen über das Cylinder-epithelium der Darmzotten. Sitzungsbd. d. k. Akad. d. Wissensch., math.-naturw. Cl., Wien, 23: 303. 320.
- Bright, J. M. (et al.) 1877. Report of post mortem examination, and on the cause of death of Harriet Staunton, aged thirty-five. Brit. Med. J., 2:604. 71, 128, 163, 181, 223, 270, 303, 313, 325, 346, 362, 371.
- Brinckmann, A. 1921. Ueber alimentäre Anämien. Das Verhalten des Blutes junger Tiere bei einseitiger und eisenarmer Ernährung. Ztschr. f. Kinderh., 30: 158-194. 256.
- Broca. 1852. Sur quelques points de l'anatomie pathologique du rachitisme. Bull. Soc. anat. de Par., 27: 141-164; 542-596. 2 pl. 145.
- Brouardel, M. 1876. De l'influence des purgations et de l'inanition sur la proportion des globules rouges contenus dans le sang. L'union méd., No. 110, p. 405-f. (Cited by Andreesen '83.) 241.
- Brown, A. 1898. Do salmon feed in fresh water? The question as viewed from the histological characters of the gut. Zool. Anz., 21: 514-515; 517-523. 310.
- . M. A. 1920. A study of malnutrition of school children. J. Am. M. A., 75: 27-30. 84.
- Brucce, M. 1920. Sulla patogenesi delle sindromi da alimentazione incompleta. Gazz. internaz. di med., chirurg., ig., etc., 26: 73-78; 85-89; 97-100; 113-116; 123-125; 133-136. (Abstr. in Ber. d. ges. Physiol., 1920, 4: 60-61.) 140, 257, 283, 343, 386, 432, 444.
- Bruch, P. 1902. Zur physiologischen Bedeutung des Kalziums in der Pflanze. Landw. Jahrb., 30: 127-144. (Cited by Reed '07.) 8.
- Bruening, H. 1914. Untersuchungen über das Wachstum von Tieren jenseits der Säuglingsperiode bei verschiedener künstlicher Ernährung. Jahrb. f. Kinderh., 79: 305-319. 2 Fig. 95, 102, 140, 319, 341.
- . 1914a. Experimentelle Studien über die Entwicklung neugeborener Tierei bei längerdauernder Trennung von der säugenden Mutter und nachheriger verschiedenartiger künstlicher Ernährung. Jahrb. f. Kinderh., 80: 65-85. 130, 140.
- . 1918. Zur Frage der Kriegsneugeborenen. Deut. med. Wchnschr., 44: 581. 79, 81, 129.
- . u. Schwalbe, E. 1912-1914. Handbuch der allgemeinen Pathologie und der pathologischen Anatomie des Kindesalters. Wiesb. Bd. 1, 1. Abt., 1912; 2. Abt., 1914; Bd. 2, Abt. 1, 1913.
- Brueninghausen. 1804. Etwas über Erleichterung schwerer Geburten. Würzburg. (Cited by Reeb '05.) 78.
- Brugia. 1901. Le alterazioni del sistema dei gangli del simpatico. Imola. (Cited by Raubitschek '15 and Harris '19.)
- Brunner. (Unpublished work under Lukjanow, cited by Jarotzky '99.) 350.
- Brunow, H. 1911. Der Hungerstoffwechsel des Flusskrebse (*Astacus fluviatilis*). Ztschr. f. allg. Physiol., 12: 297-322. 59.
- Brusa, P. 1921. Alterazioni organiche dell'apparato respiratorio indotte da deformità spiccate del torace rachitico. Riv. clin. pediat., 19: 210-227. 142.
- Buchtien, O. 1887. Entwicklungsgeschichte des Prothallium von Equisetum. Cassel. (Cited by Schultze '03.) 3.

- Budzynski, B. & Chelchowski, K. 1916. Hunger swelling in Poland. *J. Trop. Med.*, etc., 19: 141-142. Also in *Przegląd. lekarski*, 1915, vol. 54, no. 1, 2. (Cited by Maase u. Zondek.) 102, 170, 215, 254, 255, 342.
- Buerger, M. 1919. Epidemisches Oedem und Enterokolitis. *Ztschr. f. d. ges. exp. Med.*, 8: 309-366. 71.
- . 1920. Die Oedemkrankheit. *Ergeb. d. inn. Med. u. Kinderh.*, 18: 189-238. 10 Fig. 71, 236, 255.
- Buhl, L. 1861. *Klinik der Geburtskunde*. (Cited by v. Hecker u. Buhl.) 175.
- Bujard, E. 1905. Sur les villosités intestinales. *Bibl. anat.*, 14: 236-242. 10 figs. 318.
- Bullard, H. H. 1912. On the intestinal granules and fat droplets of striated muscle. *Am. J. Anat.*, 14: 1-46. 7 figs. 169, 231.
- . 1916. On the occurrence and physiological significance of fat in the muscle fibers of the normal myocardium and atrioventricular system; interstitial granules (mitochondria) and phospholipins in cardiac muscle. *Am. J. Anat.*, 19: 1-35. 2 pl. 231.
- Bulley, E. C. 1919. Note on xerophthalmia in rats. *Biochem. J.*, 13: 103-106. 218.
- von Bunge. 1895. Ueber die Eisentherapie. XIII Kongr. f. innere Med. (Cited by Lazarus '13.) 105.
- . 1901. *Lehrbuch der Physiologie des Menschen*. 2. Bd., 592 pp. Also 2. Aufl., 1905. 92.
- Buntzen, J. 1879. Om ernæringem og blodtabets indflydelse paa blodet. Kjöbenhavn. Inaug. Dissert. (Abstr. by Andreesen '83.) 250.
- Burchard, H. B. & Inglis, O. E. 1908. *Dental pathology and therapeutics*. 3d ed. (Also in 5th ed.) 158, 161.
- Burckhardt, A. E. 1893. Beiträge zur Chemie und Physiologie des Blutserums. *Arch. f. exp. Path.*, 16: 322-343. 241.
- Burk, F. 1898. Growth of children in height and weight. *Am. J. Psychol.*, 9: 253-326. (Cited by Severson '19.) 84, 97.
- Burkhardt, L. 1912. Ueber die Rückbildung der Eier gefütterter aber unbegatteter Weibchen von *Rana esculenta*. *Arch. f. mikr. Anat.*, 79: 1-40. 394.
- Byfield, A. H. & Daniels, A. L. 1923. Parental nutrition in the causation of rickets. *J. Am. M. A.*, 81: 360-362. 107.
- Byrne, C. H. C. 1919. Enlargement of the adrenal in starvation. *Brit. Med. J.*, 2: 135. 419, 428.
- Cabot, R. C. 1904. *Clinical examination of the blood*. N. Y. 242.
- Cadet, A. 1881. Étude physiologique des éléments figurés du sang et en particulier des hématoblastes. Thèse de Par. 241, 250.
- Cahn, A. 1886. Die Magenverdauung im Chlorhunger. *Ztschr. f. physiol. Chem.*, 10: 522-535. 311.
- Cajal, R. y. 1904. Variaciones morfológicas normale y pathológicas del retículo neurofibrillar. *Trab. Lab. Investig. Biol. d. la Univ. Madrid*, T. 3. (Cited by Cutore '08.) 185, 197.
- . 1904a. Variaciones morfológicas del retículo nervioso de invertebrados y vertebrados sometidos a la acción de condiciones naturales. (Nota preventiva.) *Trab. Lab. Investig. Biol.*, Madrid., 3: 287-297. 5 figs. (Abstr. by Jahresb. f. Anat., 1904, T. 1, pp. 257; 312-315. 196, 197, 204.
- Calabresi, E. 1919. Sul comportamento del condrioma nel pancreas e nelle ghiandole salivari del riccio (*Erinaceus europæus* L.) durante il letargo invernale e l'attività estiva. *Arch. ital. di anat. e di embriol.*, 17: 29-47. 2 pl. 358.
- Calderini. 1847. *Votigia med. statiche sulla pellagra*. Milano. (Cited by Marie '08, '10.) 104.
- Calkins, G. N. 1902. Studies on the life history of protozoa. I. The life history of *Paramecium caudatum*. *Arch. f. Entw. d. Org.*, 15: 139-186. 4 Fig. 17, 21.
- . 1904. Studies on the life history of protozoa. IV. Death of a series. *J. Exp. Zool.*, 1: 423-461. 21.
- Calmarza. 1870. *Memoria sobre la pelagra*. Madrid. (Cited by Goldberger and Tanner '22.) 103.

- Calmette, A. 1919. Considerations sur l'état sanitaire de la ville pendant l'occupation allemande. Bull. Acad. de méd., Par., 81: 120-125. **84, 392.**
- Camerer, W. 1893. Untersuchungen über Massenwachstum und Längenwachstum der Kinder. Jahrb. f. Kinderh., 36: 249-293. **90, 97.**
- jr. 1905. Längenwachstum und sein Verhältnis zum Gewichtswachstum bei chronischer Unterernährung. Verh. d. Ges. f. Kinderh., Meran, p. 152. **90, 135.**
- Camia, M. 1901. Sulle modificazioni acute delle cellule nervose per azione di sostanze convulsivanti e narcotizzanti. Rend. d. adunanz. d. Accad. med.-fisic. Fiorentina, sed. 20 Febb. Sperimentale, 55: 305-306. Riv. patol. nerv. e ment., 6: 1-37.
- Campbell, M. 1907. Effects of diet on the structure of the uterus in the rat. Brit. Med. J., 1: 1229-1231. (Also in Appendix of Watson's "Foods & Feeding.") **401.**
- Cantalamesa, C. 1892. Per titolo di assassinio; morte procurata con lente inanizione; studio medico-legale. Morgagni, 34: 545-582. **82, 176, 247, 314, 328, 362.**
- Carini, F. 1901. Contributo allo studio della metamorfosa grassosa. Sperimentale, 55: 53-74. **124.**
- Carrier, E. W. 1892. Contributions to the histology of the hedgehog (*Erinaceus europaeus*). J. Anat. & Physiol., 27: 85-111; 169-178; 354-360; 508-518. 5 pl. **253, 266, 310, 322, 341.**
- . 1893. Note on the structure of the suprarenal body. Anat. Anz., 8: 443-445. **430.**
- . 1896. On the pancreas of the hedgehog during hibernation. J. Anat. & Physiol., 30: 334-336. (Also in Veterinarian, London., 69: 55-61.) **350.**
- . 1905. Concerning the secretion of ferments by the liver cells and some of the changes observable in them during digestion. Cellule, 22: 431-456. 2 pl. **236.**
- & Evans, C. E. L. 1903. A chemical study of the hibernating gland of the hedgehog, together with the changes which it undergoes during winter sleep. J. Anat. & Physiol., 38: 15-31. 6 figs. **126.**
- Carrington, H. 1908. Vitality, fasting and nutrition. Rebman Co., N. Y., 648 pp. **96.**
- Carter, W. E. 1921. The Pirquet system of nutrition and its applicability to American conditions. J. Am. M. A., 77: 1541-1546. **85.**
- Carville et Bochefontaine. 1874. Note sur quelques lésions anatomo-pathologiques, consécutives a l'inanition, observées chez deux chiens. Gaz. Méd. de Par., p. 549-ff. (Also Compt. rend. Soc. biol. de Par., 1875, 26: 314-319.) **167, 182, 194, 204, 213, 274, 331, 376.**
- Casella, D. 1903. Il decorso dell'inanizione assoluta nel *Gongylus ocellatus* posto in ambiente saturo d'umidità. Studi sassaresi, Sassari, 3: 47-73.
- . Le cours de l'inanition absolue chez de *Gongylus ocellatus* placé dans un milieu saturé d'humidité. Arch. ital de biol., 42: 273-288.
- Casper-Liman. 1882. Handbuch d. gerichtl. Med., 7, 2: 371-ff. (Cited by Dün-schmann '00.) **270, 313, 325.**
- Castaldi, L. 1922. Accrescimento delle sostanze corticale e midollare della glandola surrenale e loro rapporti volumetrici. Arch. di fisiol., 20: 33-127. **429.**
- du Castel, J. 1908. Le thymus rachitique. Compt. rend. Soc. de biol., Par., 65: 725-726. **298.**
- Cattaneo, A. 1900. Influenza dell'inanizione acuta sulla funzione e sulla composizione chimica dell'occhio. Soc. med.-chir. di Bologna. Resoc. (1900), 1901, p. 70. Also in Bull. de sc. med. di Bologna, 1900, 7. s., 11: 856-870. **213, 215.**
- . 1905. Die Nebennieren bei Rachitis. V. Kongr. d. italien. Ges. f. Kinderh., Roma. (Cited by Funk '22.) **431.**
- G. 1892. Influenza del letargo sulle forme e i fenomeni delle cellule ameboidi negli invertebrati. Atti d. Soc. ligurica di sc. nat. e geogr., 3: 248-251. Also in Boll. mus. zool. e anat. comp. d. r. Univ. di Genova, 1892, No. 1, pp. 1-3. **54, 60.**
- Centani, E. 1914. Le alimentazioni unilaterali. Quad. di psichiatr., Dec., pp. 385-401. (Cited by Harris '19.) **103.**
- e Galassi, C. 1913. Sul doppio effetto tossico e unilaterali dell'alimentazione maizica. Sperimentale, vol. 67, Suppl., pp. 142-150.

- Cerri, G. 1804. Lettera sulla pellagra al cittadino G. Brambilla. Effemeridi fisico-med., Milano. (Cited by Harris '19.) 103.
- . 1805. Lettera seconda al prof. Rezia in risposta ad alcuni quesiti sulla pellagra. *Ibid.* (Cited by Harris '19.)
- Cesa-Bianchi, D. 1907. Osservazioni sul modo di comportarsi della ghiandola interstiziale dell'ovaia negli animali ibernanti. Boll. d. Soc. med.-chir. di Pavia, Sec. 5, luglio, pp. 222-233. 398.
- . 1909. Leber- und Nierenzellen während der Verhungerung. Frankf. Ztschr. f. Path., 3: 722-755. 2 pl. (Cf. also *ibid.*, pp. 461-486; 795-822.) 337, 379, 460.
- Cesaris-Demel, A. 1906. Contribution à l'étude du marasme expérimental. Arch. ital. de biol., 26: 83-87. (From orig. in Giornale d. r. Accad. di med. di Torino, anno 59, no. 5, 1896.) 252, 278, 379.
- Chabas (Habas). 1897. (On the question of the Kupffer cells and the endothelium of the blood vessels in the fatty metamorphosis of the liver.) Russian dissert., St. Petersburg. (Cited by Beeli '08.)
- Chainsky (Khainski), A. J. 1903. (Ueber Strukturveränderungen des Kerns von *Paramacium caudatum*.) (Russian.) Arbeiten d. zootom. lab. d. k. Univ., Warschau, Bd. 30, 22 pp. 27 Fig. (Abstr. in Jahresb. d. Anat., 1903, T. 1, pp. 51; 58-59.) 21.
- . 1906. (Observations physiologiques sur les Paramécies.) (Russian.) Trav. du Lab. zootom. de l'Univ. à Varsovie, 35: 1-101. (Abstr. by Lipska '10.) 17, 21.
- Chajinski—see Chainsky.
- Chamberlain, W. P., Bloombergh, H. D. & Kilbourne, E. D. 1911. A study of the influence of rice diet and of inanition on the production of multiple neuritis of fowls and the bearing thereof on the etiology of beriberi. Philip. J. Sc., Sec. B., 6: 177-209. 14 figs.
- Champy, C. 1909. Sur la structure de la cellule absorbante de l'intestin. (Notes prélim.) Compt. rend. Soc. de biol., Par., 67: 629-630. 321.
- . 1911. Recherches sur l'absorption intestinale et la rôle des mitochondries dans l'absorption et sécrétion. Arch. d'anat. micr., 13: 55-170. 2 pl.
- . 1921. Changement expérimental du sexe chez le *Triton alpestris*. Compt. rend. Soc. biol., Par., 172: 1204-1207. 397, 412.
- Chapin, H. D. (et al.) 1918. The national danger from defective development of growing children in time of war. Arch. Pediatr., 35: 54-64. (Also in Med. Rec., N. Y., 1918, 93: 89-91; and Am. J. Obstr., 1918, 77: 511-520.) 84.
- Chapman, R. N. 1920. The life cycle of the Coleoptera. Annals Entom. Soc. Amer., 13: 176. 64.
- Charteris, F. J. 1907. Record of changes observed in the blood count and in the opsonic power of a man undergoing a prolonged fast. Lancet, 85th yr., 2: 685-687. 242, 243.
- Chauvin, M. 1840. Observation curieuse d'un enfant né avant terme, qui resta pendant deux mois sans prendre de nourriture. J. de méd. et chir. prat., Par., 11: 259-264. 82.
- . Marie von. 1876. Ueber die Verwandlung des mexikanischen Axolotl in Amblystoma. Ztschr. f. wiss. Zool., 27: 522-535. 77.
- Cheadle, W. B. & Poynton, F. J. 1907. Rickets. In Allbutt's System of Med., Lond., 3: 78-117. 107, 131, 142, 170, 188, 233, 256, 267, 282, 342, 367.
- . 1909. Infantile scurvy. *Ibid.*, 5: 898-918.
- Chelmonski, A. 1921. Maladie alimentaire des os. (Osteoporosis alimentaria.) Presse méd., No. 12, pp. 115-116. 136.
- Chiari, R. 1910. Abführmittel und Kalkgehalt des Darmes. Arch. f. exp. Path. u. Therap., 63: 434-440. 236.
- Chick, H. 1920. Die Rolle der Vitamine in der Ernährung. Wien. med. Wchnschr., 70: 411-419. 111.
- . et al. 1923. Studies of rickets in Vienna, 1919-22. Report to the Accessory Foods Committee etc. Med. Research Council, London. Special Report Ser., No. 77. 230 pp. 27 figs. 13 pl. 107.
- & Dalyell, E. J. 1921. Observations on the influence of foods rich in accessory factors in stimulating development in backward children. Brit. Med. J., 2: 1061-1066. 114.

- & Hume, E. M. 1920. The production in monkeys of symptoms closely resembling those of pellagra by prolonged feeding of a diet of low protein content. *Biochem. J.*, 14: 135-146. 103.
- Hume, E. M. & Skeleton, R. F. 1918. The antiscorbutic value of cow's milk. *Biochem. J.*, 12: 131-153. 153.
- Child, C. M. 1911. A study of senescence and rejuvenescence based on experiments with Planarians. *Arch. f. Entw. d. Org.*, 31: 537-616. 44.
- . 1915. Senescence and rejuvenescence. Univ. of Chicago Press, 481 pp. 31, 44.
- . 1919. A comparative study of carbon dioxide production during starvation in Planaria. *Am. J. Physiol.*, 48: 231-257. 44.
- . 1920. Studies on the dynamics of morphogenesis and inheritance in experimental reproduction. X. Head frequency in *Planaria dorotocephala* in relation to age, nutrition and motor activities. *J. Exp. Zool.*, 30: 403-417. 44.
- & Hyman, L. H. 1919. The axial gradients in hydrozoa. *Biol. Bull.*, 36: 183-223. 38.
- Childs, G. H. 1921. Some observations on the digestive system of Diplopods, with special reference to *Parajulus*. Unpublished thesis for Ph. D. degree, Univ. of Minn., Minneapolis. 59.
- Chittenden, R. H. & Underhill, F. P. 1917. The production in dogs of a pathological condition which closely resembles human pellagra. *Am. J. Physiol.*, 44: 13-66. 103, 302, 322.
- Chorvat (Chorwat), A. N. 1897. (Zur Lehre vom Hungern. Ueber dauerhaftes Hungern bei Igel.) (Russian.) *Wratsch*, 18: 1415-1419. (Abstr. by Mühlmann in *Centralbl. f. allg. Pathol. etc.*, 1898, 9: 633.)
- Chossat, C. 1842. Note sur le système osseux. *Compt. rend. Acad. des sc.*, Par., 14: 451-454. 105, 141, 144.
- . 1843. Recherches expérimentales sur l'inanition. Mémoire auquel l'Académie des Sciences a décerné en 1841 le prix de physiologie expérimentale. Extrait des mémoires de l'academie royale des sciences. Tome 8 des savants étrangers. Paris. 67, 69, 70, 73, 74, 99, 115, 118, 122, 134, 164, 178, 192, 213, 227, 235, 249, 274, 303, 305, 316, 331, 348, 364, 376, 400, 406, 422, 428, 462.
- Chudnovski (Tschudnowsky). 1890. (Contribution to the study of the healing of skin wounds during the exhaustion of the organism through inanition, hemorrhage or infection) Russian dissert., St. Petersburg. 122.
- Chun. 1917. Beriberi. *Nat. Med. J.*, Shanghai, 3: 113. (Cited by Funk '22.) 257.
- Ciaccio, C. 1910. Contributo alla distribuzione ed alla fisio-patologia cellulare dei lipidi. *Arch. f. Zellforsch.*, 5: 235-263. 3 Taf. 423, 430.
- Citron, E. 1902. Beiträge zur Kenntniss von Syncoryne Sarsii. *Arch. f. Naturgeschichte*. Jahrg. 68. (Cited by Schultz '04 and Krahelska '13.) 39.
- Clark, A. J. 1923. Applied pharmacology. J. & A. Churchill, Lond. (p. 256.) 174.
- T. 1922. Nutrition in school children. *J. Am. M. A.*, 79: 519-525. 85.
- Sydenstricker, E. & Collins, S. D. 1923. Weight and height as an index of nutrition. Weight and height measurements of 9,973 children classified upon medical examination as "excellent," "good," "fair," or "poor" in nutrition as judged by clinical evidence. Reprint No. 809 from the Public Health Reports, U. S. P. H. S., Jan. 12 (pp. 39-58). 22 pp. Govt. Printing Office, Washington. 87.
- ————. 1923 a. Indices of nutrition. Application of certain standards of nutrition to 506 native white children without physical defects and with "good" or "excellent" standards of nutrition as judged from clinical evidence. *Ibid.*, Reprint No. 842, Jun. 8 (pp. 1239-1270). 35 pp. 87.
- Coburn, F. D. 1910. Swine in America. Orange Judd Co., N. Y., 603 pp. 462.
- Cocco-Pisano, A. 1901. Il decorso del digiuno assoluto nel *Gongylus ocellatus*. *Studi sassaresi*, 1: 126-ff. (Cited by Bardier '13.)
- . 1902. Le cours du jeune absolu chez le *Gongylus ocellatus*. *Arch. ital. de biol.*, 38: 187-199. 462.

- Coen, E. 1890. Sull' inanizione acuta. Osservazioni sperimentali. Bull. d. sc. med. di Bologna, 7. s., 1: 666-688. (Also author abstr. in Centralbl. f. allg. Pathol. etc., 1891, 2: 200-202.) 167, 183, 231, 278, 306, 317, 334, 365, 377.
- Cohen, B. & Mendel, L. B. 1918. Experimental scurvy in the guinea pig in relation to the diet. J. Biol. Chem., 35: 425-453. 113, 160.
- Cohnheim, J. 1882. Vorlesungen über allgemeine Pathologie. (Cited by Mönckeberg.)  
 ———. 1889. Lectures on general pathology. Sec. 2. Pathology of nutrition. Transl. from 2nd German ed. by A. B. McKee, New Sydenham Soc., Lond. 134, 181, 240, 271, 404.
- Cohnstein u. Michaelis. 1898. (Cited by Weber '02.)
- Colin, J. 1873. Traité de physiologie comparée des animaux. 2. éd., 2: 606. 69.
- Collard de Martigny, C. P. 1828. Recherches expérimentales sur les effets de l'abstinence complète d'aliments solides et liquides, sur la composition et la quantité du sang et de la lymphe. J. de physiol. exp., 8: 152-210. 98, 121, 164, 178, 213, 227, 240, 249, 263, 274, 305, 313, 331, 348, 364.
- Comby, J. 1901. Traité du rachitisme. 2. éd., Par., 302 pp. 37 figs. 109, 142, 158, 188, 256, 267, 282, 312, 342, 376.  
 ———. 1919. Carence et vitamines. Arch. de méd. des enf., 22: 659-667.
- Comes, S. 1907. Ricerche sperimentale sulle modificazioni morfologiche e chimiche della zona pellucida e degli inclusive dell'ovo dei mammiferi. Arch. zool., 3: 165-220. 2 tav. 394.
- Comrie, J. D. 1920. Scurvy in North Russia. Edinb. Med. J. (Apr.). 132, 151, 160, 171, 234, 258, 302.
- Coppola, F. 1890. Sui valore fisiologico e terapeutico del ferro inorganico. Rend. d. r. Accad. dei Lincei, 6: 362-ff. (Cited by Hofmeister '18.)
- Cordés, H. 1898. Untersuchungen über den Einfluss akuter und chronischer Allgemeinerkrankungen auf die Testikel, speziell auf die Spermatogenese, sowie Betrachtungen über das Auftreten von Fett in den Hoden. Arch. f. path. Anat. etc., 151: 402-428. 404.
- Cornish, W. R. Reports *re* Indian Famine, 1877-1878. (Cited by McCarrison '21.) 102.
- Corti, A. 1903. Ricerche su l'anatomia dello stomaco dei Vespertilionidi. Arch. ital. di anat. e embr., 2: 369-404. 1 pl. 311.  
 ———. 1906. Sui meccanismi funzionali della mucosa intestinale assorbente di mammifero. Atto del Congr. dei naturalisti ital., Milano, pp. 15-19. (Cited by Biscossi '08.) 321, 322.  
 ———. 1912. Studi sulla minuta struttura della mucosa intestinale di vertebrati in riguardo ai suoi diversi momenti funzionali. Memoria prima. Arch. ital di anat. e embr., 11: 1-189. 9 pl. 321, 322.
- Coudereau, C. A. 1869. Recherches chimiques et physiologiques sur l'alimentation des enfants. Thèse, Par., 116 pp. 3 pl. (Cited by Hatai '07.) 97.
- Coulter, J. M., Barnes, C. R. & Cowles, H. C. 1911. A textbook of botany. Vol. 2. Ecology. N. Y., Cinc. & Chicago, 964 pp. 4, 6.
- Coupin, H. 1921. How plants defend themselves against starvation. (Abstr. from orig. paper before the Acad. de Sc., Paris, Sept. 13, 1920.) Sc. Amer. Monthly, 3: 408. 3.
- Cowdry, E. V. 1918. The mitochondrial constituents of protoplasm. Carnegie Inst. Washington, Contrib. to Embryol., 8: 39-160.
- Cramer, W. 1920. On glandular tissue and its relation to other endocrine organs and to the vitamine problem. Brit. J. Exp. Path., 1: 184-196. 125, 131, 432.  
 ———. 1920a. Vitamines and lipid metabolism. Proc. Physiol. Soc., J. Physiol., 54: ii-iv. 432.  
 ———. 1923. Relation of vitamin deficiency to growth of cancer. In Imperial cancer research fund: scientific report. 42 pp. Taylor & Francis, Lond. (Abstr. in Lancet, Lond., 1923, 2: 1368-1369. 130, 354, 431, 442.)  
 ———. Drew, A. H. & Mottram, J. C. 1921. Similarity of effects produced by absence of vitamines and by exposure to Roentgen rays and radium. Lancet, 1: 963-964. 258, 268, 283, 299, 322.

- . 1921a. On the function of lymphocyte and of lymphoid tissue in nutrition, with special reference to the vitamin problem. *Lancet*, 2: 1201-1208. **257, 258, 268, 283, 299.**
- . 1922. On blood-platelets: their behaviour in "vitamin A" deficiency, etc. *Proc. Roy. Soc., Lond., Ser. B*, 93: 449-467. **257.**
- Cremer, M. 1890. Demonstration eines mit kalkarmer Nahrung unter Zugabe von Strontiumphosphat ernährten jungen Hundes. *Sitzungsab. d. Ges. f. Morph. u. Physiol. in München*, 6: 124-126.
- Crémieu, R. 1912. Étude des effets produits sur le thymus par les rayons X. Lyon. (Cited by Nobécourt '16.) **290, 295.**
- Croftan, A. C. 1917. Edema as a danger signal in the starvation treatment of diabetes. *J. Am. M. A.*, 69: 1962. **71, 103.**
- Cruet, M. 1902. Modifications subies par le foie sous l'influence de l'alimentation insuffisante chez les dyspeptiques. Thèse méd., Par., 98 pp. (1902-'03, No. 91.) **335.**
- Cuénot, L. 1894. L'influence du milieu sur les animaux. *Encycl. scientif. des aide-mémoire*. 176 pp. G. Masson, Par. **29, 30, 41, 58, 393, 461.**
- . 1899. Sur la détermination du sexe chez les animaux. *Bull. sc. de la France et de la Belgique*, 32: 462-535. **32, 61, 63, 80.**
- Cuffer, P. 1878. Recherches sur les altérations du sang dans quelques maladies des enfants du premier âge. *Rev. mens. de méd. et chir.*, pp. 519-531. **247.**
- Cugini. 1880. Intorno ad un anomalia della *Zea mays*. *Nuovo giorn. bot. ital.*, 12: 247. Also in *Bot. Centralbl.*, 1880, S. 1130. (Cited by Strassburger '00.) **3.**
- Cunningham, D. D. 1880. On certain effects of starvation on vegetable and animal tissues. *Quart. J. Micr. Sc., N. S.*, 20: 50-78. 11 figs. **4, 120, 250, 264, 317, 332.**
- Curran, R. H. 1874. Death from starvation; post mortem. *Indian Med. Gaz.*, Calcutta, 9: 257. **223, 270, 303, 313, 325, 371.**
- W. 1880. The pathology of starvation. *Med. Press & Circ.*, Lond., n.s., 29: 210-229.
- Curschmann, H. 1922. Ueber Unterernährung und Störungen der inneren Sekretion. *Acta med. scand.*, Stockholm, 57: 240-246. **102, 442.**
- . 1922a. Ueber die Einwirkung der Kriegskost auf die Basedow'sche Krankheit. *Klin. Wchnschr.*, 1: 1296-1298. **437, 442.**
- Curtis, L. 1882. Physiology of autonutrition: a study of blood during a prolonged fast. *Proc. Am. Assn. Adv. Sc.* (1881), 30: 95-105. **241.**
- Cushing, H. and Goetsch, E. 1915. Hibernation and the pituitary body. *J. Exp. Med.*, 22: 25-47. 2 pl. (Also abstr. in *Proc. Soc. Exp. Biol. & Med.*, N. Y., 1913-14, 11: 25.) **454.**
- Cutore, G. 1908. Modificazioni strutturali delle cellule motrici del midollo spinale durante il letargo. *Arch. ital. di anat. e embr.*, 7: 121-144. 1 pl. (Also abstr. in *Boll. Accad. Gioenia Sc. Nat. Catania*, Fasc. 94, 1907.) **198.**
- Cyr, J. 1869. Recherches sur l'inanition et l'alimentation insuffisante. *Gaz. méd. de Par.*, 24: 277; 291; 319. **79, 181, 211, 240, 267, 362.**
- . 1869a. Traité de l'alimentation dans ses rapports avec la physiologie, la pathologie et la thérapeutique. Par., 574 pp.
- Czajewicz, F. 1866. Mikroskopische Untersuchungen über die Textur, Entwicklung, Rückbildung und Lebensfähigkeit des Fettgewebes. *Arch. f. Anat., Physiol. etc.*, Jahrg. 1866, pp. 289-320. 1 Taf. (German transl. by Hoyer from the original in Polish.) **124.**
- Czerny, A. 1911. Ueber die Bedeutung der Inanition bei Ernährungsstörungen der Säuglinge. *Samml. zwangl. Abhandl. a. d. Geb. d. Verdauungs- u. Stoffwechselkrankh.*, Bd. 3, H. 2, 24 pp. Herausg. von A. Albu. (Cited by Rosenstern '11, and Tobler u. Bessau '14.) **82, 105.**
- . 1912. Atrophy of infants. *Am. J. Dis. Child.*, 3: 170-176. **81.**
- . 1921. Die Ernährung der deutschen Kinder während des Weltkrieges. *Monatschr. f. Kinderh.*, 21: 2-13. **85, 97.**
- Czervenka, K. 1917. Ueber "Kriegsamenorrhöe." *Zentralbl. f. Gyn.*, 41: 1162-1165. **391, 399, 400.**

- Daddi, L. 1897. Sul peso dell'estratto etero del sangue e della linfa nel digiuno di breve durata. *Sperimentale*, 51: 406-418.
- . 1898. Sulle alterazioni degli elementi del sistema nervoso centrale nell'insomnia sperimentale. *Riv. di patol. nerv. e ment.*, 3: 1-ff. (Abstr. in *Arch. ital. de biol.*, 30: 241-257. 9 fig.) **184, 194, 204, 462.**
- . 1898a. Sulle alterazioni del sistema nervoso centrale nella inanizione. *Riv. di patol. nerv. e ment.*, 3: 295-300. **184, 194, 204.**
- . 1898b. Sur le poids de l'extrait éthéré du sang et de la lympe dans le jeûne de courte durée. *Arch. ital. de biol.*, 30: 437-438. **241.**
- . 1898c. Sur le modifications du poids de l'extrait éthéré du sang durant de jeûne de longue durée. *Ibid.*, 30: 439-444. **241.**
- Dale, H. H. 1904. The islets of Langerhans of the pancreas. *Proc. Roy. Soc. Lond.*, 73: 84. (Cited by Gianelli e Bergamini '14a.) **345, 352.**
- . 1905. On the "islets of Langerhans" in the pancreas. *Phil. Trans. Roy. Soc. Lond.*, vol. 197, Ser. B. (Cited by Bensley '11.) **345, 352.**
- Dalyell, E. J. & Chick, H. 1921. Hungerosteomalacia in Vienna, 1920. I. Its relation to diet. *Lancet*, 201: 842-849. **136.**
- Damianovich, H. 1921. Quelques recherches sur la vitamine B. *Compt. rend. Soc. de biol., Par.*, 85: 591-592. **415.**
- Damlevski, A. 1891. (Alterations in brain tissue during starvation.) *Fiziol. sbornik (Danilevski), Kharkov*, 2: 191-205. (Cited in *Index Cat., S. G. L.*) **185.**
- Daniels, A. L., Armstrong, M. E. & Hutton, M. K. 1923. Nasal sinusitis produced by diets deficient in fat-soluble A. *J. Am. M. A.*, 81: 828-829. **367.**
- Dantschakoff, W. 1909. Ueber die Entwicklung des Knochenmarkes bei den Vögeln und über dessen Veränderungen bei Blutentziehungen und Ernährungsstörungen. *Arch. f. mikr. Anat.*, 74: 855-926. 2 Taf. **136, 137.**
- Dassonville, C. 1898. Influence des sels minéraux sur la forme et la structure des végétaux. *Rev. gén. bot.*, 10: 15; 59; 102; 161; 193; 238; 289; 335. (Cited by Reed '07.) **9.**
- Davenport, C. B. 1897. The rôle of water in growth. *Proc. Boston Soc. Nat. Hist.*, 28: 78-84. 8 figs. (Abstr. in *Science, N. S.*, 5: 423.) **115.**
- . 1899. Experimental morphology. II. Effects of chemical and physical agents upon growth. *N. Y.* **115.**
- . 1920. Height-weight index of build. *Am. J. Phys. Anthropol.*, 3: 467-475-**85.**
- . 1923. Body-build and its inheritance. *Carnegie Inst. of Washington, Publ. No. 329*, 176 pp., 9 pl., 53 figs. **85, 86, 87.**
- David, L. M. 1815. *Dissertations sur la lienterie causée par la faim et les mauvais alimens.* Thèse, Par., No. 206, 28 pp. (Cited by Collard de Martigny, 1828.) **240.**
- . M. 1922. Ueber Kriegsneugeborene. *Zentralbl. f. Gyn.*, 46: 795-802. **79.**
- Davidson, J. & Le Clerc, J. A. 1918. The effect of sodium nitrate applied at different stages of growth on yield, composition and quality of wheat. *J. Am. Soc. Agron.*, 10: 193-198. **5.**
- Davis, M. & Outhouse, J. 1921. Effect of a ration low in fat soluble A on the tissues of rats. *Am. J. Dis. Child.*, 21: 307-311. **233, 283, 343, 354, 385, 414.**
- . N. C., Hall, C. C., & Whipple, G. H. 1919. Rapid construction of liver cell protein on a strict carbohydrate diet contrasted with fasting. *Arch. Int. Med.*, 23: 689-710. **340.**
- . W. A. 1917. The phosphate depletion of the soils of Bihar; its effect on the quality and yield of crops and the contingent risks of malnutrition and endemic diseases in cattle and man. *Agr. J. India (Spec. Ind. Sci. Congr. No. 77)*. (Cited by Funk '22.)
- Decaisne, E. 1871. Des modifications que subit le lait de femme par suite d'une alimentation insuffisante. *Observations recueillies pendant le siège de Paris.* *Gaz. Méd. de Par.*, 26: 317. **129.**
- Dehon. 1905. Recherches sur l'inanition chez le jeune chat. *Méthodes. Résultats.* *Compt. rend. Soc. de biol., Par.*, 58: 837-839; 931-932. **74.**

- Déjerine. 1881. Sur les altérations des nerfs cutanés dans la pellagre. *Compt. rend. Acad. des sc., Par.*, 93: 91–ff. (Cited by Raubitschek '15 and Harris '19.)
- Demjanenko, K. 1909. Das Verhalten des Darmepithels bei verschiedenen funktionellen Zuständen. II. *Mitth. Ztschr. f. Biol.*, 52: 153–188. 4 Taf. 321.
- Demoor, M. & Slosse, M. 1920. Rationing of Belgium during the war. (Abstract of official résumé published by the Royal Academy.) *J. Am. M. A.*, 75: 188–189. 79, 84.
- Denning, A. 1899. Die Bedeutung der H<sub>2</sub>O Zufuhr für den Stoffwechsel und die Ernährung des Menschen. *Ztschr. f. phys. u. diät. Therap.*, 1: 281 and 2: 292. 259.
- Denton, M. C. & Kohman, E. 1918. Feeding experiments with raw and boiled carrots. *J. Biol. Chem.*, 36: 249–263. (Cited by Maver '20.) 102.
- Denys, J. 1887. La structure de la moelle des os, et la genèse du sang chez les oiseaux. *Cellule*, 4: 203–240. 126, 136.
- Depaul. 1849. Influence du régime débilissant sur le développement du foetus. *Compt. rend. Soc. de biol., Par.*, 1: 79; 104–105. 79.
- Determann, H. 1919. Die Bedeutung der Kriegsernährung für den Stoffwechsel und Gesundheit. *Ztschr. f. phys. u. diät. Therap.*, 33: 92–ff.; 137–ff. 314.
- Detoma, P. 1880. Del rapporto fra i globuli sanguigni bianchi e i globuli rossi del sangue. *Giorn. d. r. Accad. di med. di Torino*. (Abstr. in *Jahresb. d. Anat. etc.*, 1880, p. 26.) 241.
- De Tommasi, G. G. 1894. Contribuzione all'etiologia dell'atrofia infantile primitiva; sintomatologia, anatomia patologica, con cinque osservazioni cliniche personali. *Arch. internaz. d. spec. med.-chir., Napoli*, 10: 229–241. 122, 165, 226, 273, 347, 362.
- De Villa, S. 1911. Contributo clinico ed anatomopatologico sullo stato del pancreas nell'atrofia infantile primitiva. *Gaz. internaz. di med., Napoli*, 14: 756–758. 347.
- Diatschenko (Diayschenko), E. 1897. (Ueber die Veränderungen des Knochenwachstums bei Kaninchenembryonen durch das absolute Hungern ihrer Mütter hervorgerufen.) *Russian thesis, St. Petersburg*. (Also abstr. by Mühlmann '99.) 78, 138.
- . 1899. Sur les modifications dans la croissance des os des foetus intra-utérins des lapins sous l'influence de l'inanition complète de leurs mères. *Compt. rend. XII congr. internat. de méd., Mosc.* (1897), vol. 2, sec. 3, pp. 297–298. 78, 138.
- Dibbelt, W. 1909. Die Pathogenese der Rhachitis. II. *Arb. a. d. Gebiete d. pathol. Anat. etc.* (Tübingen), 7: 144–214. 144, 147, 343.
- . 1909a. Die Pathogenese der Rachitis und ihre experimentelle Erforschung. *Centralbl. f. allg. Pathol. etc.*, Bd. 20. *Verh. d. deut. path. Ges.*, 13: 33–40. 9 Fig.
- . 1910. Die Bedeutung der Kalksalze für die Schwangerschafts- und Stillperiode. *Beitr. z. path. Anat. etc.*, 48: 147–169. 1 Taf. 105, 147.
- . 1911. Die physiologische Bedeutung des Kalkhungers bei Brustkindern im ersten Lebensjahre. *Berl. klin. Wchnschr.*, 48: 2062–2064. 105, 141.
- Dickinson, W. H. 1869. On the enlargement of the viscera which occurs in rickets. *Med. chir. trans.*, 52: 359–377. 1 pl. (Cited by v. Starck '96.) 267.
- Dickson, C. 1908. The bone marrow. A cytological study. *Lond.* 126, 136, 137.
- . J. G. 1918. The value of certain nutritive elements in the development of the oat plant. *Am. J. Bot.*, 5: 301–324. 6, 7, 8, 9, 11.
- Dietrich, A. 1910. Die Störungen des zellulären Fettstoffwechsels. *Ergeb. d. allg. Path. etc. Abt. II* (1909), 13: 283–355. 124.
- . H. A. 1917. Kriegsamennorrhöe. *Zentralbl. f. Gyn.*, 41: 157–159. 391, 399, 400.
- Digby, W. The famine campaign in southern India, 1876–1877. (Cited by Maver '20.) 71.
- Disse, J. 1892. Ueber die Veränderungen der Nierenepithelien bei der Sekretion. *Anat. Hefte*, 2: 141–171. 1 Taf. 383.
- . 1900. Anatomie der Niere. *Sitzungsbd. d. Ges. d. Bef. d. ges. Naturw., Marburg.*, pp. 49–58. 2 Fig. (Abstr. in *Jahresb. d. Anat. etc.*, 1900, T. 3, pp. 382–383.) 383.
- . 1900a. Die Niere winterschlafender Tiere. *Ibid.*, 9, Mai, pp. 49–56. (Abstr. in *Jahresb. d. Anat. etc.*, 1900, T. 2, pp. 92–93.) 383.

- . 1902. Der Bau der Niere. In v. Bardeleben's Handb. d. Anat. Bd. 7, T. 1, pp. 64-69. **383.**
- Doenhoff, E. 1880. Ueber die Ursache warum Kaninchen sterben wenn sie nur eine Art von Nahrungsmittel bekommen. Arch. f. Anat. u. Physiol., Physiol. Abt., pp. 432-434.
- Donaggio, A. 1906. Effeti dell'azione combinata del digiuno e del freddo sui centr nervosi di mammiferi adulti. Riv. sperim. di freniatr. etc., 32: 373-393. 1 pl. (Also in Atti della Soc. Med.-Chir. di Modena, 1906.) **184, 197.**
- . 1907. Effets de l'action combinée du jeûne et du froid sur les centres nerveux de mammifères adultes. Arch. ital. de biol., 46: 407-437. 2 figs. **184, 197.**
- Donaldson, H. H. 1911. On the regular seasonal changes in the relative weight of the central nervous system of the leopard frog. J. Morphol., 22: 663-694. **179, 186.**
- . 1911a. The effect of underfeeding on the percentage of water, on the ether-alcohol extract, and on the medullation in the central nervous system of the albino rat. J. Comp. Neurol., 21: 139-145. **193.**
- . 1911b. An interpretation of some differences in the percentage of water found in the central nervous system of the albino rat and due to conditions other than age. *Ibid.*, 21: 161-176.
- . 1911c. Some effects of underfeeding on the growth of the brain. (Abstr.) Proc. Path. Soc. Phila., N. S., 14: 74.
- . 1913. An anatomical analysis of growth. Trans. XV Internat. Congr. Hyg. & Demog., Washington (1912), 2: 410-415.
- . 1915. The rat. Reference tables and data. Mem. Wistar Inst. Anat. & Biol., No. 6, 278 pp. **298, 473.**
- . Hatai, S. & King, H. D. 1915. Postnatal growth of the brain under severa experimental conditions. Studies on the albino rat. J. Nerv. & Ment. Dis., 42: 797-801 **186.**
- Donovan, D. 1848. Observations on the peculiar diseases to which the famine of last year gave origin, and on the morbid effect of insufficient nourishment. Dubl. M. Press, 19: 67-68; 129-132; 275-278. (Also transl. in J. de Méd., chir. et pharmacol., Brux., 1848, 7: 305-314.) **120, 216, 228, 241, 313, 325, 362.**
- D'Orlandi. 1899. Les globules blancs dans les troubles digestifs des nourrissons. Rev. mens. des malades de l'enfance. Juillet, p. 300-f. (Cited by Marfan '21.) **247.**
- Douglas, M. 1915. The histology of the thyroid in animals fed on various diets. J. Path. & Bact., 19: 341-348. 2 pl. **298, 343, 386, 444.**
- Downarowitsch, E. 1892. (A study of the changes in the spinal cord during total inanition.) Botkin's Hospital Gazette (Russian), 3: 609-617; 633-639. (Also abstr. by Mühlmann, '99.) **195.**
- Dreyer, G. & Hanson, G. F. 1920. The assessment of physical fitness by correlation of vital capacity and certain measurements of the body. Cassel & Co., Lond. and N. Y., 115 pp. **85, 86.**
- Dreike, P. 1895. Ein Beitrag zur Kenntnis der Länge des menschlichen Darmkanals. Deut. Ztschr. f. Chir., 40: 43-89.
- Dreyfuss, G. 1906. Die Inanition im Verlaufe von Geisteskrankheiten und deren Ursachen. Arch. f. Psychiatr. u. Nervenkrankh., Bd. 41, H. 2. (Abstr. in Wien. klin. Wchnschr., 19: 710.) **85, 181.**
- van Driël, B. M. 1920. Vitamine und innere Sekretion. Nederl. Tidschr. v. Geneesk., 64: 1350-f. (Cited by Meyerstein '22.) **432, 456.**
- Driesch, H. 1901. Die organische Regulation. Lpz., 228 pp. **32.**
- . 1906. Die Physiologie der tierischen Form. Ergeb. d. Physiol., Abt. II 5: 1-107. **32.**
- Drummond, J. C. 1916. Observations on the growth of young chickens under laboratory conditions. Biochem. J., 10: 77-88. **113, 130, 283, 298.**
- . 1918. A study of the water-soluble accessory growth-promoting substance. II. Its influence upon the nutrition and nitrogen metabolism of the rat. *Ibid.*, 12: 25-41. **234, 258, 414, 444.**

- . 1919. Note on the rôle of the antiscorbutic factor in nutrition. *Ibid.*, 13: 77-80. 113.
- . 1919a. Researches on the fat-soluble accessory substance. II. Observations on its rôle in nutrition and influence on fat metabolism. *Ibid.*, 13: 95-102.
- . 1920. Nutrition on diets practically devoid of fat. *Proc. Physiol. Soc., J. Physiol.*, 54: xxx-xxx. 104.
- & Coward, K. H. 1921. Nutrition and growth on diets devoid of true fats. *Lancet*, 2: 698-706. 104.
- Drzewina, A. 1910. Sur les éosinophiles de l'intestin de certains Téléostéens. *Compt. rend. Soc. de biol., Par.*, 68: 1012-1013. 318.
- . 1912. Cellules géantes dans l'épithélium intestinal des Téléostéens à jeun. *Ibid.*, 73: 18-19. 318.
- Dublin, L. & Gebhart, J. C. 1923. Do height and weight tables identify undernourished children? *Am. J. Publ. Health*, 13: 920-927. 87.
- Dubois, R. 1896. *Physiologie comparée de la marmotte*, p. 82. Par. (Cited by Rasmussen '16 and '17.)
- Dudgeon, L. S. 1905. A contribution to the pathology of the thymus gland. *J. Path. & Bact.*, 10: 173-210. 3 pl. 288.
- Duensmann, H. 1900. Ueber den Tod durch Verhungern vom gerichtsarztlichen Standpunkte. *Vrtljschr. f. ger. Med. etc.*, III F., 19: 203-232. 271, 287, 326.
- Duerck, H. 1908. Untersuchungen über die pathologische Anatomie der Beri-Beri. Ein Beitrag zur normalen und pathologischen Anatomie des peripherischen Nervensystems. *Beitr. z. path. Anat. etc.*, 8. Suppl., 176 pp. 41 Taf. 171, 200, 206, 233, 343, 367, 385.
- . 1908a. Pathologische Anatomie der Beriberi. *Jena.* (Cited by Funk '22.) 171, 233, 385.
- Duesberg, J. 1906. Contribution à l'étude des phénomènes histologiques de la métamorphose chez les Amphibiens anoures. *Arch. de biol.*, 22: 163-221. 2 pl. 77.
- Duesing, C. 1883. Die Factoren welche die Sexualität entscheiden. *Jen. Ztschr. f. Naturwiss.*, 16: 428-464.
- . 1884. Die Regulierung des Geschlechtsverhältnisses bei der Vermehrung der Menschen, Thiere und Pflanzen. *Jena.* Also in *Jen. Ztschr. f. Naturwiss.*, 1883, 17: 593-940.
- . 1885. Die experimentelle Prüfung der Theorie von der Regulierung des Geschlechtsverhältnisses. *Jen. Ztschr. f. Naturwiss.*, Bd. 14, Suppl. (Cited by Geddes & Thomson '01.) 80.
- Dufour, L. 1833. *Recherches anatomiques et physiologiques sur les Hémiptères.* *Mém. d. savants etrang., Acad. des sc., Par.*, 4: 129-462. 60.
- Dupérié. 1878. Globules du sang. Variations physiologiques dans l'état anatomique du sang. *Thèse méd., Par.*, No. 126, 92 pp. 249.
- Durig, A. 1901. Wassergehalt und Organfunktion, Erste Mitth. *Arch. f. d. ges. Physiol.* 85: 401-504. 172, 186, 235, 259, 344, 388.
- Dustin, A. P. 1906. Contribution à l'étude de l'influence de l'âge et de l'activité fonctionnelle sur le neurone. *Ann. Soc. R. des sc. méd. et. nat. de Brux.*, 15: 1-168. 6 pl. 196, 198.
- . 1913. Recherches d'histologie normale et expérimentale sur la thymus des Amphibiens anoures. *Arch. de biol.*, 28: 1-110. 3 pl. (Abstr. in *Jahresb. d. Anat.*, 1913, T. 3, pp. 398-399.) 295, 297.
- . 1913a. Influence de l'alimentation sur le développement du thymus de *Rana fusca*. *Compt. rend. Assoc. d. anat., Réun.* 15, pp. 28-38. 2 figs. 295.
- Dutcher, R. A. 1920. The nature and function of the antineuritic vitamin. *Proc. Nat. Acad. Sc., Washington*, 6: 10-14. 414.
- & Wilkins, S. D. 1921. Vitamin studies. VII. Influence of fresh alfalfa on weight of testes in Single Comb White Leghorn cockerels. *Am. J. Physiol.*, 57: 437-443. 415.
- Dutrochet. 1816. *Mémoires de la soc. med. d'émulation*, p. 44. (Cited by Lucas, 1826.) 241, 249.
- Dwornitschenko. 1897. Ueber die Thymus des Erwachsenen in gerichtlich-medizinischer Beziehung. *Vrtljschr. f. ger. Med.*, 3. F., 14: 51-61. (Cited by Hammar '06.) 287.

- Ebeler, F. 1917. Zur Kriegsamenorrhöe. *Zentralbl. f. Gyn.*, 41: 696-708. (Also 1918, *Schmidt's Jahrb.*, 328: 105-111.) 391, 400.
- Ebstein, W. 1870. Beiträge zur Lehre vom Bau und den physiologischen Funktionen der sogenannten Magenschleimdrüsen. *Arch. f. mikr. Anat.*, 6: 515-539. 1 pl. 309.
- Ecker, A. 1853. Article "Blutgefäßdrüsen" in Wagner's *Handwörterbuch der Physiologie*, Bd 4. Braunschweig. (Cited by Hammar '05.) 287.
- Eckles, C. H. 1915. The ration and age of calving as factors influencing the growth and dairy qualities of cows. *Univ. of Mo. Agr. Exp. Sta. Bull. No. 135*, 91 pp. 77.
- . 1916. The nutrients required to develop the bovine fetus. *Ibid.*, Research Bull. No. 26, 36 pp. 77.
- and Palmer, L. S. 1916. The influence of the plane of nutrition of the cow upon the composition and properties of milk and butterfat. *Ibid.*, Research Bull. No. 25, 107 pp. 128.
- and Swett, W. W. 1918. Some factors influencing the rate of growth and the size of dairy heifers at maturity. *Ibid.*, Research Bull. No. 31, 56 pp.
- Edwards, A. M. 1861. Experiences sur la nutrition des os. *Compt. rend. Acad. des sc., Par.*, 52: 1327. (Cited by E. Voit, '80.)
- Eggeling, H. 1908. Dünndarmrelief und Ernährung bei Knochenfischen. *Jen. Ztschr. f. Naturwiss.*, 43: 417-529. 318.
- Ehrlich, P. 1891. Farbenanalytische Untersuchungen. (Cited by Pappenheim '01.) 250.
- Ehrmann, S. 1883. Ueber Fettgewebsbildung aus dem als Winterschlagdrüse bezeichneten Fettorgane. *Sitzungsber. d. k. Akad. d. Wiss., math.-nat. cl., Abth. 3, Wien*, 87: 88-104. 2 Taf. 126.
- Eichorst, H. 1879. Die Veränderungen der quergestreiften Muskeln bei Vögeln in Folge von Inanition. *Centralbl. f. d. med. Wiss.*, 17: 161-163. 167, 230.
- Eijkman, C. 1897. Eine Beriberiähnliche Krankheit der Hühner. *Arch. f. path. Anat. etc.*, 148: 523-532. 112, 113, 207.
- . 1913. Ueber die Ursache der Beriberikrankheit. *Münch. med. Wchnschr.*, 60: 871-872. 207.
- . 1916. (The influence of feeding and deprivation of food in the production of polyneuritis gallinarum.) *Genesk. Tidschr. v. Nederl. Indie*, 56: 257-294. Also in *Trop. Dis. Bull.*, 8: 465. (Cited by Hoffman '22.)
- & Van Hoogenhuyze, C. J. C. 1916. The effect of feeding and of starvation on the development of polyneuritis. *Kon. Akad. v. Wentensch. Wis. on Natuurk. Afd.*, 24: 1471-1484. (Cited by Hoffman '22 from *Physiol. Abstr.*, 1916, 1: 236.)
- Eimer, G. H. T. 1888. Die Entstehung der Arten auf Grund von Vererben erworbener Eigenschaften nach den Gesetzen organischen Wachsens. 1. Theil. *Jena*. 65.
- Th. 1867. Zur Fettersorption und zur Entstehung der Schleim und Eiterkörperchen. *Arch. f. path. Anat. etc.*, 38: 428-432. 320.
- Ekstein, E. 1917. Ueber erworbene Amenorrhöe. *Zentralbl. f. Gyn.*, 41: 333-335. 391, 399.
- Elbe, R. 1899. Histologische Untersuchungen über die Veränderungen besonders den vermehrten Fettgehalt der Organe bei der Iodoform- und Arsenintoxikation des Kaninchens. *Dissert. Rostock*. (Cited by Rabe '10.) 335.
- Elliot, W. E., Crichton, A. & Orr, J. B. 1922. The importance of the inorganic constituents of the food in nutritional disorders. I. Rickets in pigs. *Brit. J. Exp. Path.*, 3: 10-19. 105, 109, 148.
- Ellis, C. & Macleod, A. L. 1922. Vital factors of foods. *Vitamins and nutrition*. D. Van Nostrand Co., N. Y., 391 pp. 13, 110.
- W. G. 1898. A contribution to the pathology of beriberi. *Lancet*, 2: 985-986. 206, 233, 283, 312, 367.
- Elsässer, K. L. 1843. Der weiche Hinterkopf; ein Beitrag zur Physiologie und Pathologie der ersten Kindheit. *Stuttgart*. (Cited by Comby '01 and Wohlaue '11.)
- Emerson, W. R. P. 1922. *Nutrition and growth in children*. Appleton & Co., N. Y. and Lond., 342 pp. 87, 157.

- & Manny, F. A. 1920. Weight and height in relation to malnutrition. Arch. Pediatr., 37: 468-485. 8 charts. 85, 87.
- Emery, C. 1894. Die Entstehung und Ausbildung des Arbeiterstandes bei den Ameisen. Biol. Centralbl., 14: 53-59. 65.
- Emmett, A. D. 1920. The fat-soluble A vitamin and xerophthalmia. Science, N. S., 52: 157-158. 218.
- & Allen, F. P. 1919. Nutritional studies on the growth of frog larvae (*Rana pipiens*). Proc. Am. Soc. Biol. Chemists, XIII. J. Biol. Chem., 41: ix. 102, 113.
- . 1920. Pathogenesis due to vitamines deficiency in the rat. Proc. Am. Soc. Biol. Chem. XIV. J. Biol. Chem., 41: liii. 131, 218, 233, 234, 283, 299, 322, 343, 354, 368, 432.
- & Sturtevant, M. 1920. Relation of vitamins and iodine to the size and development of tadpoles. *Ibid.*, 41: lix. 106, 113, 218.
- & Peacock, G. E. 1922. The chick as an experimental animal in vitamin studies. *Ibid.*, 50: xl. Also in Science, N. S., 56: 610. 113, 150, 218, 414, 432.
- & Stockholm, M. 1920. Water-soluble B vitamin: II. Are the antineuritic and the growth-promoting vitamins the same? Proc. Am. Chem. Soc., Div. Biol. Chem. (Abstr), Science, 1920, Oct. 29.
- Engel, St. 1920. Rickets in Germany; a study of the effects of war on children. Lancet (1), 198: 188-190. 109, 142, 170.
- . 1920a. Die Rachitis, eine Verkümmerngskrankheit. Med. Klinik, Berl., 16: 383-385. 109.
- Enright, J. I. 1920. War oedema in Turkish prisoners of war. Lancet (1), 198: 314-316. 71, 102, 255, 281, 342, 367, 431.
- Enzmann, C. 1856. Die Ernährung der Organismen, besonders des Menschen und der Thiere im hungernden Zustande. Dresden, 205 pp. (Cited by Bardier '13.)
- Erdely, A. 1905. Untersuchungen über die Eigenschaften und die Entstehung der Lymphe. 5. Mitth. Ueber die Beziehungen zwischen Bau und Funktion des lymphatischen Apparates des Darmes. Ztschr. f. Biol., 46: 119-152. 264, 318.
- Erdheim, J. 1903. Zur normalen und pathologischen Histologie der Glandula thyreoidea, parathyreoidea und Hypophysis. Beitr. z. path. Anat. etc., 33: 158-236. 32 Fig. 436, 445, 449.
- . 1914. Epithelkörperchen und Rachitis. Denkschr. d. k. Akad. d. Wiss., Wien, Bd. 90. 106, 446.
- . 1918. Ueber das Barlowherz. Wien. klin. Wchnschr., pp. 1293-1295. 151, 234, 343, 368.
- Erdmann, R. 1910. Depression und fakultative Apogamie bei Amoeba diploidea. Festchr. z. 60. Geburtstag R. Hertwigs. Bd. 1. (Cited by Erdmann '12.) 18.
- . 1912. Quantitative Analyse der Zellbestandteile bei normalem, experimentell verändertem und pathologischem Wachstum. Ergeb. d. Anat. u. Entw., Bd. 20, 2. Hälfte, pp. 471-566. 16.
- Erhard, H. 1911. Glykogen in Nervenzellen. (Vorl. Mitteil.) Biol. Centralbl., 31: 472-475. 47, 54.
- Esser, 1907. Die Aetiologie der Rachitis. Münch. med. Wchnschr., 54: 817-820. 107.
- Evans, H. M. & Bishop, K. S. 1922. On the relations between fertility and nutrition. II. The ovulation rhythm in the rat on inadequate nutritional regimens. J. Metab. Res., 1: 335-356. 7 figs. 76, 102, 104, 105, 112, 397, 398, 399, 401.
- . 1922a. On the existence of a hitherto unrecognized dietary factor essential for reproduction. Science, N. S., 56: 650-651. 111, 390, 399, 401.
- . 1923. The cause of reproductive upset in dietary deficiencies due to lack of vitamin A. Proc. Am. Assn. Anat., Anat. Rec., 25: 129. 399, 401.
- . 1923a. On the relations between fertility and nutrition. IV. The production of sterility with nutritional regimes adequate for growth and its cure with other foodstuffs. J. Metab. Res., 3: 233-316. 111, 401.

- . 1923b. Existence of a hitherto unknown dietary factor essential for reproduction. *J. Am. M. A.*, 81: 889-892. **111, 390, 401.**
- Eve, F. C. 1896. Sympathetic nerve cells and their basophil constituent in prolonged activity and repose. *J. Physiol.*, 20: 334-353. 1 pl. **205.**
- Evvard, J. M. 1912. Nutrition as a factor in fetal development. *Proc. Am. Breeders Assn.*, 8: 549-560. **105, 129.**
- Cox, A. W. & Guernsey, S. C. 1914. The effect of calcium and protein fed pregnant swine upon the size, vigor, bone, coat and condition of the offspring. *Am. J. Physiol.*, 34: 312-325. **102, 129, 140, 142.**
- Ewald, P. 1902. Ueber Fettgehalt und multiple Adenombildung in der Nebenniere. *Inaug.-Dissert., München.* **423.**
- Eyselein, K. 1914. Untersuchungen über den Fettgehalt der Herzmuskulatur. *Arch. f. path. Anat. etc.*, 218: 30-47. (Also *Med. Dissert., Bonn, 1914, 9 pp.*) **229.**
- Fabre-Domergue et Biétrix. 1898. Rôle de la vésicule vitelline dans la nutrition larvaire des poissons marins. *Compt. rend. Soc. de biol., Par.*, 50: 466-468. **76.**
- Falck, F. A. 1875. Physiologische Studien über die Ausleerungen des auf absolute Carenz gesetzten Hundes. *Beitr. z. Physiol., Hyg., Pharmak. u. Toxikol.*, 1: 128. 6 Taf. **70, 74, 120, 122, 128, 134, 182, 214, 216, 230, 278, 306, 317, 331, 365, 376, 415, 462.**
- . 1881. Tod durch Entziehung von Nahrung. *Handb. d. ger. Med. (Maschka's).* Tübingen, 1: 721-758. **69, 71, 72, 75, 120, 128, 163, 240, 303, 313, 331.**
- u. Scheffer, T. 1854. Untersuchungen über den Wassergehalt der Organe durstender und nicht durstender Hunde. *Arch. f. physiol. Heilk.*, 13: 508-522. **115, 132, 134, 154, 172, 190, 202, 221, 259, 284, 299, 302, 312, 344, 355, 360, 368, 387, 445.**
- Falke. 1910. (Cited by Thompson & Mendel '18 from *Zentralbl. f. allg. exper. Biol.*, 1: 271.) **89, 135.**
- Falta, W. 1917. Ueber das Kriegsoedem. *Wien. klin. Wchenschr.*, 30: 1637-1642.
- u. Nockgerath, C. T. 1906. Fütterungsversuch mit künstlicher Ernährung. *Beitr. z. chem. Physiol. u. Path.*, 7: 313-ff. **216.**
- Farret, U. 1896. Contribution à l'étude du thymus chez l'enfant. Thèse, Par. **287.**
- Fatta, G. e Mundula, S. 1908. Il decorso dell'inanizione assoluta nel *Carabus morbillosus* alla luce e nell'oscurità. *Studi sassaresi, Sassari*, vol. 5, suppl., pp. 1-25. **64.**
- . 1908a. Le cours de l'inanition absolue chez le "*Carabus morbillosus*" à la lumière diffuse et dans l'obscurité. *Arch. ital. de biol.*, 49: 65-78.
- Fayolle, H. M. 1910. La croissance de l'encephale dans l'hypotrophie. Thèse, Par., 88 pp. (1909-10, No. 145.) **177.**
- Fede, F. 1897. Sulle alterazioni anatomico-patologiche della mucosa gastro-enterica nell'atrofia primitiva infantile. *Pediatria*, 5: 260-265. 4 fig. (Also abstr. in suppl. to *Policlin.*, Roma, 1897-8, 4: 299; and in *Compt. rend. Congr. internat. de méd.* (1897), Moscow, 1898, vol. 3, sect. 6, pp. 385-389.) **304, 314.**
- . 1898. Sur les altérations anatomo-pathologiques de la muqueuse gastro-intestinale dans l'atrophie primitive infantile. *Arch. de med. d. enf.*, 1: 728-732. **263, 304, 314.**
- . 1900. Nuove osservazioni anatomico-patologiche sulle alterazioni della mucosa gastro-enterica nell'atrofia primitiva infantile. *Atti d. Congr. pediatr. ital.* (1898), Torino, 3: 89-93. **314.**
- . 1900a. Altérations anatomo-pathologiques de la muqueuse gastro-intestinale dans l'atrophie primitive artificiellement produite sur les petits chiens. XIII. *Congr. internat. de méd., Par.*, Sec. de med. de l'enfance, pp. 224-226. **307, 317.**
- . 1901. Sull'anatomia patologica e patogenesi dell'atrofia infantile primitiva e atresia di Parrot. *Atti d. IV Congr. pediatr. ital.*, Firenze, pp. 39-51. **314.**
- . 1901a. *Congr. pédiatr. de Florence; Congr. de Madrid.* (Cited by Thiercelin '04.) **304, 315.**
- Federici, F. 1903. Su alcuni particolari caratteri del grasso contenuto nelle cellule delle capsule surrenali. *Sperimentali*, 57: 795-797. **423, 430.**

- Feigel, L. 1872. (Ueber den Bau und die Bestimmung des Knochengewebes.) *Jahrb. d. k. k. wiss. Ges., Krakau (Polish)*, 21: 206-234. (Abstr. by Hoyer in *Jahresb. d. Anat. etc.*, 1872, pp. 110-111.) **125.**
- Feigenbaum, D. 1917. Ein Beitrag zur Kenntnis der Rückenmarkblutungen beim Skorbut. *Wien. klin. Wchnschr.*, 30: 1455-1457. (Cited by Funk '22.) **202.**
- Feilchenfeld, W. 1920. Auge und Kriegszustand. *Deut. med. Wchnschr.*, 46: 575. **211, 220.**
- Feldzer, E. 1910. Le thymus des athrepsiques. *Essai d'opothérapie thymique. Thèse med., Par.*, (1909-10, No. 147), 75 pp., 1 pl., 3 figs. **289.**
- Fenger, S. 1873. Benmarvens Udvikling og Bidrag till den udviklede Marvs normale Histologie. (Die Entwicklung des Knochenmarkes und Beiträge zur normalen Histologie des entwickelten Markes.) Kjöbenhavn. (Abstr. by Retzius in *Jahresb. d. Anat. etc.*, 1873, p. 94. **125.**
- Fernet, C. 1901. Amaigrissement extrême, et mort par inanition. *Bull. de la Soc. méd. des Hôp.*, pp. 1361-1363. **71, 96.**
- Ferralis, G. V. 1906. Expériences sur le cours du jeûne absolu chez le *Gongylus ocellatus* en diverses conditions de la température du milieu. *Arch. ital. de biol.*, 46: 39-50. (From orig. in *La Sardegna Sanitaria*, 1905.) **462.**
- Ferrata, A. 1905. Sui fenomeni di secrezione della cellule renale. *Arch. fisiol.*, 2: 581-588. 2 pl. **383.**
- . 1905a. Sull'anatomia e sulla funzione del rene. *Arch. ital. di anat. e embr.*, 4: 505-550. 4 pl. **383.**
- Ferry, E. 1913. The rate of growth of the albino rat. *Anat. Rec.*, 7: 433-441. **94.**
- Fetzer, M. 1913. Studien über den Stoffhaushalt in der Gravidität nach experimentellen Untersuchungen des Verhaltens trächtiger Tiere und ihrer Früchte bei eisenreicher und eisenarmer Ernährung. *Ztschr. f. Geburtsh. u. Gyn.*, 74: 542-578. **106.**
- Ficker, M. 1905. Ueber den Einfluss des Hungerns auf die Bakteriendurchlässigkeit des Intestinaltractus. *Arch. f. Hyg.*, 54: 354-374. **318.**
- Fiessinger, N. 1911. La cellule hépatique. *Rev. gen. d'histol.*, 4: 387-751. 88 figs. **338.**
- Filatow (Filatoff), N. 1898. Diagnostic et séméiologie des malades de l'enfance. *Transl. from Russian by E. Perier, Par.*, 548 pp. (Cited by Lesage '11.)
- Filipi, Severi e Montalti. 1889. *Manuale de medicina legale*, Milano. (Cited by Coen '90.) **181, 195.**
- Filliozat, É. 1909. Considérations sur l'insuffisance d'alimentation chez le nourrisson. *Thèse, Par.*, No. 348, 130 pp. (Cf. also *La clin. inf.*, 1909.) **97.**
- Filomusi-Guelfi, G. 1895. Valuatazione dell'atrofia del timo come segno della morte da inanizione nei bambini. *Gior. di med. legale, Lanciano*, 2: 188-201. (Cited by Dünschmann '20.) **287.**
- Findlay, G. M. 1920. A study of the leucocyte changes in pellagra compared with those occurring in beriberi. *J. Path. & Bact.*, 23: 490-498. **113, 255, 257.**
- . 1921. An experimental study of avian beriberi. *Ibid.*, 24: 175-191. **150, 171, 178, 185, 189, 200, 205, 207, 234, 276, 283, 297, 299, 312, 343, 354, 386, 399, 415, 432, 444, 447, 456, 478.**
- . 1921a. The blood and blood-vessels in guinea-pig scurvy. *Ibid.*, 24: 446-453. **234, 237, 259.**
- . 1921b. A note on experimental scurvy in the rabbit; and on the effects of antenatal nutrition. *Ibid.*, 24: 454-455. 2 figs. **113, 154.**
- & Mackenzie, R. D. 1922. The bone marrow in deficiency diseases in rats. *Ibid.*, 25: 402-403. (Proc.) (Cited in *Physiol. Abstr.*, 1922, 7: 361.) **140, 150.**
- L. & Ferguson, M. 1918. A study of social and economic factors in the causation of rickets, with an introductory historical survey. *Med. Research Council, Lond., Spec. Rep. Ser.*, No. 20. **108.**
- Fingerhuth. Unpublished observations. (Cited by Lucas, 1826.) **64.**
- Finkelstein, H. & Meyer, L. F. 1922. Diseases of the digestive system. In *Feer's Textbook of pediatrics*. *Transl. by Sedgwick & Scherer. Sec. III*, pp. 242-346. *J. B. Lippincott, Phila. & Lond.* **316.**

- Finotti e Tedeschi. 1902. Alterazione delle capsule surrenali e pellagra. *Riforma med.*, (XVIII) 2: 230-235; 243-245. (Cited by Raubitschek '15 and Harris '19.) 431.
- † Fiocco. 1912. Istopatologia dei pellagrodermi. *Atti del V Congr. Pel. Ital.*, Bergamo, pp. 305-312. (Cited by Harris '19.) 130.
- ‡ Fisch, M. E. & Emmel, V. E. 1924. Reduction in the percentage of erythrocytic reticulation and polychromasia in acute inanition. (Abstr.) *Anat. Rec.*, 27: 181. 253.
- Fischer, H. 1912. Ueber die Langerhan'schen Inseln im Pankreas von Amphibien. *Arch. f. mikr. Anat.*, 79: 276-306. 345, 353.
- . 1923. Hungerblockade und Körpermasse. *Klin. Wchnschr.*, 2: 752-754.
- W. 1910. Histologische Untersuchungen über den Fettgehalt der Nieren unter normalen und pathologischen Verhältnissen. *Beitr. z. path. Anat. etc.*, 49: 34-85. (Cited by Fischer '12.)
- . 1912. Zur Kenntnis der Lokalisation des Fettes in der Leber. *Arch. f. path. Anat. etc.*, 208: 1-12.
- Fleischmann, L. 1877. *Klinik der Pädiatrik*, 2 Bd. Wien. (Cited by Comby '01 and Wohlaer '11.)
- . 1907. *K. k. Ges. d. Aerzte in Wien*, 8, Nov. (Cited by Weichselbaum & Erdheim '09.) 159.
- Fleischner, E. C. 1906. The relation of weight to the measurements of children during the first year. *Arch. Pediatr.*, 23: 739-757. 12 charts. 85, 91.
- Flemming, W. 1871. Ueber Bildung und Rückbildung der Fettzelle im Bindegewebe. *Arch. f. mikr. Anat.*, 7: 32-80. 3 pl. 124.
- . 1871a. Weitere Mittheilungen zur Physiologie der Fettzelle. *Ibid.*, 7: 328-371. 1 Taf. 124.
- . 1876. Beobachtungen über Fettgewebe. *Ibid.*, 12: 434-507. 2 Taf. (Abstr. in *Jahresb. d. Anat. etc.*, 1876, pp. 80-82.) 124.
- . 1882. *Zellsubstanz, Kern und Zelltheilung*. 424 pp. Lpz. (Cited by Bardier '13.)
- Florschütz, H. 1895. Kritik der Versuche, durch eine bestimmte Diät der Mutter die Gefahren der Beckenenge zu umgeben. *Dissert.*, Giessen, 32 pp. (Cited by Reeb '05.) 78.
- Fluegge, C. 1922. (Effects of food conditions in Germany in the last 7 years.) *Norsk. Mag. f. Laegevidensk.*, 83: 321-ff. (Abstr. in *Int. Med. & Surg. Surv.*, July, 5b-4.) 71.
- Foà, P. 1899. Beitrag zum Studium des Knochenmarkes. *Beitr. z. path. Anat.*, 25: 376-391. 2 Taf. 137.
- Forbes, E. B. 1919. The mineral elements in animal nutrition with special reference to source and administration of iodine and phosphorus. *Scient. Amer. Suppl.*, No. 2257, p. 218. (Abstr. from *Jour. Wash. Acad. Sc.*) 104, 140.
- Formad, H. F. & Birney. 1891. The intestinal lesions of starvation. *Tr. Path. Soc. Phila.*, 15: 37-41. 271, 314, 326, 346.
- Forster, J. 1873. Versuche über die Bedeutung der Aschenbestandteile in der Nahrung. *Ztschr. f. Biol.*, 9: 297-380. 104, 188.
- . 1876. Ueber die Verarmung des Körpers, speciell der Knochen, an Kalk bei ungenügender Kalkzufuhr. *Ibid.*, 12: 464-474. 140.
- Fortescue-Brickdale, J. M. 1905. Observations on the thymus gland in children. *Lancet*, 159: 1029-1031. (Cited by Hammar '06.) 288.
- Fowler, R. 1870. The presence of fat and absence of attenuation of the intestines in the body of Sarah Jacob, the Welch fasting girl. *Lancet*, 2: 150-152. 69, 122, 313.
- Fracassi, G. 1922. Alcuni casi di edema da fame in ex-prigionieri italiani in Austria e in Serbia (con reporto istologico). *Ann. d'igiene, Roma*, 32: 371-380. 102, 281, 342, 385.
- Fraenkel, E. 1896. *Tagesfragen der operativen Gynäkologie*. 130 pp. Wien u. Lpz. (Cited by Reeb '05.) 79.
- . 1904. Untersuchungen über die Möller-Barlow'sche Krankheit. *Fortschr. a. d. Geb. d. Röntgenstr.* Bd. 7, No. 5-6, p. 231-ff, 291-ff. Also *ibid.*, 1906, 10: 1-20; and *Ergänzungsbd.* 18, 1908. (Cited by Funk '22.) 151, 153.

- . 1906. Ueber die Möller-Barlowsche Krankheit (infantiler Skorbut). Münch. med. Wchnschr., 53: 2185-2189; 2247-2250. **151, 153, 258.**
- . M. 1869-70. Leichenbefunde bei Pellagra. Arch. f. path. Anat. etc., 47: 511-516; 49: 579-582; 51: 150-152. **104, 140, 170, 187, 206, 232, 236, 281, 322, 342, 385.**
- Francke, C. 1891. Die menschliche Zelle. Grundzüge ihres Daseins und ihrer Gesundheitspflege. Cellular-Biologie und Cellular-Hygiene. Lpz., 746 pp.
- Frankenberger, Z. 1917. Kausal-analytische Untersuchungen über die Herkunft des Chromatins. 2. Ueber den Einfluss protrahierter Hungerung auf die Struktur der Nervenzellkerne. Arch. f. Entw. d. Org., 42: 564-579. 1 Taf. **185, 197.**
- Frankl, L. u. Freund, E. 1884. Ueber Schwund in der Skelettmusculatur. Sitzungsber. d. k. Akad. d. Wiss., Wien, Math.-Naturw. Cl. (1883), 88: 115-138. 2 Taf. **168.**
- Fraser, H. & Stanton, A. T. 1909. The etiology of beri-beri. Studies from the Inst. for Med. Res., Federated Malay States, Singapore, p. 10-ff. Also *ibid.*, 1911, p. 12-ff; and in *Lancet*, 1909, 1: 451-455. (Cited by Walshe '18.)
- Freise, E. 1920. Experimentelle Untersuchungen über die Ernährungsbedingungen des Wachstums. Jahrb. f. Kinderh., 91: 79-127.
- , Goldschmidt, M. & Frank, A. 1915. Experimentelle Beiträge zur Aetiologie der Keratomalazie. Vorl. Mitth. Monatschr. f. Kinderh., Orig., 13: 424-430. (Cited by Stepp '17.) **216.**
- Frerichs. 1866. *Traité pratique des maladies du foie*, etc. (Cited by Statkewitsch '94.) **325.**
- Freund, W. 1909. Zur Pathologie des Längenwachstums bei Säuglingen und über das Wachstum debiler Kinder. Jahrb. f. Kinderh., 70: 752-773. **91, 135.**
- Friedberger, F. & Fröhner, E. 1908. *Veterinary pathology*. 6th ed. Vol. 2. W. T. Keener Co., Chicago. (Cited by Maver '20.) **102, 255.**
- Friedenthal, H. 1914. Allgemeine und spezielle Physiologie des Menschenwachstums. J. Springer, Berl., 170 pp. 3 Taf.
- Friedleben, A. 1858. Die Physiologie der Thymusdrüse in Gesundheit und Krankheit. Frankfurt a. M., 336 pp. **287, 293.**
- . 1860. Beiträge zur Kenntnis der physikalischen und chemischen Constitution wachsender und rachitischer Knochen der ersten Kindheit. Jahrb. f. Kinderh., 3: 61-140; 147-178. **141, 143, 144, 145.**
- Frischholz, E. 1909. Sur Biologie von Hydra. Depressionserscheinungen und geschlechtliche Fortpflanzung. Biol. Centralbl., 29: 182-192; 206-215; 239-255; 257-290. **28, 36, 38.**
- Froehner, E. u. Zwick, W. 1915. *Lehrbuch der speziellen Pathologie und Therapie der Haustiere*. 8. Aufl. Bd. 1. Stuttgart. **102, 170, 187, 232, 255, 367.**
- Froelich, T. 1912. Experimentelle Untersuchungen über den infantilen Skorbut. Ztschr. f. Hyg. u. Infektionskr., 72: 155-182. **153.**
- Fuhge, G. 1918. Eine Stoffwechsel-Untersuchung an Kindern im Alter von 6-14 Jahren im dritten Kriegsjahre. Jahrb. f. Kinderh., 88: 43-59. (Abstr. in J. Am. M. A., Apr. 5, 1919.) **84, 85.**
- Funk, C. 1922. The vitamins. Transl. from 2nd German ed. by H. E. Dubin. Williams and Wilkins Co., Balt., 502 pp. **13, 103, 110, 131, 171, 207, 233.**
- & Douglas, M. 1914. Studies on beriberi. VIII. The relationship of beri-beri to glands of internal secretion. J. Physiol., 47: 475-478. **283, 298, 343, 354, 386, 399, 414, 432, 444, 455.**
- & Macallum, A. B. 1914. Die chemischen Determinanten des Wachstums. Ztschr. f. physiol. Chem., 92: 13-20. 1 Taf. **102, 131.**
- . 1915. Studies on growth. II. On the probable nature of the substance promoting growth in young animals. J. Biol. Chem., 23: 413-421. **112.**
- & Paton, J. B. 1922. Studies on vitamins B and D. J. Metab. Res., 1: 737-761. **111.**
- E. H. 1923. The effects of chronic starvation. Progr. Med., Phila., 2: 248-250.

- Gage, S. H. 1895. The processes of life, revealed by the microscope; a plea for a physiological histology. Proc. Am. Micr. Soc., 18th ann. meeting. Vol. 17, 29 pp.
- . 1920. The free granules (chylomicrons) of fresh blood as shown by the dark-field microscope, and their dependence upon the kind of food ingested. Proc. Am. Assn. Anat., Anat. Rec., 18: 233-234. 241, 244, 248.
- . 1921. The digestion and assimilation of fatty food as determined by the aid of the dark-field microscope, and a fat-soluble dye (American sudan.) *Ibid.*, 21: 63-64. (Cf. also Gage & Fish, J. Am. Vet. Med. Assn., 1921, 58: 384.) 241, 244, 248.
- Gaglio, G. 1884. Sulle alterazioni istologiche e funzionali dei muscoli durante l'inanizione. Arch. per le sc. med., 7: 301-310. 164, 167.
- . 1884a. Influenze dell'inanizione sulla struttura del fegato e dello stomaco. Ricerche istologiche. *Ibid.*, 8: 149-159. 306, 332.
- Gagniespan, F. 1919. Vegetable "plethora." Results of over-feeding of plants and differences in habitat between individuals of the same species. Scientific Amer. Suppl. No. 2283, Oct. 11. (Transl. from orig. in La Rousse Mensuel, Paris, Apr.) 3.
- Gallerani, G. 1892. Resistenza della emoglobina nel digiuno. Annali di chim. e farmacol., 16: 141-159. 250.
- Gama Lobo. 1866. (Cited by Blegvad ('24) from Ullersberger, Klin. Monatsbl. f. Augenh., 1866, IV, Aarg., S. 65.) 211, 216.
- Ganfani, C. 1897. Sulle alterazioni delle cellule nervose dell'asse cerebrospinale consecutive all'inanizione. Monit. zool. ital., 8: 221-227. 1 tav. 183, 195, 196.
- . 1902. Le cellule interstiziali del testicolo negli animali ibernanti. Boll. Accad. med. Genova, 17: 279-284. (Cited by Jahresb. d. Anat. etc., 1903, T. 2, p. 108.) 412.
- Gans, O. 1915. Zur Pathogenese der Knochenwachstums-störungen. Frankf. Ztschr. f. Path., 16: 37-57. 1 Taf. 136, 438, 451.
- Garner, W. W., McMurtrey, J. E. & Moss, E. G. 1922. Sand drown, a chlorosis of tobacco and other plants resulting from magnesium deficiency. Science, 56: 341-342. 10.
- Gaspard, B. 1821. Effets des alimens végétaux herbacés sur l'économie humaine. J. de physiol. exp. etc., 1: 237-242. 71, 390, 398, 399.
- Gaube, J. 1897. Cours de minéralogie biologique. Par., 230 pp. (Cited by Baudrand '11.) 104.
- Gaule, A. L. 1893. Biological changes in the spleen of the frog. J. Morph., 8: 393-414. (Cited by Morgulis '11.) 276, 412.
- J. 1901. Die Veränderungen des Froschorganismus (*R. esculenta*) während des Jahres. Arch. f. d. ges. Physiol., 87: 473-537. 164, 276, 341, 397.
- Gay, M. 1900. Alcune osservazioni sulla inanizione in certi artropodie. (Sunto.) Monit. zool. ital., Anno 11, Suppl., p. 38. (Cited in Jahresb. d. Anat. etc., 1900, T. 2, p. 89.)
- Geddes, P. & Thomson, J. A. 1901. The evolution of sex. 2nd ed., Lond., 342 pp. 3, 17, 80.
- Geelmuyden, H. C. 1886. Das Verhalten des Knochenmarkes in Krankheiten u. s. w. Arch. f. path. Anat. etc., 105: 136-169. 125, 126.
- Geeraerd, N. 1901. Les variations fonctionnelles des cellules nerveuses corticales chez le Cobaye, étudiées par la méthode de Nissl. Trav. Lab. Inst. Solvay, T. 4. (Cited by Legendre '09.) 184.
- Gehewe, C. W. 1852 (1853?). De corpusculo quodam adiposo in hominum genis obvio. Dissert., Dorpat, 40 pp. (Cited by Scammon '19.) 123.
- Geiling, E. M. K. & Green, H. H. 1921. Studies in the regeneration of the blood. Proc. Soc. Exp. Biol. & Med., 18: 191-192. 254.
- Geissler, A. 1892. Messungen von Schulkindern in Gohlis-Leipzig. Schulgesundheitspflege, 5: 249-253. (Cited by Severson '19.) 83.
- u. Uhlitzsch, R. 1888. Die Grössenverhältnis der Schulinder in Schulinspektionsbezirk Freiberg. Ztschr. d. k. sächs. statist. Bureaus, 34: 28-40. (Cited by Severson '19.) 83.

- Gemelli, A. 1906. Su l'ipofisi delle marmotte durante il letargo e nella stagione estiva. Contributo alla fisiologia dall'ipofisi. Arch. per le sc. med., 30: 341-349. (Also in Rendic. Roy. Ist. Lomb. sc. e lett., ser. 2, vol. 39.) 454.
- . 1906a. Nuove osservazioni su l'ipofisi delle marmotte durante il letargo e nella stagione estiva; contributo alla fisiologia dell'ipofisi. Biologica, Torino, 1: 130-146. 454.
- Gerber, E. 1921. Die Bestimmung des Ernährungszustandes aus Gewicht und Länge. Med. Klinik, Berl., 17: 1261-fl. 85, 87, 122.
- Gerhartz, H. 1906. Geschlechtsorgane und Hunger. Biochem. Ztschr., 2: 154-156. 276, 336, 397, 408.
- . 1908. Geschlechtsorgane und Hunger. 2. Mitteil. Centralbl. f. Physiol., 22: 65-67. 408.
- . 1917. Eine essentielle bradykardische Oedemkrankheit. Deut. med. Wchnschr., 43: 514-518. 254, 255.
- Gerlach. 1800. Freywilliger Hungertod, nebst Sectionsbericht. (Hufeland's) J. d. pract. Arztnkde, III, 10; 181-190.
- . W. 1896. Kritische Bemerkungen zur gegenwärtigen Lehre von der Darmatrophie. Deut. Arch. f. klin. Med., 57: 83-103. 1 Taf. u. 2 Textfig. 314.
- Gerpott, O. 1913. Experimentelle Untersuchungen über die aktuelle Reaktion des Blutserums bei Verdauung, Hunger und in pathologischen Zuständen. Med. Dissert., Lpz., 27 pp. (Cited by Jahresverz. d. Schriften, Bd. 29, 1913.) 241.
- Gerstenberger, H. J. 1918. Pathogenesis of infantile scurvy: an hypothesis. Am. J. Med. Sc., 155: 253-268. 237.
- Ghika, C. 1901. Études sur le thymus. Thèse. Par., No. 404. 228 pp. (Cited by Feldzer '10.) 287.
- Giannelli, L. 1916. Contributo allo studio del pancreas nei Teleostei. Pancreas di *Tinca vulgaris* in condizioni normali di nutrizione e dopo prolungato digiuno. Monit. zool. ital., 27: 176-188. 275, 320, 340, 345, 353.
- e Bergamini, A. 1914. Nuove ricerche sulla repartizione delle isole di Langerhans nel pancreas dei rettili, e sulla loro invariabilità durante il digiuno. *Ibid.*, 25: 132-144. 4 fig. 345, 353.
- ———. 1914a. Sulla costituzione e sulla invariabilità durante il digiuno delle isole di Langerhans in *Rana esculenta*, con qualche cenno sui condotti escretori del pancreas e del fegato. *Ibid.*, 25: 289-304. 4 fig. 345, 353.
- ——— e Lampronti, G. 1914. Invariabilità di numero di grandezza e di costituzione generale delle isole di Langerhans nel digiuno. Atti della Accad. di sc. med. e nat. di Ferrara, 88: 109-137. 4 fig. 345, 353.
- Giard, A. 1905. Résistance du jeûne et changements de coloration chez le Némertien *Lincea bilineatus*. Feuille jeun. natural. (4) Ann. 35, p. 12. (Inaccessible.) 44.
- Gierke, E. 1907. Physiologische und pathologische Glykogenablagerung. Ergeb. d. allg. Path., etc., 11: 871-900.
- . 1921. Störungen des Stoffwechsels. In Aschoff's Pathologische Anatomie, 5. Aufl., 1: 393-451. G. Fischer, Jena. 169.
- Giesecke, A. 1917. Zur Kriegsamennorrhöe. Zentralbl. f. Gyn., 41: 865-873. 391, 392, 399, 400.
- Giglioli, B. 1922. Grassi e lipoidi della corteccia surrenale nel digiuno. Arch. per le sc. med., 45: 24-42. 2 pl. 427.
- Gilbert, A. et Jomier, J. 1904. Contribution à l'étude de la fonction adipopexique du foie. Sur la teneur du foie en graisse pendant l'inanition de courte durée. Compt. rend. Soc. de biol., Par., 57: 494-496. 336.
- . 1905. Note sur la teneur du foie en glycogène suivant le moment de l'ingestion alimentaire. *Ibid.*, 58: 63-64. 336.
- . 1905a. Note sur la répartition du glycogène hépatique à l'état d'inanition. *Ibid.*, 58: 81. 336.
- . 1906. Étude histologique du foie pendant l'inanition. Bull. et mém. Soc. anat. de Par., 81: 301-314. 336.

- . 1907. Structure de la cellule hépatique aux divers temps de la digestion, et dans les divers régimes. *Ibid.*, 82: 313-319. 336.
- . 1908. Cellules hépatiques claires. Travées hépatiques normales. *Presse méd.*, pp. 353-354. 2 figs. 336.
- . 1909. Les cellules hépatiques claires, leur nombre relatif à l'état normal, leur charge glycogénée. *Ibid.*, pp. 49-51. 6 figs.
- Gile & Carrero. 1916. Assimilation of iron by rice from certain nutrient solutions. *J. Agr. Res.*, 7: 503-528. (Cited by Hoagland '19.) 10.
- Girou de Buzareingues. 1828. De la génération. *Par.* (Cited by Geddes & Thomson '01.) 80.
- Glaser, R. W. 1923. The effect of food on longevity and reproduction in flies. *J. Exp. Zool.*, 38: 383-412. (Cited by Pearl & Parker '24.) 62.
- Glisson, F. 1650. De rachitide, sive morbo puerili qui vulgo the rickets dicitur, tractatus. *London*, 416 pp. (Abstr. by N. Moore, *The history of the first treatise on rickets*. *St. Bartholomew's Hosp. Rep.*, *London*, 1884, 20: 71-82.) 108, 142, 157, 170, 188, 267.
- Goeldi, E. A. 1885. Aphorismen, neue Resultate und Conjecturen zur Frage nach den Fortpflanzungs-Verhältnissen der Phytophthiren enthaltend. Schaffhausen. (Cited by Keller '87.) 61.
- Goetting, H. 1909. Ueber die bei jungen Tieren durch kalkarme Ernährung und Oxalsäurefütterung entstehenden Knochenveränderungen. *Arch. f. path. Anat. etc.*, 197: 1-16. 147.
- Goldberger, J. 1922. The relation of diet of pellagra. *J. Am. M. A.*, 78: 1676-1680. 103.
- & Tanner. 1922. Amino-acid deficiency probably the primary etiological factor in pellagra. *U. S. Publ. Health Rep.*, 37: 462-486. 103, 130.
- Waring, C. H. & Willets, D. G. 1915. The prevention of pellagra. A test of diet among institutional inmates. *Ibid.*, vol. 30. (No. 43, Oct. 22.) 103.
- & Wheeler, G. A. 1915. Experimental pellagra in the human subject brought about by a restricted diet. *Ibid.*, vol. 30. (No. 46, Nov. 12.) 103.
- ———. 1920. The experimental production of pellagra in human subjects by means of diet. *U. S. Publ. Health Service, Hyg. Lab. Bull. No. 120*, pp. 7-116. 103, 104.
- & Sydenstricker, E. 1918. A study of the diet of nonpellagrous and of pellagrous households. *J. Am. M. A.*, 71: 944-949. 103.
- *et al.* 1923. The campaign against malnutrition. Prepared by the Advisory Committee on Foods and Nutrition of the National Child Health Council in cooperation with the United States Public Health Service. *Pub. Health Bull. No. 134*. *Treas. Dept. U. S. P. H. S., Washington*, 39 pp. 87.
- Goldschmidt, M. 1915. Experimenteller Beitrag zur Aetiologie der Keratomalazie *Arch. f. Ophth.*, 9: 354-366. 4 Fig. 216.
- Goldstein, F. 1922. Klinische Beobachtungen über Gewichts- und Längenwachstum unterernährter schulpflichtiger Kinder bei Wiederauffütterung. *Ztschr. f. Kinderh.*, 32: 178-198. 85, 97, 139.
- Gordon, M. B. & Bartley, E. H. 1919. Malnutrition in children. A study of the examination of 900 children under 8 years of age. *Arch. Pediatr.*, 36: 257-267.
- Gotta, H. 1923. Vitamin B et glandes sexuelles. *Compt. rend. Soc. de biol., Par.*, 88: 373-375. 113, 399, 415.
- Gouin, A. et Andouard, P. 1905. Influence du régime alimentaire sur l'hydratation des tissus du corps des bovidés. *Compt. rend. Soc. de biol., Par.*, 58: 813-815.
- de Gouva. 1883. *Arch. f. Ophth.*, 29: 167. (Cited by Blegvad '24.) 211, 216.
- Grabley, P. 1919. Die Demineralisation der Nahrung als Ursache zurzeit endemisch auftretender Wachstumsstörungen und Stoffwechselkrankheiten. *Deut. med. Wchnschr.*, 45: 1238-1239. 105.
- von Graefe, A. 1866. *Arch. f. Ophth.*, 12: 198-ff; 250-ff. *Abt. II.* (Cited by Blegvad '24.) 211, 216.
- Graefe, M. 1917. Ueber Kriegsamennorrhöe. *Münch. med. Wchnschr.*, 64: 579-581. 391, 399, 400.

- Graff, E. und Novak, J. 1921. Regressive Drüsenveränderungen der Corpusschleimhaut bei Kriegsamennorrhöe. *Ztschr. f. Gyn.*, 83: 502-510. 5 Fig. (Cf. also *ibid.*, pp. 289-312.) 400.
- Grandis, V. 1889. La spermatogenese durante l'inanizione. *Atti R. Accad. dei Lincei*, vol. 5, fasc. 8-9. (Cited by Traina '04.) 406.
- . 1889a. La spermatogénèse durant l'inanition. *Arch. ital. de biol.*, 12: 214-222; 680-682. 406.
- Grassi. (Cited by Emery '94.) 60.
- Grawitz, E. 1895. Untersuchungen über den Einfluss ungenügender Ernährung auf die Zusammensetzung des menschlichen Blutes. *Berl. klin. Wchnschr.*, No. 48, pp. 1047-1052. 240, 242.
- . 1896. *Klinische Pathologie des Blutes*. Berl., 333 pp.
- Green, H. H. 1916. Dietetic deficiency. *S. Afr. J. Sc.*, 12: 289-ff. (Cited by Funk '22.)
- W. R. 1919. Studies in the life cycle of *Simocephalus vetulus*. *Biol. Bull.*, 37: 49-95. 29, 58.
- Greene, C. W. 1910. An experimental determination of the speed of migration of salmon in the Columbia River. *J. Exp. Zool.*, 9: 579-591. 2 figs. 77, 310, 397, 412.
- . 1912. The storage of fat in the salmon muscular tissue and its resorption during the migration fast. *Proc. Am. Soc. Biol. Chem.*, 2: 52-54; *J. Biol. Chem.*, 11: xviii-xx. 77, 168.
- . 1912a. A new type of fat-storing muscle in the salmon, *Oncorhynchus Tschawytscha*. *Am. J. Anat.*, 13: 175-181. 1 pl. 168.
- . 1913. An undescribed longitudinal differentiation of the great lateral muscle of the king salmon. *Anat. Rec.*, 7: 99-101. 164, 168.
- . 1918. The composition of the ovaries of the salmon during migration. *J. Biol. Chem.*, 33: xiii. 164.
- . 1919. Biochemical changes in the muscle tissue of king salmon during the fast of spawning migration. *J. Biol. Chem.*, 39: 435-456. 164, 168.
- & Greene, C. H. 1914. The skeletal musculature of the king salmon. *Bul. Bureau of Fisheries, Washington*, 33 (1913): 21-59. 2 pl. 168.
- & Skaer, W. F. 1913. Evidences of fat absorption by the mucosa of the mammalian stomach. *Am. J. Physiol.*, 32: 358-368. 307.
- & Summers, W. S. 1916. The fat and lipase content in the blood in relation to fat feeding and to fasting. *Am. J. Physiol.*, 40: 146-147. 241.
- Greenwood, M. 1888. On digestion in Hydra. *J. Physiol.*, 9: 317-344. 2 pl. 35, 38.
- Gregor, A. 1907. Beiträge zur Kenntniss der pellagrösen Geistesstörungen. *Jahresb. f. Psychiatr.*, 28: 215-309. (Cited by Raubitschek '15 and Harris '19.)
- Greig, E. D. W. 1911. Epidemic dropsy in Calcutta. *Scientif. Mem. Med. Off. Gov't. Print. India*, No. 45, 47 pp. Also *ibid.*, 1912, 2 E. 49. (Cited by McCarrison '21.)
- Gibbon, M. R. & Ferguson, M. I. H. 1921. Nutrition in Vienna. *Lancet*, 200: 474-477. 84.
- . Paton, D. N. *et al.* 1921. Nutrition in Vienna. *II. Lancet*, No. 5119, Oct. 8, 2: 747. 84.
- Grieves, C. J. 1922. The effect of defective diets on teeth. The relation of calcium, phosphorus and organic factors to caries-like and attaching-tissue defects. *J. Am. M. A.*, 79: 1567-1573. 6 figs. 159.
- Griffini, L. 1870. Studio della cute dei pellagrosi etc. *Giron. ital. d. mal. ven. ed d. pelle*, 5: 344-348. 130.
- Groll, S. 1887. Untersuchungen über den Hämoglobingehalt des Blutes bei vollständiger Inanition. *Dissert., Königsberg*, 29 pp. (Cited by Bardier '13.) 250.
- Gruber, A. 1886. Beiträge zur Kenntniss der Physiologie und Biologie der Protozoen. *Bericht d. naturforsch. Ges. zu Freiburg i. B.*, 1: 18-21. (Cited by Maupas '88.) 19.
- . 1911. Experimentelle Untersuchungen an *Amoeba proteus*. *Sitzungsber. d. Ges. f. Morph. u. Physiol., München*, 27: 1-15. 18.

- Gruenhagen, A. u. Krohn. 1889. Ueber Fettresorption im Darne. Arch. f. d. ges. Physiol., 44: 535-544. 321, 322.
- Gruner, O. C. 1914. The biology of blood cells. Wm. Wood & Co., N. Y., 392 pp. 244.
- Guerber, A. 1889. Zahlenwerthe zu dem Oekus des Frosches (Herausg. von J. Gaule). II. Die Gesamtzahl der Blutkörperchen und ihre Variation. Arch. f. Anat. u. Physiol., Physiol. Abt., pp. 83-95. 259.
- Guérin, J. R. 1839. Mémoire sur les caractères généraux du rachitisme. Par. (Cited by Beylard '52; also, with later papers, by Comby '01 and Wohlauer '11.) 144, 145.
- Guerrero, L. E. & Conception, I. 1920. Xerophthalmia in fowls fed on polished rice and its clinical importance. Philip. J. Sc., 17: 99-103. 218.
- Guerrini, G. 1904. Sulla funzione della ipofisi. Ricerche sperimentale. Sperimentale. 58: 837-882. 450.
- . 1915. Contributo allo studio della inanizione. Atti d. Soc. lomb. di sc. med. e biol., Milano, 4: 113-119. ("Phagocytic index.")
- Guillermin, R. et Guyot, F. 1919. Sous-alimentation et oedème de famine. Rev. méd. de la Suisse Romande, Geneva, 39: 115-120.
- Gulland, G. L. 1898. The minute structure of the digestive tract of the salmon and the changes which occur in it in fresh water. Report of the Fishery Board for Scotland to Parliament on the life history of the salmon. 10 pp. 6 pl. Also in Anat. Anz., 14: 441-455. 12 figs. (Abstr. in Jahresb. d. Anat. etc., 1898, T. 3. p. 167 and in J. Physiol., 22: 333.) 310, 317, 335, 350.
- Gulliver, G. G. 1842. Elements of the general and minute anatomy of man and the mammalia. (Transl. of the Handb. d. allg. Anat. d. Menschen u. d. Haussäugethiere, by Fr. Gerber.) Notes and additions. (Cited from Watney by Hammar '06.) 293.
- Gundobin, N. P. 1912. Die Besonderheiten des Kindesalters. Deutsche Ausgabe von S. Rubenstein. Berl., 592 pp. 81.
- Gurd, F. B. 1911. A histological study of the skin lesions in pellagra. J. Exp. Med., 13: 98-114. 130.
- Gurewitsch, M. J. 1908. Ueber die Neurofibrillen und deren Veränderungen unter verschiedenen pathologischen Bedingungen. Dissert., St. Petersburg. (Abstr. in Jahresb. d. Anat. etc., 1908, T. 1, pp. 278-280.) 196, 197.
- . 1908a. Zur Morphologie des fibrillären Apparates der Nervenzellen im normalen und pathologischen Zustande. Folia Neurobiol., 2: 197-210. 197.
- Gurlt. (Cited by Schwann, 1839, Mikroskopische Untersuchungen, etc., pp. 142-143.) 124.
- Gusmita, M. 1893. Sulle alterazioni delle ossa indotte dalla inanizione. Giorn. internaz. d. sc. med., Napoli, n. s., 15: 94-104. 134, 136.
- . 1893a. Sur les altérations des os produites par l'inanition. Arch. ital. de biol., 19: 220-232. 134, 136.
- Guttman, M. 1922. Ist eine objective Beurteilung des Ernährungszustandes des Menschen möglich? Arch. f. Kinderh., 72: 23-49. 3 Fig. 86.
- Guyénot, E. 1913. Études biologiques sur une mouche, *Drosophila ampelophila* Löw. IV. Nutrition des larves et fécondité. Compt. rend. Soc. de biol., Par., 74: 270-272. 29, 61.
- . 1913a. Études biologiques sur une mouche, *Drosophila ampelophila* Löw. V. Nutrition des adultes et fécondité. *Ibid.*, 74: 332-334. 61.
- . 1913b. Études biologiques sur une mouche, *Drosophila ampelophila* Löw. VI. Resorption des spermatozoïdes et avortement des oeufs. *Ibid.*, 74: 389-391. 61.
- . 1913c. Études biologiques sur une mouche, *Drosophila ampelophila* Löw. VII. Le déterminisme de la ponte. *Ibid.*, 74: 443-445. 61.
- Habas (Chabas). 1897. Zur Frage über das Verhalten der Kupffer'schen Zellen und des Endothels der Leberblutgefäße bei Fettablagerung in diesem Organ. St. Petersburg. (Cited by Traina '04; cf. Ergeb. d. allg. Path. etc., 1898.) 334.
- Hadzi, J. 1909. Rückgängig gemachte Entwicklung einer Scyphomeduse. Erste Mitteilung. Zool. Anz., 34: 94-100. 39.

- Haenel, E. 1908. Vererbung bei ungeschlechtlicher Fortpflanzung von *Hydra grisea*. Jen. Ztschr. f. Naturw., 43: 321-372. **28, 36.**
- Haeusermann, E. 1897. Die Assimilation des Eisens. Ztschr. f. physiol. Chem., 23: 555-592. **256.**
- Haigh, L. D., Moulton, C. R., & Trowbridge, P. F. 1920. Composition of the bovine at birth. Univ. of Mo., Coll. of Agr., Exper. Sta. Res. Bull. 38, 47 pp. (Also prelim. report in Proc. Am. Soc. Animal Production, Nov. 1914, p. 100.) **105, 216.**
- Halban, J. 1894. Die Dicke der quergestreiften Muskelfasern und ihre Bedeutung. Anat. Hefte, 3: 268-308. 1 Taf. **167.**
- Hall, F. G. 1922. The vital limit of exsiccation. Biol. Bull., 42: 31-51. **27, 115, 116.**
- W. S. 1894. Ueber die Resorption des Carniferins. Arch. f. Anat. u. Physiol., Physiol. Abt., pp. 455-490. **256.**
- . 1896. Einige Bemerkungen über die Herstellung eines künstlichen Futters. *Ibid.*, pp. 142-153. **256.**
- Haller, A. 1771. Elementa Physiologiae, T. VI, Lib. XIX, Sect. II, pp. 164-187. (Cited by Lucas 1826 *et al.*) **59, 241, 249.**
- Hamburger, F. 1921. Das Hungerödem der Säuglinge. Münch. med. Wechnschr., 68: 579-580.
- Hamill, R. C. 1912. Examination of the central nervous system in seven cases of pellagra. J. Inf. Dis., 10: 190-191. **187, 200.**
- Hammar, J. A. 1895. Zur Kenntniss des Fettgewebes. Arch. f. mikr. Anat., 45: 512-574. 2 Taf. **125, 126.**
- . 1905. Ueber Thymusgewicht und Thymuspersistenz. Verh. d. Anat. Ges., 19. Versamml. Genf. Ergänzungsheft z. Anat. Anz. 27: 121-125. **288.**
- . 1905a. Zur Histogenese und Involution der Thymusdrüse. *Ibid.*, 27: 23-30; 41-89. 20 Fig. **288, 293.**
- . 1906. Ueber Gewicht, Involution und Persistenz der Thymus im Postfötalleben des Menschen. Arch. f. Anat. u. Physiol., Anat. Abt., Suppl. Bd., pp. 91-182. 4 Taf. **286, 288.**
- . 1909. Zur Kenntnis der Teleostierthymus. Arch. f. mikr. Anat., 73: 1-68. 3 Taf. u. 10 Fig. **265, 294.**
- . 1910. Fünfzig Jahre Thymusforschung. Ergeb. d. Anat. u. Entw., 19: 1-274. **286.**
- . 1917. Beiträge zur Konstitutionsanatomie. I. Mikroskopische Analyse der Thymus in 25 Fällen Basedow'scher Krankheit. Beitr. z. klin. Chir., Bd. 104. (Cited by Biedl '22.) **291.**
- . 1918. Das Verhalten der Thymus bei akuten Infektionen, etc., Ztschr. f. angew. Anat. u. Konstitutionsl., 4: 1-107. 27 Fig. **291.**
- . 1920. Mikroskopische Analyse der Thymus in einigen Fällen von Lues congenita. Beitr. z. path. Anat. etc., Bd. 66. (Cited by Biedl. '22.) **291.**
- . 1921. The new views as to the morphology of the thymus gland and their bearing on the problem of the function of the thymus. Endocrinol., 5: 543-572. **286, 291.**
- Hammer, U. 1920. Verzögerung der Frakturheilung unter dem Einfluss der Kriegsnährschäden. Deut. med. Wechnschr., 46: 738-740. **139.**
- Hammond, W. A. 1879. Fasting girls; their physiology and pathology. N. Y., 76 pp. **69.**
- Hannes, W. 1917. Kriegsamennorrhoe. Deut. med. Wechnschr., 43: 1000-1002. **391, 399, 400.**
- von Hansemann, D. 1896. Ueber die grossen Zwischenzellen der Hoden. Verh. d. physiol. Ges. zu Berlin, 21: 2-3. Also Arch. f. Anat. u. Physiol., Physiol. Abt., pp. 176-177. **404, 412.**
- . 1898. Ueber den Einfluss der Winterschlafes auf die Zellteilung. Verh. d. physiol. Ges. zu Berlin. Arch. f. Anat. u. Physiol., Physiol. Abt., pp. 262-263. **122, 412.**
- . 1902. Untersuchungen über das Winterschlaforgan. *Ibid.*, pp. 160-166 **126.**

- Hansen, O. 1894. Ueber die Thymusdrüse und ihre Beziehungen zur Entwicklung der Kinder. Inaug.-Dissert., Kiel, 25 pp. (Cited by Hammar '05.) 287.
- Hantell. 1896. (Cited by Samuel, article "Inanition" in Eulenberg's Realenzyklopädie, Wien u. Lpz.) 462.
- Happ, W. M. 1922. Occurrence of anemia in rats on deficient diets. Johns Hopkins Hosp. Bull., 33: 163-172. 9 figs. 256, 257, 258.
- Harden, A. and Zilva, S. S. 1918. Accessory factors in the nutrition of the rat. Biochem. J., 12: 408-ff.
- . 1919. Oedema observed in a monkey fed on a diet free from fat-soluble "A" accessory food factor and low in fat. Lancet, Lond., 2: 780-781. 102.
- . 1919a. Experimental scurvy in monkeys. J. Path. & Bact., 22: 246-251. 154.
- . 1920. Dietetic experiments with frogs. Biochem. J., 14: 263-266. (Cited by Funk '22.)
- Harms, W. 1909. Ueber den Einfluss des Hungers auf die Wirbelsäule der Tritonen. Verh. d. deut. Zool. Ges., 19. Vers., Frankfurt a. M., pp. 307-312. 92, 135, 137.
- . 1909a. Ueber Degeneration und Regeneration der Daumenschwielen und -Drüsen bei *Rana fusca*. Arch. f. d. ges. Physiol., 128: 25-47. 2 Taf. 121.
- Harris, H. F. 1910. Pathology of pellagra. Trans. Nat. Conference on Pellagra. 1st meeting, pp. 86-93. 187, 200, 431.
- . 1919. Pellagra. Macmillan Co., N. Y., 421 pp. 7 pl. 25 figs. 103, 140, 137, 200, 206, 232, 267, 281, 302, 322, 342, 367, 385.
- Hart, C. u. Lessing, O. 1913. Der Skorbut der kleinen Kinder. F. Enke, Stuttgart. (Cited by Hess '20 and Funk '22.) 154.
- . E. B. & McCollum, E. V. 1914. The influence of restricted rations on growth. (Abstr.) Proc. Am. Soc. Biol. Chem. (1913). J. Biol. Chem., 17: xlv-xlv. 104.
- & Fuller, J. G. 1909. The rôle of inorganic phosphorus in the nutrition of animals. Am. J. Physiol., 23: 246-277. Also in Univ. of Wisc. Agr. Exp. Sta. Res. Bull. No. 1, 38 pp. 106, 142.
- Steenbock, H. & Humphrey, G. C. 1911. Physiological effect on growth and reproduction of rations balanced from restricted sources. Univ. of Wisc. Agr. Exp. Sta. Res. Bull. No. 17, pp. 131-205. 101.
- . 1919. Balanced rations from restricted sources. Their physiological effect on growth and reproduction. Scient. Am. Suppl. No. 2256, p. 202. (From Proc. Nat. Acad. Sc.)
- Miller, W. S. & McCollum, E. V. 1916. Further studies on the nutritive deficiencies of wheat and grain mixtures and the pathological conditions produced in swine by their use. J. Biol. Chem., 25: 239-260. 5 pl. 201.
- & Steenbock, H. 1918. Milk necessary for the nation's welfare. Univ. of Wisc. Agr. Exp. Sta. Bull. 291, 20 pp.
- . 1918a. Hairless pigs. The cause and remedy. Univ. Wisc. Agr. Exp. Sta. Bull. No. 297, 11 pp. 5 figs. 131, 443.
- . 1919. Maintenance and reproduction with grains and grain products as the sole dietary. J. Biol. Chem., 39: 209-234. 105.
- K. 1912. Ueber die experimentelle Erzeugung der Möller-Barlow'schen Krankheit und ihre endgültige Identifizierung mit dem klassischen Skorbut. Arch. f. path. Anat. etc., 208: 367-396. 154, 172, 323, 368, 386, 433.
- P. C. 1917. Eine menschliche Hungerthymus. Arch. f. path. Anat., 224: 72-75. (Endocrinol., vol. 2, no. 1.) 291.
- Hartmann. 1900. Casuistisches zum Hungertod. Münch. med. Wchnschr., 47: 1110-1111. 122.
- Harvey, G. 1675. The disease of London or a new discovery of the scorvey, etc. Lond., 296 pp. (Cited by Holst & Frölich '12.) 150.
- W. 1651. Exercitationes de generatione animalium, etc. Amstelaedami. (Also Engl. transl. for the Sydenham Soc. by R. Willis, 1847.) 240.

- Harvier, P. 1909. Recherches sur la tétanie et les glandes parathyroïdes. Thèse de Par. 446.
- Hassin, G B.. 1924. Brain changes in starvation. Arch. Neurol. & Psychiatr., 11: 551-556. 181.
- Hatai, S. 1904. The effect of partial starvation on the brain of the white rat. Am. J. Physiol., 12: 116-127. 102, 186.
- . 1907. Effect of partial starvation, followed by a return to normal diet, on the growth of the body and central nervous system of albino rats. *Ibid.*, 18: 309-320. 94, 95, 102, 186, 199.
- . 1908. Preliminary note on the size and condition of the central nervous system in albino rats experimentally stunted. J. Comp. Neurol., 18: 151-156. 179, 193.
- . 1915. The growth of the body and organs in albino rats fed with a lipid-free ration. Anat. Rec., 9: 1-20. 104, 140, 188, 199, 399, 413.
- . 1917. On the composition of *Cassiopea xamachana* and the changes in it after starvation. Carnegie Inst. of Washington, Publ. No. 251, Papers from the Dept. of Marine Biol., pp. 95-109. 1 fig. (Also abstr. in Proc. Nat. Acad. Sc., Balt., 1917, 3: 15.) 40.
- . 1918. The refractive index of the blood serum of the albino rat at different ages. J. Biol. Chem., 35: 527-552. 241, 401.
- Haugsted, F. C. 1831. Thymi in homine ac per seriem animalium descriptionis anatomico-physiologicae particula prior, thymi in homine coeterisque mammalibus descriptionem anatomicam figuris xxxiv illustratam exhibens. Havniae, ex off. Roberti, 135 pp. 3 pl. (Cited by Hammar '06.) 287.
- Hausmann, T. 1922. Das Blutbild bei Skorbut mit Berücksichtigung der Linkverschiebung. Ztschr. f. klin. Med., 93: 346-357. (Abstr. in J. Am. M. A.) 258.
- Hayashi, A. 1914. Ueber das Verhalten des Fettes in der Leber bei atrophischen Säuglingen und bei Inanition. Monatschr. f. Kinderh. (Orig.), 12: 221-228. 329.
- Hayden, E. M., Wenner, W. T., & Rucker, C. W. 1924. Production of goiter in rats by restricted iodine feeding. Proc. Soc. Exp. Biol. & Med., 21: 546-547. 443.
- Hayem, G. 1877. Recherches sur l'anatomie pathologique des atrophies musculaires. Par., 162 pp. 166, 229.
- . 1882. Leçons sur les modifications du sang. Par. 241, 250.
- . 1889. Du sang et de ses alterations anatomiques. Masson, Par., 1035 pp. 126 figs. 241, 250.
- Heape, W. 1905. Ovulation and degeneration of ova in the rabbit. Proc. Roy. Soc. Lond., Ser. B, 76: 260-268. (Cited by Marshall '22.) 394.
- von Hecker, C. u. Buhl, L. 1861. Klinik der Geburtskunde. Lpz.
- . J. F. C. 1844. Epidemics of the middle ages. Transl. by Babington from the German. Sydenham Soc., Lond., 344 pp. 71.
- Hedinger, E. 1915. Pathological investigations into lamieziekte in cattle. V and VI. Dep't. Agr., Union S. Africa. (Cited by Funk '22.) 232, 311.
- . 1920. Ueber Störungen des Knochenwachstums junger Rinder bei Unternahrung. Ztschr. f. angew. Anat. u. Konstitutionsl., 5: 293-301. (Ber. ges. Physiol., 1920, 4: 59.) 136.
- Hehir, P. 1922. Effects of chronic starvation during the siege of Kut. Brit. Med. J., 1: 865-868. 314.
- Heidenhain, R. P. 1857. Disquisitiones criticae et experimentales de sanguinis quantitate in mammalium corpore extantis. Dissert. Halis. (Cited by Manassein '69 and Benzançon et Labbé '04.) 240, 249.
- . 1870. Untersuchungen über den Bau der Labdrüsen. Arch. f. mikr. Anat., 6: 368-406. 309.
- . 1875. Beiträge zur Kenntniss des Pancreas. Arch. f. d. ges. Physiol., 10: 557-632. 1 Taf. 348.
- . 1880. Die Milchabsonderung. In Hermann's Handb. d. Physiol. (Cited by Arnold '14.) 332.

- . 1883. Die Absonderung und die Aufsaugung. (Ueber feineren Bau der Leberzellen.) In Hermann's Handb. d. Physiol., Bd. 5, Abt. 1, p. 221–ff. (Cited by Boehm '08.) 332.
- . 1888. Beiträge zur Histologie und Physiologie der Dünndarmschleimhaut. Arch. f. d. ges. Physiol., Suppl. Heft, 43: 1–103. 4 Taf. 320.
- Heidkamp, H. 1909. Ueber die Einwirkung des Hungers auf weibliche Tritonen. Arch. f. d. ges. Physiol., 128: 226–237. Taf. 10. 394, 400.
- Heitz, F. A. 1918. *Salmo salar* Lin., seine Parasitenfauna und seine Ernährung im Meer und im Süßwasser. Arch. f. Hydrobiol., 12: 311–372. 77, 310.
- . J. 1912. Sur l'état du myocard dans l'inanition. Arch. d. mal. du coeur etc. (Jahresb. d. Anat. etc., 1912, T. 3, pp. 286, 288.) 228, 231.
- . 1912a. Note sur l'état du myocard dans l'inanition. Compt. rend. Soc. de biol., Par., 72: 814–815. 231.
- Hellman. (Cited by Hammar '09, Källmark '11 *et al.*) 265.
- Helly, K. 1906. Die hämatopoetischen Organe. In Ehrlich-Lazarus: Die Anämie, 1. Abt., 2. Teil. Nothnagel-Frankl-Hochwart's Spezielle Pathologie and Therapie, Bd. 8. 125, 136.
- . 1911. Studien über den Fettstoffwechsel der Leberzellen. Morphologischer Teil. Beitr. z. path. Anat. etc., 51: 462–489. 2 Taf. 326.
- Helmholz, H. F. 1909. Beitrag zur pathologischen Anatomie der Pädatrie (Dekomposition). Jahrb. f. Kinderh., 70: 458–465. 3 Fig. 230, 248, 277, 315, 328, 347, 374, 420, 437, 446.
- Helmreich, E. u. Kassowitz, K. 1923. Körperbau und Ernährungszustand in ihrem Einfluss auf den Index der Körperfülle. Ztschr. f. Kinderh., 35: 67–78. 4 Fig. 85, 87.
- Hérard, H. V. 1847. Du spasme de la glotte. Thèse, Par., No. 3, 111 pp. (Cited by Hammar '06 from Friedleben '58.) 287.
- Herbst, C. 1897. Ueber die zur Entwicklung der Seeigellarven notwendigen anorganischen Stoffe, ihre Rolle und ihre Vertretbarkeit. I. Theil. Die zur Entwicklung notwendigen anorganischen Stoffe. Arch. f. Entw. d. Org., 5: 649–793. 3 Taf. 39, 40, 41, 44, 48–51, 53, 66.
- . 1900. Ueber das Auseinandergehen von Furchungs- und Gewebezellen in kalkfreiem Medium. *Ibid.*, 9: 424–463. 51, 66.
- . 1913. Entwicklungsmechanik oder Entwicklungsphysiologie der Tiere. In Handb. d. Naturwiss. Jena, 3: 542–634.
- Hermann. 1905. Ueber Vorkommen und Veränderungen von Myelinsubstanz in der Nebenniere. Inaug. Dissert., Tübingen. (Cited by Kawamura '11.) 418, 423.
- . L. 1888. Untersuchungen über den Hämoglobingehalt des Blutes bei vollständiger Inanition. (Nach Versuchen von S. Groll mitgetheilt.) Arch. f. d. ges. Physiol., 43: 239–244. 250.
- Herter, C. A. 1897. An experimental study of some of the nutritional changes resulting from fat starvation. Proc. N. Y. Path. Soc. (1896), pp. 72–76. 125, 150, 233, 385, 432.
- . 1898. An experimental study of fat starvation, with especial reference to the production of serious atrophy of fat. J. Exp. Med., 3: 293–314. 2 pl. 126, 135, 186.
- . 1908. On infantilism from chronic intestinal infection. N. Y. 248, 315.
- Hertwig, O. 1920. Allgemeine Biologie. 5. Aufl. G. Fischer, Jena, 800 pp. 65.
- . R. 1899. Was veranlasst die Befruchtung der Protozoen? Sitzungsber. d. Ges. f. Morph. u. Physiol., München, 15: 62–69. 16.
- . 1903. Ueber das Wechselverhältnis von Kern und Protoplasma. *Ibid.*, 18: 77–100. 16, 17, 20.
- . 1903a. Ueber Korrelation von Zell- und Kerngrösse und ihre Bedeutung für die geschlechtliche Differenzierung und die Teilung der Zelle. Biol. Centralbl., 23: 49–62; 108–119. 16, 17, 18.
- . 1904. Ueber physiologische Degeneration bei *Actinosphaerium Eichorni*; nebst Bemerkungen zur Aetiologie der Geschwülste. Denkschr. d. med.-nat. Ges. Jena, 54 pp. 4 Taf. 18.

- . 1906. Ueber Knospung und Geschlechtsentwicklung von *Hydra fusca*. Biol. Centralbl., 26: 489-508. **28, 35.**
- Herzog, F. 1921. Ueber experimentellen Skorbut bei Meerschweinchen. Frankf. Ztschr. f. Path., 26: 50-79. 2 Fig. **259.**
- Hess, A. F. 1915. The influence of infantile scurvy on growth (length and weight). Proc. Soc. Exp. Biol. & Med., 13: 50. **114.**
- . 1916. Infantile scurvy. III. Its influence on growth (length and weight). Am. J. Dis. Child., 12: 152-165. **114.**
- . 1918. The rôle of antiscorbutics in our dietary. J. Am. M. A., 71: 941-943.
- . 1918a. Focal degeneration of the lumbar cord in a case of infantile scurvy. J. Inf. Dis., 23: 438-442. 4 figs.
- . 1920. Scurvy, past and present. J. B. Lippincott Co., Phila. & Lond., 279 pp. **113, 114, 132, 150, 151, 154, 160, 171, 189, 208, 221, 234, 237, 258, 268, 284, 299, 302, 312, 323, 343, 355, 368, 386, 401, 415, 433.**
- . 1922. Newer aspects of the rickets problem. J. Am. M. A., 78: 1177-1183. (See also Chapter 32 in Abt's Pediatrics, vol. 2, 1923.) **106, 111, 148.**
- . 1923. Infantile scurvy (Barlow's disease). In Abt's Pediatrics, Saunders & Co., Phila., 2: 849-875. **108, 114.**
- & Fish, M. 1914. Infantile scurvy: the blood, the blood-vessels and the diet. Am. J. Dis. Child., 8: 386-405. **237, 258.**
- McCann, G. F. & Pappenheimer, A. M. 1921. Experimental rickets in rats. II. The failure of rats to develop rickets on a diet deficient in vitamine A. J. Biol. Chem., 47: 395-409. 3 pl. **107, 111, 150, 218.**
- & Unger, L. J. 1919. The rôle of fat-soluble vitamins in the dietary of infants. Proc. Soc. Exp. Biol. & Med., 17: 49-50. **107, 220, 257.**
- . 1920. Scorbutic beading of the ribs. Am. J. Dis. Child., 19: 331-336. (Cf. also Brit. Med. J., 1920, p. 154.) **151.**
- J. H. 1923. Premature infants. In Abt's Pediatrics, Saunders & Co., Phila., 2: 437-523.
- Heubner, O. 1901. Zur Kenntniss der Säuglings-Atrophie. Jahrb. f. Kinderh., 53: 35-49. 6 Fig. (Also in Verh. d. Ges. deut. Naturf. u. Aerzte (1900), Lpz., 1901, Bd 72, pt. 2, H.2, pp. 154-158.) **315.**
- . 1906. Lehrbuch der Kinderheilkunde. 2. Aufl., Lpz., 1: 666-709. **146, 147.**
- . 1909. Sitz d. Ges. f. Kinderh. in Salzburg. Verh. d. Ges. f. Kinderh., Bd. 26. (Cited by Lipschütz '10.)
- u. W. 1910. Zur Lehre von der energetischen Bestimmung des Nahrungsbedarfs beim Säugling. Jahrb f. Kinderh., 72: 121-148. **115.**
- W. 1910. Versuche über den Phosphorumsatz des wachsenden Organismus. Verh. d. 26. Versamml. d. Ges. f. Kinderh in Salzburg (1909), 26: 149-161. **142.**
- . 1911. Versuche über den Nahrungsphosphor. Münch. med. Wchnschr., pp. 2543-2544. **106.**
- Heumann, G. 1850. Mikroskopische Untersuchungen an hungernden und verhungerten Tauben. Dissert. Giessen, 57 pp. **167, 331, 348, 376.**
- Hewitt, G. 1879. On chronic starvation. Lancet, Lond., 1: 38-42. **400.**
- Heyer, F. 1884. Untersuchungen über das Verhältniss des Geschlechtes bei einhäusigen und zweihäusigen Pflanze, unter Berücksichtigung des Geschlechtsverhältnis bei den Tieren und den Menschen. Ber. d. landwirtsch. Inst. Halle, 5: 1-152. **3.**
- Heymans, J. F. 1896. Recherches expérimentales sur l'inanition chez le lapin. Arch. de pharmacod., Gand et Par., 2: 315-353. 3 charts.
- de Hieronymis. 1885. Breve studio con una nuova contribuzione sulla anatomia, patologia e sull'etiologia della pellagra. Napoli. (Cited by Raubitschek '15 and Harris '19.)
- Higier, H. 1922. Endemie dysalimentärer Osteoarthropie, Osteomalacie und Spätrachitis und ihre Stellung zur neuen Lehre von den Vitaminen oder Nutraminen. Ztschr. f. klin. Med., 95: 445-468. **107, 145.**

- Hilferding. 1917. Zur Statistik der Amenorrhöe. Wien. klin. Wchnschr., Nr. 27. (Abstr. in Zentralbl. f. Gyn., 1917, 41: 1139.) 391, 399.
- Hille, G. 1923. Arch. f. Kinderheilk., 73: 134-139. (Abstr. in J. Am. M. A., 81: 1565.) 122.
- Hillman, O. S. 1913. Am. J. Med. Sc., Apr.-Sept. Also J. Am. M. A., vol. 43, Sept. 26, 1914. (Cited by Huck '23.) 255.
- Hindhede, M. 1920. The effect of food restriction during war on mortality in Copenhagen. J. Am. M. A., 74: 381-382.
- . 1923. Protein and pellagra. *Ibid.*, 80: 1685-1689. 103.
- Hinks, Allman & Schneider. (Cited by Semper '81.)
- Hirsch, C. 1899. Ueber die Beziehungen zwischen dem Herzmuskel und der Körpermuskulatur und über sein Verhalten bei Herzhypertrophie. Deut. Arch. f. klin. Med., 64: 597-634. 224.
- Hirschsprung. 1861. Den medtodte Tillukning af Spiservoret etc. Afhandl. Kjobenhavn, 132 pp. (Cited by Falck '81.) 69.
- Hoagland, D. R. 1919. Relation of the concentration and reaction of the nutrient medium to the growth and absorption of the plant. J. Agr. Res., 18: 73-117. 5, 10.
- . 1920. Optimum nutrient solutions for plants. Science, N. S., 52: 562-564.
- Hoare, E. W. 1915. A system of veterinary medicine. Alex. Eger, Chicago, 2: 1290. 102, 170, 255, 322.
- Hojer, J. A. 1924. Studies in scurvy. Acta paediatr., Upsala, vol. 3 (Suppl.), 286 pp. 6 pl. 127 figs. 150, 151, 154, 172, 234, 237, 268, 284, 344, 360, 386, 434.
- von Hoesslin, H. 1882. Ueber Ernährungsstörungen infolge Eisenmangels in der Nahrung Ztschr. f. Biol., 18: 612-643. 131, 170, 254, 256, 342.
- . 1890. Ueber den Einfluss ungenügender Ernährung auf die Beschaffenheit des Blutes. Münch. med. Wchnschr., pp. 654-656; 673-676.
- Hoffman, C. F. 1922. Biochemical properties of the blood in pigeons in polyneuritis and simple inanition as compared with the blood of normal pigeons. Unpublished thesis for Master's degree, Univ. of Minn. (Cf. Palmer & Hoffman '22.) 113, 234, 250, 257.
- Hoffmann, G. 1920. Anatomische Befunde bei Amenorrhöe während der Kriegszeit. Inaug. Dissert., Breslau, 35 pp. 392, 400.
- . H. 1885. Ueber Sexualität. Bot. Ztg., Nos. 10, 11. Also in Biol. Centralbl., 1887, 7: 667. (Cited by Thomson '88.) 3.
- . 1887. Kulturversuchen ueber Variation im Pflanzenreiche (1855-1887). Bot. Ztg. pp. 260, 772, 773. (Cited by Thomson '88.) 3.
- Hofmann, H. 1919. Ueber den Einfluss der Kriegskost auf die Geburtsmasse der Kriegsneugeborenen. Arch. f. Gyn., 110: 451-474. 79, 81.
- Hofmeister, F. 1881. Zur Lehre vom Pepton. III. Ueber das Schicksal des Peptons im Blute. Ztschr. f. physiol. Chem., 5: 127-151. 320.
- . 1887. Ueber Resorption und Assimilation der Nährstoffe. 3 Mitth. Arch. f. exp. Path., 22: 306-324. 1 Taf. 264, 317, 320.
- . 1892. Cited by Wiesel, Lubarsch-Ostertag Ergeb., 1912, 15: 543. 293.
- . 1918. Ueber qualitativ unzureichende Ernährung. Ergeb. d. Physiol., 16: 1-39; 510-589.
- . 1922. Studien über qualitative Unterernährung. I. Mitteilung. Die Rattenberiberi. Biochem. Ztschr., 128: 540-556. 189, 207
- Hofstätter. 1918. Ueber die Mucosa des amenorrhöischen Uterus (mit spezieller Berücksichtigung der Kriegsamennorrhoe). Wien. klin. Wchnschr., 37: 753-756. (Index med.) 400.
- Holm, E. 1922. Sur la xerophthalmie du rat. Compt. rend. Soc. de biol., Par., 87: 463-464. 218.
- Holmberg. 1919. Svenska La Karesalls, Forhandl (Dec., 31). (Epit., Brit. Med. J., 1920, Mar. 6, p. xxxix.) (Cited by McCarrison '21.) 391, 392, 400.
- Holmes, C. D. 1910. The effect of starvation for five successive generations on the sex-ratio in *Drosophila ampelophila*. Indiana U. Studies, No. 2, pp. 16-23. 29.

- . G. 1903. On morphological changes in exhausted ganglion cells. *Ztschr. f. allg. Physiol.*, 2: 502-515. (Cited in *Jahresb. d. Anat.*, etc., 1903, from Ref. in *Neurol. Centralbl.*, 1903, 22: 778-779.) 196.
- Holmgren, E. 1902. Weiteres über die "Trophospongien" der Leberzellen und der Darmepithelzellen. *Anat. Anz.*, 22: 313-323. 8 Fig. 335.
- Holmström, R. 1911. Ueber das Vorkommen von Fett und fettähnlichen Substanzen im Thymusparenchym. *Arch. f. mikr. Anat.*, 77: 323-345. 1 Taf. 265, 295.
- . 1912. Om förekomsten of fett eller fettlicknaude substanser i thymusparenkymet. *Upsala lökareförenings förhandlingar*, N. F., Bd. 17. (Abstr. in *Jahresb. d. Anat.*, etc., 1912, T. 3, pp. 509; 517-518.) 295.
- Holst, A. & Frölich, T. 1907. Experimental studies relating to ship-beriberi and scurvy. II. On the etiology of scurvy. *J. Hyg., Cambridge*, 7: 634-671. 2 pl. 113, 131, 153, 154, 160, 171, 234.
- . 1912. Ueber experimentellen Skorbut. Ein Beitrag zur Lehre von dem Einfluss einer einseitigen Nahrung. *Ztschr. f. Hyg. u. Infektionskr.*, 72: 1-120. 3 Taf. 113, 131, 153, 154, 160, 171, 208, 234.
- Holt, C. M. 1917. Studies on the olfactory bulbs of the albino rats. I. Effect of a defective diet and of exercise. II. Number of cells in bulb. *J. Comp. Neurol.*, 27: 201-239. 187.
- . L. E. 1918. Standards for growth and nutrition. *Am. J. Dis. Child.*, 16: 359-375. 85, 87, 97.
- Holthusen, H. 1910. Ueber den histologischen Nachweis verschiedener Fettarten mit Rücksicht auf das Verhalten des Fettes in den Lymphknoten. *Beitr. z. path. Anat. etc.*, 49: 595-637. 264, 265, 321.
- Hooper, C. W. & Whipple, G. H. (See Whipple & Hooper.)
- Hopkins, F. G. 1906. The analyst and the medical man. *Analyst*, 31: 385-404. 109.
- . 1912. Feeding experiments illustrating the importance of accessory factors in normal dietaries. *J. Physiol.*, 44: 425-460. 109, 110.
- . 1919. Vitamins, unknown but essential accessory factors of diet. (Abstr.) *Lancet*, 1: 363.
- . *et al.* 1920. Discussion on the present position of vitamins in clinical medicine. *Brit. Med. J.*, 2: 147-160.
- . Chick, H., Drummond, J. C., Harden, A. & Mellanby, E. 1919. Report on the present state of knowledge concerning accessory food factors (vitamins). Compiled by a committee appointed jointly by the Lister Institute and the Medical Research Committee. *Med. Res. Council, Lond.*, Publ. No. 38, 107 pp. 110.
- Hornowski, J. 1913 (?). Anatomisch-pathologische Untersuchungen über das Verhältnis der Thymus zu den Parathyroiddrüsen und zu den Nebennieren sowie über das Verhalten der Thymus beim Status thymo-lymphaticus. (Polish.) *Lwoski Tygod. lek. Lemberg*, 8: 577-580; 591-594; etc. (Cited in *Jahresb. d. Anat. etc.*, 1913.) 290.
- Hottes. Unpublished observations cited by Howe ('12). 5.
- Houbert. 1919. Rôle des vitamines dans la croissance. *Paris méd.*, 33: 473-476. 414.
- Howe, P. E. 1912. General aspects of fasting. *Biochem. Bull.*, 2: 90-100. 98.
- & Hawk, P. B. 1909. A study in repeated fasting. *J. Biol. Chem.*, 7: xlvii-xlviii. 462.
- . 1912. Fasting studies IX. On the differential leucocyte count during prolonged fasting. *Am. J. Physiol.*, 30: 174-181. (Also abstr. in *Proc. Soc. Biol. Chem.*, 1910, p. xxi, *J. Biol. Chem.*, vol. 9.) 244, 252.
- . Mattill, H. A. & Hawk, P. B. 1909. Fasting studies on men and dogs. *J. Biol. Chem.*, 7: xlvii-xlix. 75, 94.
- . P. R. 1920. Effect of a scorbutic diet upon the teeth. *Dental Cosmos*, 62: 586 (636?); 921-ff. (Cited by Funk '22.) 161.
- . 1921. Food accessory factors in relation to the teeth. *J. Dent. Res.*, 3: 7-12. 12 pl. 50 figs. 154, 161.

- . 1922. Decalcification of teeth and bones, and regeneration of bone through diet. *J. Am. M. A.*, 79: 1565-1567. 8 figs. 161.
- Howell, W. H. 1914. The coagulation of lymph. *Am. J. Physiol.*, 35: 483-491. 266.
- Hoyer, H. 1873. *Neuer Beitrag zur Histologie des Knochenmarkes.* (Polish.) *Denkschr. (Pamientnik) d. Warschauer ärztl. Ges., Warschau*, H. 3, pp. 261-285. 125.
- Huck, J. G. 1923. The blood picture of uncomplicated pellagra, with a review of the literature. *Johns Hopkins Hosp. Bull.*, 34: 157-164. 255.
- Huebschmann. 1921. *Zur pathologischen Anatomie der Ernährungsstörungen der Säuglinge.* (Selbstbericht.) XVIII. Tagung d. deut. path. Ges. in Jena. *Centralbl. f. allg. Path. etc.*, 31: 568. 329, 421.
- Huelse, W. 1917. Die Oedemkrankheit in den Gefangenlagern. *Munch. med. Wchnschr.*, Nr. 28, p. 921. 232, 281, 342, 367.
- . 1918. Untersuchungen über Inanitionsödeme. Ein Beitrag zur Pathologie des Oedems. *Arch. f. path. Anat. etc.*, 225: 234-283. 232, 430.
- Huenekens, E. J. 1917. Rickets, with special reference to premature infants. *Journal-Lancet, Minneapolis*, 37: 804-810. 108.
- Huth, A. 1921. Ernährungszustand und Körpermasse. *Ztschr. f. Kinderh.*, 30: 39-43. 85, 87.
- Hutinel et Tixier, L. 1909. Modifications de la moelle osseuse des rachitiques. *Compt. rend. Soc. de biol., Par.*, 66: 946-948. 146.
- Hutyra, F. & Marek, J. 1916. *Pathology and therapeutics of the diseases of domestic animals.* A. Eger, Chicago, Vol. 1, pp. 914-915. 102, 255.
- Iapichino-Paterno. 1902. *Studio clinico sperimentale dell'atrepsia del Parrot.* *Pediatrics, Anno 10, No. 9.* (Cited by Pagano '06.) 318.
- Ide, F. 1912. Gefäßveränderungen bei der Möller-Barlowschen Krankheit. *Ztschr. f. Kinderh.*, 32: 165-177. 4 Fig. 237.
- Ikeda, Y. 1921. (On the changes in the viscera, especially of the hematopoietic organs, and the fat metabolism in hunger.) *Jikken Igaku Zasshi (Jap. J. Exp. Med.)*, Vol. 5, No. 1. (Abstr. in *Jap. Med. World*, 1921, 1: 18.) 266.
- . 1922. Beiträge zur Pathologie des Hungers mit besonderer Berücksichtigung der Fettwanderung und der Veränderung der lymphatischen und hämatopoetischen Organe. *Mitt. a. d. Med. Fak. d. kais. U. Tokyo*, 29: 131-178. (Abstr. in *Ber. d. ges. Physiol.*, 1923, 17: 331.) 137, 253, 266, 297.
- Immerman. (Cited by Lazarus '13.) 256.
- Ingier, A. 1913. Beiträge zur Kenntnis der Barlowschen Krankheit. *Frankf. Ztschr. f. Path.*, 14: 1-86. 3 Taf. 153, 154, 208.
- . 1915. A study of Barlow's disease experimentally produced in fetal and newborn guinea-pigs. *J. Exp. Med.*, 21: 525-538. (Also in *Nord. Med. Ark.*, 1915, 48: 1-) 154.
- Ingle. 1908. Mineral constituents of foods. *J. Agr. Sc.*, 3: 22-ff. (Cited by Elliot, Crichton & Orr '22.)
- Inlow, W. DeP. 1922. Spleen and digestion. Study III. The spleen in inanition; effect of removal of external secretion of pancreas on spleen. *Am. J. Med. Sc.*, 164: 173-187. 276, 280.
- Irvine, R. & Woodhead, G. S. 1889. Secretion of carbonate of lime by animals. II. *Proc. Roy. Soc. Edinb.*, 16: 324-354. (Also Part I, *ibid.*, 1888, 15: 308-316.) 59.
- Isaëw, W. 1887. (Zur Frage über die Veränderung der Darmganglien, bei Tuberkulose und einigen anderen Erkrankungen.) *These, St. Petersb.* (Abstr. by Mühlmann '99.) 205, 230, 317, 333, 377.
- Ishido (Koshu Chosen, Japan). 1923. Ueber den kompensatorischen Einfluss des ultravioletten Lichtes auf die avitaminösen Störungen am Knochenmarke. *Biochem. Ztschr.*, 137: 184-192. 4 Textabb. 150.
- Issakowitsch, A. 1905. Geschlechtsbestimmende Ursachen bei den Daphniden. *Biol. Centralbl.*, 25: 529-536. (Cf. also *Arch. f. mikr. Anat.*, 69: 223-244.) 29, 58.

- Ivanovsky, A. 1923. Physical modifications of the population of Russia under famine. *Am. J. Phys. Anthrop.*, 6: 331-353. 79, 86, 93, 96, 120, 304, 314, 391, 392.
- Iwabuchi, T. 1922. Ueber Nebennierenveränderungen beim experimentellen Skorbut, nebst einigen Angaben über die Knochenbefunde. *Beitr. z. path. Anat. etc.*, 70: 440-458. 2 Taf. 433.
- Jackson, C. M. 1904. Zur Histologie und Histogenese des Knochenmarkes. *Arch. f. Anat. u. Physiol., Anat. Abt.*, pp. 33-70. 2 Taf. u. 5 Fig. 125, 126, 136, 139.
- . 1915. Effects of acute and chronic inanition upon the relative weights of the various organs and systems of adult albino rats. *Am. J. Anat.*, 18: 75-116. 2 figs. (Also abstr. in *Proc. Am. Assn. Anat., Anat. Rec.*, 1915, 9: 90.) 92, 93, 118, 134, 135, 164, 179, 192, 213, 228, 275, 307, 338, 366, 380, 395, 409, 429, 438, 451, 462, 467.
- . 1915a. Changes in the relative weights of the various parts, systems and organs of young albino rats held at constant body weight by underfeeding for various periods. *J. Exp. Zool.*, 19: 99-156. (Also abstr. in *Proc. Am. Assn. Anat., Anat. Rec.*, 1915, 9: 91.) 75, 89, 90, 119, 135, 138, 157, 165, 180, 193, 212, 228, 275, 296, 307, 338, 366, 380, 395, 409, 429, 438, 451, 467.
- . 1916. Effects of inanition upon the structure of the thyroid and parathyroid glands of the albino rat. *Am. J. Anat.*, 19: 305-352. 14 figs. (Also abstr. in *Proc. Am. Assn. Anat., Anat. Rec.*, 1916, 10: 208.) 439, 440, 441, 446, 461.
- . 1917. Effects of inanition and refeeding upon the growth and structure of the hypophysis in the albino rat. *Am. J. Anat.*, 21: 321-358. 5 figs. 451-455.
- . 1919. The postnatal development of the suprarenal gland and the effects of inanition upon its growth and structure in the albino rat. *Am. J. Anat.*, 25: 221-289. 10 figs. 424-428.
- . 1921. The effects of various types of inanition upon growth and development, with special reference to the skeleton. (*Abstr.*) *Proc. Am. Assn. Anat., Anat. Rec.*, 21: 68-69. 82, 140.
- . 1922. Changes in body length and in weights of the body and of various organs in atrophic infants. (*Abstr.*) *Proc. Am. Assn. Anat., Anat. Rec.*, 23: 22. 88, 92, 135, 178, 422, 428, 463.
- . 1923. Dystrophic morphology and its significance. *Science*, 67: 537-546. 91, 457.
- & Carleton, R. 1922. Organ weights in albino rats with experimental rickets. (*Abstr.*) *Proc. Soc. Exp. Biol. & Med.*, 20: 181-182. 109, 215, 233, 312, 367, 399, 432.
- . 1923. The effect of experimental rickets upon the weights of the various organs in albino rats. *Am. J. Physiol.*, 65: 1-14. 131, 144, 171, 188, 215, 233, 282, 298, 343, 367, 385, 399, 413, 432, 455, 476.
- & Stewart, C. A. 1918. The effects of under feeding and refeeding upon the growth of the various systems and organs of the body. *Minn. Med.*, 1: 403-414. 94, 95, 135, 139, 180, 396.
- . 1919. Recovery of normal weight in the various organs of albino rats on refeeding after underfeeding for various periods. *Am. J. Dis. Child.*, 17: 329-352. 94, 96, 120, 139, 166, 180, 193, 212, 228, 276, 297, 307, 340, 366, 381, 396, 409, 429, 438, 451, 471.
- . 1920. The effects of inanition in the young upon the ultimate size of the body and of the various organs in the albino rat. *J. Exp. Zool.*, 30: 97-128. (Also abstr. in *Proc. Am. Assn. Anat., Anat. Rec.*, 1919, 16: 153.) 94, 95, 96, 139, 165, 166, 181, 193, 212, 228, 276, 307, 340, 366, 381, 396, 409, 429, 438, 473.
- L & Moore, J. J. 1916. Studies on experimental scurvy in guinea pigs. *J. Inf. Dis.*, 19: 478-510. 14 figs. 154, 160, 172, 258, 268, 284.
- Jacob, L. 1906. Fütterungsversuche mit einer aus den einfachen Nahrungsstoffen zusammengesetzten Nahrung an Tauben und Ratten. *Ztschr. f. Biol.*, 48: 19-62.
- Jacobsohn L. 1897. Ueber das Aussehen der motorischen Zellen im Vorderhorn des Rückenmarks nach Ruhe und Hunger. *Neurol. Centralbl.*, 16: 946-948. 196, 198.
- Jacobsthal, H. 1900. Zur Pathologie der Knochenkrankungen bei Barlow'scher Krankheit. *Beitr. z. path. Anat. etc.*, 27: 173-194. 1 Taf. 151, 221, 299, 433.

Jacquet, L. et Jourdanet. 1912. Histologie comparée de la muqueuse gastrique du chien, a jeun et après repas de viande grossièrement divisée ou pulpée. Bull. et mém. de la Soc. med. d. hôp. de Par., 28: 185-192. 310.

Jaegerroos, B. H. 1902. Studien über den Eiweiss-, Phosphor- und Salzumsatz während der Gravidität. Arch. f. Gyn., 67: 517-590. (Cited by Reeb '05.) 77.

Jaffé, R. 1921. Pathologisch-anatomische Veränderungen der Keimdrüsen bei Konstitutionskrankheiten, im besonderen bei der Pädatrie. Frankf. Ztschr. f. Path., 26: 250-257. (Also abstr. in Centralbl. f. allg. Path. etc., 1921, 31: 571; and in Endocrinol., 1922, 6: 567.) 406.

Jahreiss. 1919. Die Kriegskinder 1918 und 1919. Münch. med. Wchnschr., 66: 1421-1422. 79.

von Jaksch, R. 1918. Das Hungerödem. Wien. med. Wchnschr., 68: 1029-1036. (Ref. in Centralbl. f. allg. Path. etc., 29: 609.) 232.

Jansen, W. H. 1918. Blutbefunde bei Oedemkranken. Münch. med. Wchnschr., 65: 925-927. 255.

———. 1918a. Untersuchungen über Stoffumsatz bei Oedemkranken. *Ibid.*, Nr. 1 pp. 10-13; cf. also *ibid.*, Nr. 40. (Cited by Maase u. Zondek, '20.) 232.

Jarotski (Jarotzky or Yarotski), A. J. 1898. (Ueber die Veränderungen der Grösse und der Structur der Pancreaszellen bei einigen Hungerformen.) Dissert., St. Petersburg., 78 pp. (Abstr. by Mühlmann '99, and in Jahrb. d. Anat. etc., 1898, T. 3, pp. 219; 234-235.) 350.

———. 1899. Ueber die Veränderungen in der Grösse und im Bau der Pankreaszellen bei einigen Arten der Inanition. Arch. f. path. Anat. etc., 156: 409-450. 1 Taf. 345, 350, 351.

von Jaworski, J. 1916. Mangelhafte Ernährung als Ursache von Sexualstörungen bei Frauen. Wien. klin. Wchnschr., 29: 1068. (Cited by Vaerting '18.) 391, 399, 400.

———. 1916a. Aus der Biologie der Tumoren. Einfluss mangelhafter Ernährung auf den Zustand bestimmter Neubildungen, hauptsächlich der Tumoren der weiblichen Sexualorgane. *Ibid.*, pp. 1646-1648. (Cited by v. Jaworski '17.) 400.

———. 1917. Senkung und Prolaps von Uterus und Scheide als Folge ungenügender Ernährung. Zentralbl. f. Gyn., 41: 708-710. 400.

Jégourel, H. 1904. De l'atrophie ponderale d'origine gastro-intestinale chez les nourrissons au sein. 98 pp. Thèse, méd., Par. ('03-'04, No. 305.)

Jenner, W. 1895. Clinical lectures and essays on rickets, tuberculosis, abdominal tumors and other subjects. Macmillan Co., N. Y., 329 pp. 109, 142, 144, 158, 170, 267.

Jennings, H. S. 1908. Heredity, variation and evolution in protozoa. Proc. Am. Phil. Soc. Phila., 47: 393-546. 17, 21, 22.

Jensen. 1899. In Verworn's General Physiology. (Transl. by F. S. Lee from 2nd German ed.) Macmillan Co., N. Y. & Lond. 19.

Jewett, W. E. 1875. Some pathological details of the "remarkable case of fasting," etc. *Penins. J. Med.*, Detroit, 11: 65-67. 122, 303.

Jickili, C. F. 1902. Die Unvollkommenheit des Stoffwechsels als Veranlassung für Vermehrung, Wachstum, Differenzierung, Rückbildung und Tod der Lebewesen im Kampf ums Dasein. Berl., xvi, u. 353 pp. (Cited by Hertwig '03a and Morgulis '11.) 16.

Jobling, J. W., Pappenheimer, A. M., Hess, A. F. *et al.* 1922. Experimental rickets in rats. Proc. N. Y. Path. Soc., N. S., 22: 2-27. 148.

Joerg, I. C. G. 1806. Versuche und Beyträge geburtshülfliches Inhalts. 264 pp. Lpz. (Cited by Reeb '05.) 79.

Johannson, Landergreen, Sonden u. Tigerstedt. 1897. Beiträge zur Kenntnis des Stoffwechsels beim hungernden Menschen. Skand. Arch. f. Physiol., 7: 1-.

Jolly, J. 1901. Phénomènes histologiques de la répartition du sang chez les Tritons anémiés par un long jeûne. *Compt. rend. Soc. de biol.*, Par., 53: 1183-1184. 250.

———. 1911. Sur les modifications histologiques de la bourse de Fabricius a la suite du jeûne. *Ibid.*, 71: 323-325. 265.

———. 1914. Modifications des ganglions lymphatiques à la suite du jeûne. *Ibid.*, 76: 146-149. 266, 275, 280.

- . 1920. Modifications histologiques de la moelle osseuse dans l'inanition. *Ibid.*, 83: 899-900. **136, 137.**
- . 1924. Le noyau cellulaire et les réserves nucléaires dans l'inanition. *Bull. Acad. de méd., Par.*, 91: 742-745. **266, 341.**
- et Levin, S. 1911. Sur les modifications de poids des organes lymphoïdes à la suite de jeûne. *Ibid.*, 71: 320-323. **265, 295.**
- . 1911a. Sur les modifications histologiques du thymus à la suite de jeûne. *Ibid.*, 71: 374-377. **295.**
- . 1912. Evolution des corpuscules de Hassall dans le thymus de l'animal jeuneur. *Ibid.*, 72: 642-644. **295.**
- . 1912a. Sur les modifications histologiques de la rate à la suite du jeûne. *Ibid.*, 72: 829-831. **275, 278.**
- Jomier, J. 1905. Contribution à l'étude du foie digestif. *Th. méd., Par.*, 107 pp. **336.**
- Jones, J. 1856. Investigations, chemical and physiological, relative to certain American vertebrata. *Smithsonian Contrib. to Knowledge, Vol. 8, Chapt. 3*, 137 pp. **249, 331.**
- W. J. 1889. Criminal neglect; death from inanition; autopsy. *Virginia Med. Monthly*, 16: 709-711. **81.**
- Jonson, A. 1909. Studien über Thymusinvolution. Die accidentelle Involution bei Hunger. *Arch. f. mikr. Anat.*, 73: 340-443. 2 Taf. u. 11 Fig. (Also in *Upsala Läkaref. Förhandl.*, 1908, N. F., Bd. 13, H. 6.) **294.**
- Joukowsky, D. 1898. Beiträge zur Frage nach den Bedingungen der Vermehrung und des Eintritts der Conjugation bei den Ciliaten. (Dissert.) *Verhandl. d. naturhist. u. med. Vereins zu Heidelberg, N. F.*, 6: 22-. (Cited by Wallengren '01.) **17, 20.**
- Juaristi, V. 1919. (The rachitic penis.) *Arch. espanol. de pediatri.*, 3: 286-ff. (Cited by Funk '22.) **215, 413,**
- Judson, S. E. 1916. Changes in the ash content of the white mouse in relation to diet and growth. *Dissert., Yale Univ.* (Cited by Thompson & Mendel '18.) **89, 120.**
- Juergens. 1916. Besteht ein Zusammenhang der Oedemkrankheit in den Kriegsgefangenenlagern mit Infektionskrankheiten? *Berl. klin. Wchnschr.*, 53: 210-213.
- Jundell, I. 1922. Pathogenesis and treatment of rachitis. *Acta paediatr.*, 1: 355-380. (Abstr. in *J. Am. M. A.*) **109.**
- Just, J. 1909. Ueber den Einfluss verschiedener Nährstoffe auf die Zahl der Blutkörperchen bei Pflanzenfressern mit einfachem Magen. *Centralbl. f. Physiol.*, 23: 379-391.
- Kaeding, K. 1922. Alter und Fettpolsterdicke als alleiniger Massstab für den Ernährungszustand. *Münch. med. Wchnschr.*, 69: 433-434. **122.**
- Kaellmark, F. 1911. Zur Kenntnis des Verhaltens der weissen Blutkörperchen bei Inanition. *Folia haematol.*, 11: 411-429. 3 Taf. **251, 252, 295.**
- Kagen (Kagan or Kahan), 1883 or 1884. (Blood and blood pressure in starving animals.) *Russian thesis, St. Petersburg*, 103 pp. (Cited by Mühlmann '99 and Bardier '13 as "Kahan, 1883;" and by Ash '15 as "Kagen 1884.") **250.**
- . 1885. (Influence of starvation upon the body weight in animals refed after a period of inanition.) (Russian.) *Russ. Med.*, 10: 327-329; 343-345; 363-364. **70, 94.**
- . 1886. (Wiederholtes acutes Hungern.) *Russ. Med.*, No. 26-27. (Abstr. by Mühlmann '99.) **94.**
- . 1886a. (Mit Auffütterung abwechselnde acute experimentelle Inanition.) *St. Petersburg. med. Wchnschr.*, N. F., 275-278. (Cited by Morgulis '12.) **94.**
- . 1904. (Study of intermittent starvation and refeeding.) (Russian.) *Trans. IX. Pirogoff-Congress, Sect. Gen. Path.* (Abstr.), pp. 129-130. **94.**
- . 1904a. (Influence of starvation upon the maturation and laying of eggs.) (Abstr.) *Ibid.*, p. 130. **394.**
- Kahle, H. 1913. Histologische Untersuchungen über Veränderungen der Magendrüsenzellen bei der Landschildkröte (*Testudo graeca*) während verschiedener Verdauungsstadien. *Arch. f. d. ges. Physiol.*, 152: 129-167. 2 Taf. u. 10 Fig. **310.**

Kammerer, P. 1912. Experimente über Fortpflanzung, Farbe, Augen, und Körperreduktion bei *Proteus anguineus* Laur. (Zugleich: Vererbung erzwungener Farbeveränderungen. III.). Arch. f. Entw. d. Org., 33: 349-461. 4 Taf. 92, 94, 135, 215.

———. 1913. Verebung erzwungener Farbeveränderungen. IV. Mitt. Das Farbekleid des Feuersalamanders (*Salamandra maculosa* Laurente) in seiner Abhängigkeit von der Umwelt. *Ibid.*, 36: 4-193. 15 Taf. 121, 395, 409.

Karger, P. 1920. Zur Kenntnis der zerebralen Rachitis. Monatschr. f. Kinderh., 18: 21-26. 188.

Karr, W. G. 1920. Some effects of water-soluble vitamin upon nutrition. J. Biol. Chem., 44: 255-277. (Cf. also *ibid.*, 44: 277-282. (Cited by Sherman & Smith '22.) 113, 207.

Kartschagin, L. 1889. (Beiträge zur Lehre über die relative Trockenernährung. Einfluss der beschränkten Wasserzugabe auf den quantitativen und qualitativen Stoffwechsel, auf die Assimilierung des Stickstoffs der Nahrung, auf die Perspiration und Wassersecretion des Organismus gesunder Leute.) Russian thesis, St. Petersburg. (Abstr. by Mühlmann '99.)

Kasanzeff (Kasanzev), W. 1901. Experimentelle Untersuchungen über *Paramecium caudatum*. Diss. phil., Zürich, 60 pp. 2 Taf. (Abstr. in Jahresb. d. Anat. etc., 1902, T. 1, pp. 54; 59-60; and by Erdmann '08.) 17, 20.

Kassowitz, M. 1878. Die Bildung und Resorption des Knochengewebes und das Wesen der rachitischen Knochenerweichung. Zentralbl. f. d. med. Wiss., Nr. 44. (Cited by Wohlauey '11.) 146.

———. 1882-1885. Die normale Ossification und die Erkrankungen des Knochensystems bei Rachitis und hereditärer Syphilis. II. Theil: Rachitis. 1. Abt. (1882), 151 pp. 4 Taf.; 2. Abt. (1885), Die Pathogenese der Rachitis, 148 pp. W. Braunmüller, Wien. 145, 146.

———. 1912. Ueber Rachitis. II. Osteochondritis rachitica. Jahrb. f. Kinderh., 75: 194-212; 334-349; 489-505; 581-600. 15 Fig. 145, 236.

Kato, G. & Shizume, S. 1919. Physiologic and pathologic examination of nerves and muscles of domestic fowls suffering from so-called "polished rice disease." Jap. Med. World, Nov. 23, No. 210. (Cf. also Paguchi, *ibid.*, 1919, Dec. 14, No. 313.) (Cited by Funk '22.) 171, 207.

Kauffman, A. B. 1922. Deficiency diseases of the ear, nose and throat. 1, Otosclerosis. 2, Hyperplastic ethmoiditis. Laryngoscope, 32: 50-55. 142.

———. Creekmur, F. & Schultz, O. T. 1923. Changes in the temporal bone in experimental rickets: their relation to otosclerosis. J. Am. M. A., 80: 681-685. 5 figs. 142.

Kaufman, L. 1918. Researches on the artificial metamorphosis of axolotls. Bull. Acad. Sc., Cracovie, pp. 32-75. (Cited by Morgulis '23.) 77.

Kawamura, R. 1911. Die Cholesterinverfettung (Cholesterinsteatose). Ein differentialdiagnostische morphologische Studie über die in den menschlichen und tierischen Geweben vorkommenden Lipoide. Verlag G. Fischer, Jena. 418, 423.

Kayser, R. 1879. Ueber mikroskopische Veränderungen der Leberzellen während der Verdauung. Bresl. ärztl. Ztschr., 1: 185. Also in article by R. Heidenhain in Hermann's Handb., Bd. 5, Abth. 1. (Abstr. by Afanassiew '83.) 331.

Kehrer, F. A. 1870. Ueber die Ursachen der Gewichtsveränderungen bei Neugeborenen. Arch. f. Gyn., 1: 124-145. (Cf. also Kézmarszky, *ibid.*, 5: 547-ff.) 80, 81.

———. 1910. Die Ursachen des Infantilismus. Beitr. z. Geburtsh. u. Gyn., 15: 222-225.

———. 1911. Zwergwuchs. *Ibid.*, 16: 462-474.

Keilhack, v. L. 1906. Zur Biologie des *Polyphemus pediculus*. Zool. Anz., 30: 911-912. (Cited by Shull '11.)

Keilmann, K. 1923. Ueber das reguläre Thymusgewicht kranker und gesunder Säuglinge und Kinder im zweiten Lebensjahr und die Beziehungen des Thymusgewichts zu den Nebenieren. Ztschr. f. Kinderheilk., 35: 25-37. 2 Fig. 292.

Keith, N. M. 1922. Blood volume changes following water abstinence. Proc. Am. Physiol. Soc., Am. J. Physiol., 59: 452-453. 260.

- Rowntree, L. G. & Geraghty, J. T. 1915. A method for the determination of plasma and blood volume. *Arch. Int. Med.*, 16: 547-576.
- Kellaway, C. H. 1921. The effect of certain dietary deficiencies on the suprarenal glands. *Proc. Roy. Soc. Lond., Ser. B*, 92: 6-27. 432.
- Keller, C. 1887. Die Wirkung des Nahrungsentzuges auf *Phylloxera vastatrix*. *Zool. Anz.*, 10: 583-588. 29, 61.
- Kellner, O. 1887. Chemische Untersuchungen über die Ernährung und Entwicklung des Seidenspinners (*Bombyx mori*). *Landw. Versuchst.*, vol. 33. (Cited by Kopeč '24.) 63.
- . 1916. Die Ernährung der landwirthschaftlichen Nutztiere. 7. Aufl., Berl. 141.
- Kellogg, V. L. & Bell, R. G. 1903. Variations induced in larval, pupal and imaginal stages of *Bombyx mori* by controlled varying food supply. *Science, N. S.*, 18: 741-748. 29, 63.
- . 1904. Notes on insect bionomics. *J. Exp. Zool.*, 1: 357-367. 29, 63.
- Kerb, H. 1910. Ueber den Nährwert der im Wasser gelösten Stoffe. *Internat. Rev. d. ges. Hydrobiol. u. Hydrogr.*, 3: 496-505. 59.
- Kerhervé, L. B. de. 1892. De l'apparition provoquée des éphippies chez les Daphnies. (*Daphnia magna*). *Mém. Soc. Zool. France*, 5: 227-236. 29, 58.
- Kettner, A. H. 1916. Die offene Säuglingsfürsorge in Krieg und Frieden. *Ztschr. f. Säuglingsschutz*, 8: 1-14; 67-92. 79.
- . 1916a. Zur Frage der "Kriegsneugeborenen." *Ibid.*, pp. 329-334. 79.
- Keuthe, W. 1907. Ueber die funktionelle Bedeutung der Leukocyten im zirkulierenden Blute bei verschiedener Ernährung. *Deut. med. Wchnschr.*, 33: 588-592. 252.
- Khainski—see Chainsky.
- Kieseritzky, G. 1902. Experimentelle Untersuchungen über die Einwirkungen von Nahrungsentziehung auf das Blut. *Deut. Aerzte-Zeitung*, pp. 73-77. 251.
- Kilbourne, E. D. 1910. Preliminary report of multiple neuritis of fowls due to inanition. *Bull. Manila Med. Soc.*, 2: 238.
- Kimura, O. 1919. Histologische Degenerations- und Regenerationsvorgänge im peripherischen Nervensystem. *Mitth. Path. Inst. Univ. Sendai, Japan*, 1: 1-160. 5 pl. (Cited by Funk '22.) 207.
- King, H. D. 1907. Food as a factor in the determination of sex in amphibians. *Biol. Bull.*, 13: 40-56. 2 figs. 80.
- . 1915. On the weight of the albino rat at birth and the factors that influence it. *Anat. Rec.*, 9: 213-231. 78.
- . 1916. On the postnatal growth of the body and of the central nervous system in albino rats that are undersized at birth. *Ibid.*, 11: 41-52.
- . 1918. Studies on inbreeding. I. The effects of inbreeding on the growth and variability in the body weight of the albino rat. *J. Exp. Zool.*, 26: 1-54. 157, 396.
- . 1921. A comparative study of the birth mortality in the albino rat and in man. *Anat. Rec.*, 20: 321-353. 78.
- Kintschitz (Okintschitz), E. O. 1893. Ueber die Zahlenverhältnisse verschiedener Arten weisser Blutkörperchen bei vollständiger Inanition und bei nachträglicher Auffütterung. *Arch. f. exp. Path. u. Pharmak.*, 31: 383-397. (Cited by Bardier '13.)
- Kissel, A. A. 1897. Ueber die Häufigkeit der englischen Krankheit in Moskau bei Kindern unter 3 Jahren. *Arch. f. Kinderh.*, 23: 270-291. 108.
- Kitamura, S. 1910. Ein Beitrag zur Kenntnis der Netzveränderung beim Skorbut. *Deut. med. Wchnschr.*, 36: 403-404. 221.
- Kitt. 1918. Lehrbuch der allgemeinen Pathologie für Tierärzte. 4. Aufl., Stuttgart, 593 pp. 227.
- Kittelson, J. A. 1920. Effects of inanition and refeeding upon the growth of the kidney in the albino rat. *Anat. Rec.*, 17: 281-296. 381.
- Klebs, G. 1895. Ueber einige Probleme der Physiologie der Fortpflanzung. *Jena*, 26 pp. (Cited by Geddes & Thomson '01.) 3.

- . 1896. Die Bedingungen der Fortpflanzung bei einigen Algen und Pilzen. Jena. (Cited by Geddes & Thomson '01.) 3.
- . 1903. Willkürliche Entwicklungs-Veränderungen bei Pflanzen. Jena. (Cited by Schultze '03.) 3.
- Kleinenberg, N. 1872. Hydra. Eine anatomischentwicklungsgeschichtliche Untersuchung. W. Engelmann, Lpz., 90 pp. 4 pl. 35.
- Klose, E. 1913. Zur Kenntnis der Körperzusammensetzung bei Ernährungsstörungen. Verhandl. d. Ges. f. Kinderh. zu Münster (1912), pp. 268-272. 1 Taf. 122, 140, 170.
- Knack, A. V. u. Neumann, J. 1917. Beiträge zur Oedemfrage. Deut. med. Wchnschr., pp. 901-906. Also (abstr.) in Lancet, 1917, 2: 248. 254.
- Knapp, P. 1908. Experimenteller Beitrag zur Ernährung von Ratten mit künstlicher Nahrung und zum Zusammenhang von Ernährungsstörungen mit Erkrankung der Conjunctiva. Ztschr. f. exp. Path. u. Therap., 5: 147-169. 1 Taf. 216.
- Knoll, P. 1880. Ueber Myokarditis und die übrigen Folgen der Vagussektion bei Tauben. Ztschr. f. Heilk., 1: 255-315. 167, 230, 231.
- . 1889. Lesioni dei muscoli striate nella inanizione, nello avvelenamento per fosforo, nella paralisi. Rif. med., Roma, 5: 1583-ff. (Cited by Coen '90.) 167.
- u. Hauer, A. 1892. Ueber das Verhalten der protoplasmaarmen und protoplasmareichen quergestreiften Muskelfasern unter pathologischen Verhältnissen. Sitzungsber. d. k. Akad. d. Wiss., math.-naturw. Cl., Wien, Bd. 101, Abt. 3, pp. 315-348. 8 pl. (Cited by Bullard '12.) 167.
- Knop. 1864. (Cited by v. Liebig '76.) 10.
- Koch, M. & Voegtlin, C. 1916. Chemical changes in the central nervous system as a result of a restricted vegetable diet. U. S. Hyg. Lab., Bull. No. 103, pp. 5-49. 187, 199.
- Koehler, H. 1919. Ueber Kriegsamennorrhöe. Zentralbl. f. Gyn., 43: 359-368. 9 Fig. 391, 392, 400.
- R. 1917. Ovarienbefund bei Kriegsamennorrhöe. Gyn. Rundschau, 11: 315-317. 391, 392.
- . 1918. Ovarienbefunde bei "Kriegsamennorrhöe." Zentralbl. f. Gyn., 42: 250-255. 391, 392, 400.
- Koelliker, A. 1889. Handbuch der Gewebelehre. 6. Aufl., 1: 297ff. 136.
- Koelsch, K. 1902. Untersuchungen über die Zerfliessungserscheinungen der ciliaten Infusorien. Zool. Jahrb., Abt. Anat. u. Ontog. d. Tiere., 16: 273-422. 3 Taf. u. 5 Fig. 24.
- Koepchen, A. 1919. Ueber die gegenwärtigen Kriegsknochenkrankungen. Zentralbl. f. inn. Med., 40: 961-973. 136.
- Kohl, F. G. 1886. Die Transpiration der Pflanzen und ihre Einwirkung auf die Ausbildung pflanzlicher Gewebe. Braunschweig. (Cited by Palladin '18.) 6, 7.
- Kohlschütter, E. 1887. Veränderung des allgemeinen Körpergewichts durch Krankheiten. Volkmann's Samml. klin. Vorträge, No. 303 (Inn. Med. No. 103). 3 Taf. 73.
- Kohman, E. A. 1919. A preliminary note on the experimental production of edema as related to "war dropsy." (Abstr.) Proc. Soc. Exp. Biol. & Med., 16: 121. 102.
- . 1920. The experimental production of edema as related to protein deficiency. Am. J. Physiol., 51: 185; 378-405. 102, 170, 255, 267, 384, 413.
- Koiransky, E. 1904. Ueber eigentümliche Gebilde in den Leberzellen der Amphibien. Anat. Anz., 25: 435-455. 336.
- Kolster, R. 1911. Mitochondrien und Sekretion in den Tubuli contorti der Niere. Eine experimentelle Studie. Beitr. z. path. Anat. etc., 51: 209-226. 1 Taf. 384, 388.
- Kon, Y. & Okazaki, M. 1917. On the contribution to the disease of pigeon due to partial inanition. Sei-I-Kwai Med. J., Tokyo, 36: 91-100.
- Konstantinovitsch. 1903. (On the question of fatty degeneration.) Russian thesis, Kieff. (Cited by Beeli '08.) 121, 168, 231, 318, 335, 351, 366, 407, 423.
- Kopeć, S. 1921. L'influence de l'inanition sur le développement et la durée de la vie des Insects. Mem. de l'Inst. Nat. Polonais d'Econ. Rurale a Pulawy, vol. 1. (Cited by Kopeć '24.)

- . \* 1922. Further research on the influence of inanition on the development of animals. Experiments on tadpoles. *Ibid.*, vol. 3 (2?). (Cited by Kopeč '24.) 77.
- . 1922a. Experimental studies on the influence of inanition on the development and weight of amphibians. *Bull. Acad. Pol. des Sc., Cl. Sc. Math. et Nat., Ser. B, Cracovie*, pp. 149-171. 77.
- . 1924. Studies on the influence of inanition on the development and the duration of life in insects. *Biol. Bull.*, 46: 1-21. 63.
- . 1924a. On the heterogeneous influence of starvation of male and female insects on their offspring. *Ibid.*, pp. 22-34. 63.
- Korenchevsky, V. 1921. Experimental rickets in rats. *Brit. Med. J.*, 2: 547-550. (Also in *N. Y. Med. J. & Med. Rec.*, 1922, 115: 612.) 148.
- . 1922. The influence of parathyroidectomy on the skeleton of animals normally nourished, and on rickets and osteomalacia produced by deficient diet. *J. Path. & Bact.*, 25: 366-392. 2 pl. 145, 148.
- . 1922a. The aetiology and pathology of rickets from an experimental point of view. *Med. Research Council, Lond., Special Rep. Ser., No. 71*, 172 pp. 18 pl. 148.
- . 1923. The influence of the parents' diet before conception and during pregnancy and lactation upon the young of the rat. *Proc. XI Internat. Physiol. Congr. in Edinburgh. Quart. J. Exper. Physiol., Suppl. vol.*, pp. 158-160. 105, 112.
- . 1923a. Glands of internal secretion in experimental avian beriberi. *J. Path. & Bact.*, 26: 382-388. (Abstr. *J. Am. M. A.*, 81: 1474.) 284, 299, 432.
- & Carr, M. 1923. Influence of mother's diet during pregnancy and lactation on growth, general nourishment and skeleton of young rats. *Ibid.*, 26: 389-398. (Abstr. *J. Am. M. A.*, 81: 1474.) 148.
- Kornfeld, W. 1922. Ueber den Zellteilungsrythmus und seine Regelung. *Arch. f. Entw. d. Org.*, 50: 526-592. 29 Fig. 215.
- Korsakov, N. 1892. Sur la réproduction artificielle du rachitisme chez quelques animaux. *Intern. Zool. Kongr., Moskau.* (Cited by Lehnerdt '10.) 147.
- Kosiniski, I. 1902. Die Atmung bei Hungerzuständen und unter Einwirkung von mechanischen chemischen Reizmitteln bei *Aspergillus niger*. *Jahrb. wiss. Bot.*, 37: 137-204. (Abstr. in *Jahresb. d. Anat. etc.*, 1902, T. 1, p. 69.) 4.
- Kossel, A. 1882. Zur Chemie des Zellkerns. *Ztschr. f. physiol. Chem.*, 7: 7-22.
- Koun, L. A. M. H. 1903. De la kératomalacie, affection cornéene chez les enfants athrepsiques. Thèse de Bordeaux, 66 pp. (Cited by Ross '21.) 216.
- Kozowski (Kozowsky). 1904. Zur pathologischen Anatomie der Pellagra. *Bechterew's Journ.* (Cf. also Korsakov's *Journ.*, Bd. 1.) (Cited by Raubitschek '15.)
- . 1912. Die Pellagra. *Arch. f. Psychiatr. u. Nervenkr.*, 49: 204-241; 556-613; 873-935. (Cited by Raubitschek '15 and Harris '19.) 187, 200, 206, 232, 236, 267, 281, 322, 342, 385, 431.
- Krahelska, M. 1910. Ueber den Einfluss der Winterruhe auf den histologischen Bau einiger Landpulmonaten. *Jen. Ztschr. f. Naturw.*, 46: 363-444. 3 Taf. 54.
- . 1912. Reduktionserscheinungen in der Eiweissdrüse von *Helix pomatia*. *Vorl. Mitt. Bull. de l'Acad. d. Sc., Cracovie, Juin.* (Cited by Krahelska '13.) 54, 55.
- . 1913. Drüsenstudien. Histologischer Bau der Schneckeneiweissdrüse und die in ihm durch Einfluss des Hungers, der funktionellen Erschöpfung und der Winterruhe hervorgerufenen Veränderungen. *Arch. f. Zellforsch.*, 9: 552-622. 2 Taf. 54-57.
- Kramer, J. G. H. 1720. *Medecina Castrensis.* (Cited by Sherman & Smith '22.) 113.
- Krapfenbauer, A. 1908. Einwirkung der Existenzbedingungen auf die Fortpflanzung von Hydra. *Dissert., Munchen*, 46 pp. (Cited by Koelitz, *Arch. f. Entw. d. Org.*, 31: 199.) 28, 36.
- Kraus, F. 1919. Die Aushungerung Deutschlands. *Berl. klin. Wchnschr.*, 56: 3-4. 71, 102, 398, 400.
- Krause, R. 1911. *Kursus der normalen Histologie.* Berl. u. Wien, 453 pp. 98 pl. (Cited by Bullard '12.) 169.

- Krehl, L. 1890. Ein Beitrag zur Fettresorption. Arch. f. Anat. u. Physiol., Anat. Abt., pp. 97-112. 321.
- . 1893. Ueber fettige Degeneration des Herzens. Deut. Arch. f. klin. Med., 416-450. 229.
- Krieger, M. 1920. Ueber die Atrophie der menschlichen Organe bei Inanition. Ztschr. f. angew. Anat. u. Konstitutionsl., 7: 87-134. 175, 225, 229, 271, 326, 327, 347, 372, 373, 405, 419, 428, 436, 449.
- Kriznecky, J. 1914. Ueber die beschleunigende Einwirkung des Hungers auf die Metamorphose. Biol. Centralbl., Bd. 34. (Cited by Kopec '24.) 64.
- Kubli, T. 1887. Zur Lehre von der epidemischen Hemeralopie. Arch. f. Augenh., 17: 409-411. (Cited by Blegvad '24.) 211, 216.
- Kuckein, F. 1882. Beitrag zur Kenntniss des Stoffverbrauchs beim hungernden Huhn. Ztschr. f. Biol., 18: 17-40. 70, 462.
- Kudo, T. 1921. Studies on the effects of thirst. I. Effects of thirst on the weights of the various organs and systems of adult albino rats. Am. J. Anat., 28: 399-430. 115, 132, 154, 172, 190, 202, 209, 221, 235, 284, 299, 312, 344, 355, 370, 368, 388, 416, 434, 445, 456, 474.
- . 1921a. Studies on the effects of thirst. II. Effects of thirst upon the growth of the body and of the various organs in young albino rats. J. Exp. Zool., 33: 435-461. 116, 132, 155, 172, 190, 202, 209, 221, 235, 237, 284, 299, 312, 344, 355, 360, 369, 399, 402, 416, 434, 445, 456, 475.
- Kuetting, A. 1921. Ueber die Geburtsgewichte und Entwicklung der Kinder in den ersten Lebenstagen, sowie ueber die Stillfähigkeit während des Krieges. Zentralbl. f. Gyn., 45: 166-171. 81, 129.
- Kulagin, M. M. 1898. Zur Frage über den Bau des Magens bei der Fledermaus (*Vesperugo abramus*) und der Zieselmäusen (*Spermophilus citellus*) und des Blutes bei letzteren während des Winterschlafes. Le Physiologiste Russe, Vol. 1, No. 3-7, 5 pp. (Cited in Jahresb. d. Anat. etc., 1898, T. 3, p. 168.)
- Kulisch, G. 1891. Die Veränderungen der Gewebe durch Inanition. Thesis, Halle a. S., 44 pp.
- Kumagawa, M. 1894. Aus dem Mitteil. d. med. Fak. d. K. Japan. Univ., Tokio, 6: 1-ff. (Cited by E. Voit '05.) 164.
- u. Miura, R. 1898. Zur Frage der Zuckerbildung aus Fett im Tierkörper. Arch. f. Physiol., pp. 431-450. (Cited by Weber '02.) 462.
- Kuniziki, R. V. 1904. (Ueber den Dünndarmsaft des Rindes.) Compt. rend. trav. spéc. Inst. vétar. à Kharkoff, 6: 397-ff. (Abstr. by Weinberg '07.) 318.
- Kunkel, A. J. 1887. Studien über die quergestreifte Muskelfasern. Festschr. A. v. Kölliker, pp. 225-234. 167, 168.
- . 1895. Blutbildung aus anorganischen Eisen. Arch. f. d. ges. Physiol., 61: 595-606. 256.
- Kuriyama, S. 1918. The adrenals in relation to carbohydrate metabolism. III. The epinephrin content of the adrenals in various experimental conditions. J. Biol. Chem., 34: 299-319. 427.
- Kusmin. 1896. (Ueber die Bedeutung der Hyperthermie bei verschiedenen Formen des Hungerns.) (Russian.) Russ. Arch. f. Path., Bd. 1. (Abstr. by Maximow u. Korowin '00.) 228, 231, 275, 306, 334, 365, 378.
- Kuttner, O. 1909. Untersuchungen über Fortpflanzungsverhältnisse und Vererbung bei Cladoceren. Internat. Rev. d. ges. Hydrobiol. u. Hydrogr., Bd. 2. (Cited by Green '19.)
- Kux, L. 1886. Ueber die Veränderungen der Froschleber durch Inanition. Dissert., Würzburg, 14 pp. 333.
- Kyber. 1813. Erfahrungen über Blattläuse. Germar's Mag. d. Entomol. (Cited by Nussbaum '98.) 29.
- Labbé, H. 1908. L'inanition; see aspects physiologiques et sociaux. Rev. scient., Par., 5. s., 9: 545-552.

- Laborde, J.-V. 1886. Du rôle de l'eau potable dans l'inanition. *Compt. rend. Soc. de biol., Par.*, 8. S., 3: 632-636. Also in *Trib. méd., Par.*, 1887, 19: 4-6. **94.**
- Lackschewitz, P. 1893. Untersuchungen über die Zusammensetzung des Blutes hungerrnder und durstender Thiere. *Dissert., Dorpat.* **241, 250.**
- Laguesse, E. 1899. Sur la variabilité du tissu endocrine dans le pancréas. *Compt. rend. Soc. de biol., Par.*, 51: 900-903. **345, 351.**
- . 1909. Preuve expérimentale du balancement dans les îlots endocrines du pigeon. *Ibid.*, 67: 94-96. **345, 351.**
- . 1909a. Sur l'évolution des îlots endocrines dans le pancréas de l'homme adulte. *Arch. d'anat. micr.*, 11: 1-93. 3 pl. **345, 346, 351.**
- Lahmann, H. 1891. Ueber den Einfluss der Diätetik in der Schwangerschaft auf die Grösse der Frucht. *Internat. klin. Rundschau*, 5: 1759-1760; 1801-1803. Also in *Frauenarzt*, 1892, 7: 67-75.
- Lahousse, E. 1887. Contribution à l'étude des modifications morphologiques de la cellule hépatique pendant la sécrétion. *Arch. de biol.*, 7: 167-185. 1 pl.
- Laignel-Lavastine et Jonnesco, V. 1912. Dégénérescence lipoidique de la cellule de Purkinje. *Compt. rend. Soc. de biol., Par.*, 73: 52-55. **185, 333.**
- Lambert, R. A. & Yudkin, A. M. 1923. Changes in the paraocular glands accompanying the ocular lesions which result from a deficiency of vitamin A. *J. Exp. Med.*, 38: 25-32. 4 pl. **219.**
- LaMer, V. K. & Campbell, H. L. 1920. Changes in organ weight produced by diets deficient in antiscorbutic vitamin. *Proc. Soc. Exp. Biol. & Med.*, 18: 32. **234, 343, 380, 433.**
- Landa, E. 1917. (Deficiency edema.) *Gaceta méd., Mexico*, 11: 67. (Abstr. in *J. Am. M. A.*, 1918, 78: 424.) **71, 254.**
- Landau, M. 1910. Zur Frage der Fettdegeneration der quergestreiften Muskelfasern. *Arb. a. d. neurol. Inst., Wiener Univ.*, 18: 294-311. **166.**
- . 1913. Nebenniere und Fettstoffwechsel. *Deut. med. Wchnschr.*, 39: 546-549. **419, 433.**
- Landauer, A. 1895. Ueber den Einfluss des Wassers auf den Organismus. *Ung. Arch. f. Med.*, 3: 136-188. (Cited by Rosenstern '11.)
- Landé, L. 1919. Entwicklung und Schicksal der im Kaiserin Auguste Victoria Haus geborenen Kinder. *Ztschr. f. Kinderh.*, 20: 1-74. **129.**
- Landsberger. 1887. Das Wachstum im Alter der Schulpflicht. *Biol. Centralbl.*, 7: 281-288; 311-320. **83.**
- Lang, P. 1912. Ueber Regeneration bei Planarien. *Arch. f. mikr. Anat.*, 79: 361-426. **44, 204.**
- de Lange, C. 1900. Zur normalen und pathologischen Histologie des Magendarmkanals beim Kinde. *Jahrb. f. Kinderh.*, 51: 621-649. 1 Taf. **315.**
- Lange, F. 1917. Ueber das Auftreten eigenartiger Oedemzustände. *Deut. med. Wchnschr.*, pp. 876-878. (Also abstr. in *Lancet, Lond.*, 1917, 2: 248.) **71, 102, 236, 254.**
- . R. u. Feldmann, H. 1921. Herzgrößenverhältnisse gesunder und kranker Säuglinge bei Röntgendurchleuchtung. *Deut. med. Wchnschr.*, 47: 960-961. **226.**
- Langendorff, O. 1886. Untersuchungen über die Zuckerbildung in der Leber. *Arch. f. Anat. u. Physiol., Physiol. Abt., Suppl. Bd.*, pp. 269-292. 1 Taf. **341.**
- Langley, J. N. 1882. Preliminary account of the structure of the cells of the liver, and the changes which take place in them under various conditions. *Proc. Roy. Soc., Lond.*, 34: 20-26. **332, 341.**
- . 1886. On variation in the amount and distribution of fat in the liver-cells of the frog. *Ibid.*, 39: 234-238. **332, 341.**
- Langstein L. u. Edelstein, F. 1917. Die Rolle der Ergänzungsstoffe bei der Ernährung wachsender Tiere. Ernährungsversuche an jungen wachsenden Ratten. *Ztschr. f. Kinderh.* 16: 605-f. (also *ibid.*, 1918, 17: 255-327.) (Cited by Abderhalden '19.) **110.**
- Lasarew—see Lazareff.
- Lascoux, P. 1908. Étude sur l'accroissement du poids et de la taille des nourrissons. Croissance physiologique. Anomalies de la croissance. *Thèse méd., Par.*, 76 pp. **91, 135.**

Lasègue, C. et Legroux, A. 1871. L'épidémie de scorbut dans les prisons de la Seine et a l'Hôpital de la Pitié. Arch. gén. de méd., Par., 2: 5; 680. (Cited by Hess '20 and Findlay '21a.) 132.

Lassablière. 1908. (Cited by Lascoux '08.) 89.

Lazareff (Lasarev), N. S. 1895. (On the study of the change in weight and cellular elements of several organs and tissues in various periods of complete starvation.) Russian dissert., Warsaw, 80 pp. 70, 118, 134, 179, 192, 227, 275, 306, 317, 334, 350, 365, 378, 462, 468, 469.

———. 1897. (Der tägliche Gewichtsverlust und die Temperaturabnahme bei hungernden Tieren in verschiedenen Perioden des vollständigen Hungerns.) Russ. Arch. f. Path. etc., 3: 399-ff. (Abstr. by Mühlmann '99.) (Cf. 3: 390-413; 423-425.)

Lazarus, A. 1913. Klinik der Anaemien. In "Die Anaemie" von Ehrlich u. Lazarus, Bd. 2, Aufl. 2. (In Nothnagel's spez. Path. u. Therap., Bd. 7.) Wien u. Lpz. 244, 256.

Lebard. 1886. (Cited by Pernice u. Scagliosi '95.)

Lebedew, S. 1887. (Zur Frage über das minerale Hungern.) Russian thesis, St. Petersburg. (Cited by Mühlmann '99.)

Lebrun, H. 1902. La vésicule germinative et les globules polaires chez les batraciens. Cellule, 20: 1-99. 4 pl. 393.

Lefholz, R. 1923. The effects of diets varying in calorie value and in relative amounts of fat, sugar and protein upon the growth of lymphoid tissue in kittens. Am. J. Anat., 32: 1-35. 15 figs. (Also abstr. in Proc. Am. Assn. Anat., Anat. Rec., 25: 140.) 266, 267, 281, 298, 303, 322.

Legendre, R. 1909. Contribution à la connaissance de la cellule. La cellule nerveuse d'*Helix pomatia*. Arch. d'anat. micr., 10: 287-554. 2 pl. 54.

———. 1913. A propos du pigment des cellules nerveuses d'*Helix pomatia*. Compt. rend. Soc. de biol., Par., 74: 262-263. 54.

Legge, F. 1899. Sulle variazioni della fine struttura che presentano, durante l'ibernazione, le cellule cerebrali dei pipistrelli. Monit. zool. ital., 10: 152-159. 185, 197, 198.

Lehmann. 1878. (Cited by Schabad '10 from Maly's Jahrb., p. 272.) 145.

——— C, Müller, F., Munk, I., Senator, H. u. Zuntz, N. 1893. Untersuchungen an zwei hungernden Menschen. Arch. f. path. Anat. etc., Suppl. zum. 131. Bd., pp. 1-228. 1 Taf. 242.

Lehndorff, H. 1907. Ueber das Wangenfettpolster der Säuglinge. Jahrb. f. Kinderh., 66: 286-299. 123.

Lehnerdt, F. 1909. Zur Frage der Substitution des Calciums im Knochensystem durch Strontium. Beitr. z. path. Anat. etc., 46: 468-572. 3 Taf. 148.

———. 1910. Warum bleibt das rachitische Knochengewebe unverkalkt? Ergeb. d. inn. Med. u. Kinderh., 6: 120-191. 107, 144, 145, 148.

v. Lenhossek, M. 1903. Das Problem der geschlechtsbestimmenden Ursachen. G. Fischer, Jena, 99 pp. (Cited by O. Schultz '03.)

Lenoble, E. 1908. Recherches sur les réactions sanguines dans les anémies et les états infectieux de l'enfance, surtout accompagnés de gros foie et de grosse rate. Arch. de méd. expér. et d'anat. path., 20: 88; 336. (Cited by Nobécourt '16.) 248.

Lenssen. 1898. Contribution à l'étude du développement et de la maturation des oeufs chez l'*Hydatina senta*. Cellule, 14: 421-451. 28, 57.

Leonard, Alice. 1887. Der Einfluss der Jahreszeit auf die Leberzellen von *Rana temporaria*. Arch. f. Anat. u. Physiol., Physiol. Abt., Suppl. Bd., pp. 28-47. 1 Taf. 250, 341.

——— H. J. 1920. School dental clinic at Virginia and Eveleth. Minn. Publ. Health Assn. J., 4: 495-496. 157.

Lépine, R. 1874. Article "Inanition" in N. dict. de méd. et chir. prat., Par., 18: 473-512. 167, 230, 331, 376, 422.

———. 1875. De l'influence de la privation de nourriture sur la croissance chez les cobayes. Compt. rend. Soc. de biol., Par. (1874) 26: 351-352.

———. 1875a. De l'influence de la croissance sur la perte de poids chez les jeunes animaux privés de nourriture. *Ibid.*, pp. 352-353. 94.

- Léri, A. et Beck, T. 1919. Le "petit rachitisme" etc. *Ann. de méd.*, 6: 449-468. (Cited by Funk '22.)
- Lesage, A. 1911. *Traite des maladies du nourrisson*, Par. 81, 91, 120, 135, 142, 151, 178, 236, 248, 290, 315, 329, 363.
- . 1914. *Essai sur les atrophies du nourrisson*. *Méd. inf.*, Par., 11: 32-40. 138, 178, 273, 329, 363, 374, 437.
- et Cléret, M. 1914. *Recherches sur l'anatomie pathologique de l'atrophie spasmodique congénitale du nourrisson*. *Compt. rend. Soc. de biol.*, Par., 76: 369-371. 139, 277, 315, 329, 363, 374, 437.
- Leupold. 1920(?). (Cited by Schilf '22.) 169, 230, 290, 419, 420, 428.
- Levi, G. 1898. *Sulle modificazioni morfologiche della cellule nervosa di animali a sangue freddo durante l'ibernazione*. *Riv. patol. nerv. e ment.*, 3: 443-459. 2 tav. 7 fig. (Abstr. in *Jahresb. d. Anat. etc.*, 1898, T. 1, pp. 180; 247-249.) 185, 198.
- Levin, S. 1912. *Recherches expérimentales sur l'involution du thymus*. *Trav. labor. d'histol.*, Collège de France. Thèse, Par., No. 256, 103 pp. 295.
- Lewaschew, S. W. 1886. *Ueber eine eigenthümliche Veränderung der Pankreaszellen warmblütiger Thiere bei starker Absonderungsthätigkeit der Drüse*. *Arch. f. mikr. Anat.*, 26: 453-485. 1 Taf. 345, 349, 350.
- Lewinski, J. 1903. *Beobachtungen über den Gehalt des Blutplasmas an Serumalbumin, Serunglobulin und Fibrinogen*. *Arch. f. d. ges. Physiol.*, 100: 611-633. 241.
- Lewis, M. R. 1921. *The formation of vacuoles in the cells of tissue cultures owing to the lack of dextrose in the media*. (Abstr.) *Proc. Am. Assn. Anat.*, *Anat. Rec.*, 21: 71. 459.
- R. W. & Pappenheimer, A. M. 1916. *A study of the involutional changes which occur in the adrenal cortex during infancy*. *J. Med. Res.*, 34: 81-93. 421.
- W. H. 1919. *Degenerative granules and vacuoles in the fibroblasts of chick embryos cultivated in vitro*. *Johns Hopkins Hosp. Bull.*, 30: 81-91. 1 pl. 459.
- Leydig. (Date?) *Der Eierstock und Samentasche der Insecten*. *Nova acta, Acad. Leopold.*, 33: 1865. (Cited by Nussbaum '98.) 28, 29, 57, 58.
- Leys, J. F. 1914. *Epidemic dropsy*. In *Ref. Handb. of the Med. Sc.*, 3d ed., W. Wood & Co., N. Y., 3: 696. (Cited by Maver '20.) 71.
- Liberge. (Cited by Kitt '18.) 94.
- von Liebig, J. 1861. *Chemistry in its applications to agriculture and physiology*. Edited from the 4th. Lond. ed. by Playfair & Gregory. J. Wiley, N. Y.
- . 1876. *Die Chemie in ihrer Anwendung auf Agriculture und Physiologie*. 9. Aufl., Braunschweig, 698 pp. 5, 8, 9, 10, 13.
- Lillie, F. R. 1900. *Some notes on regeneration and regulation in planarians*. *Amer. Nat.*, 34: 173-177. 41.
- von Limbeck, R. 1892. *Grundriss einer klinischen Pathologie des Blutes*. Jena. (Cited by Hatai '18.) 242.
- Lind, J. 1753. *A treatise on the scurvy*. Edinb., 456 pp. (Cited by Maver '20.)
- . 1772. *A treatise on the scurvy*. 3d ed., Lond. (Cited by Hess '20.) 150, 268.
- Lindemann, W. 1899. *Ueber pathologische Fettbildung*. *Beitr. z. path. Anat. etc.*, 25: 392-430. 1 Taf. 125, 335.
- von Linden, M. 1907. *Die Veränderungen des Körpergewichts bei hungernden Schmetterlingen*. *Biol. Centralbl.*, 27: 449-457. 62.
- von Lingen, L. 1921. *Kriegsamenorrhöe in Petersburg*. *Zentralbl. f. Gyn.*, 45: 1247-1248. 391, 400.
- Linke, H. 1919. *Ueber die Einflüsse des Krieges auf die Geschlechtsbildung, die Gewichte der Neugeborenen und die Stillfähigkeit der Mütter*. *Dissert.*, Heidelberg, 42 pp. 79, 80.
- Linko, A. 1900. *Observations sur les méduses de la mer blanche*. *Trav. Soc. J. d. Natur. de St. Pétersb.*, Vol. 29, Livr. 4. (Cited by Schultz '04.) 39.
- Lipschütz, A. 1910. *Untersuchungen über den Phosphorgehalt des wachsenden Hundes*. *Arch. f. exp. Path. u. Pharm.*, 62: 210-243. 6 Fig. 106, 109, 142, 148, 153.

- . 1911. Ueber den Hungerstoffwechsel der Fische. *Ztschr. f. allg. Physiol.*, 12: 118-124. **106, 148, 462.**
- . 1911a. Zur Physiologie des Phosphorhungers im Wachstum. *Arch. f. d. ges. Physiol.*, 143: 91-98. **142, 148.**
- . 1913. Die Ernährung der Wassertiere durch die gelösten organischen Verbindungen der Gewässer. (Eine Kritik.) *Ergeb. d. Physiol.*, 13: 1-46. **59.**
- . 1918. Zur allgemeinen Physiologie des Hungers. Heft 26 der Tagesfragen a. d. Gebieten der Naturw. u. d. Technik. Verlag F. Vieweg, Braunschweig, 91 pp. **99.**
- Lipska, I. 1910. Recherches sur l'influence de l'inanition chez *paramecium caudatum*. *Rev. suisse de zool.*, 18: 591-646. 1 pl. (Also Thèse, Sc., Genève, 1910.) **15, 16, 17, 22-25.**
- Lipski, A. A. 1892. (Hunger and the diseases it produces.) (Russian.) *St. Petersb.*, 25 pp.
- Liubomadrow (Luibomudrow, etc.) P. 1893. (Veränderung des Blutes und einiger Organe beim Hungern.) Russian thesis, *St. Petersb.*, 71 pp. (Abstr. by Mühlmann '99.) **250.**
- Livi, R. 1886. *Antropometria*. Milano. (Cited by Guttman '22.) **85.**
- . 1898. L'indice ponderale o rapporto tra la statua et il peso. *Atti Soc. rom. di antrop.*, 5: 125-153. (Cited by Guttman '22.)
- . 1899. L'indice pondérale ou le rapport entre la taille et le poids. *Arch. ital. de biol.*, T. 32. (Cited by Guttman '22.)
- Lodato, G. 1898. Sulle alterazioni oculari nella inanizione. *Arch. di ottalm.*, Palermo, 5: 285-298. 1 pl. (Also abstr. in *Ergeb. d. allg. Path. etc.*, 5: 886-887.) **205, 214.**
- . 1898a. Sulle alterazioni oculari negli animali (cani) sottoposti al digiuno sperimentale. *Acc. med. clin. di Palermo*. 3 Aprile. (Cited by Barbacci '99.) **214.**
- Loeb, J. 1892. Untersuchungen zur physiologischen Morphologie der Tiere. II. Organbildung und Wachstum. Würzburg, 81 pp. 4 Taf. (Cited by Herbst '97.) **39, 52.**
- . 1896. Untersuchung über die physiologischen Wirkungen des Sauerstoffmangels. *Arch. f. d. ges. Physiol.*, 62: 249-294. 2 Taf. **116.**
- . 1905. *Studies in general physiology*. 2 vols. Univ. of Chicago Press. **39, 52.**
- . 1911. The rôle of salts in the preservation of life. *Science*, N. S., 34: 653-665. **52, 59.**
- . 1915. The simplest constituent required for growth and the completion of the life cycle in an insect (*Drosophila*). *Ibid.*, 41: 169-170. **61.**
- . 1915a. The salts required for the development of insects. *J. Biol. Chem.*, 23: 431-434. (Cited by Funk '22.) **61.**
- & Northrup, J. H. 1916. Nutrition and evolution. *Ibid.*, 27: 309-312. (Cited by Funk '22.) **29, 61.**
- . 1917. On the influence of food and temperature upon the duration of life. *Ibid.*, 32: 103-121. **62.**
- L. 1917. Factors in the growth and sterility of the mammalian ovary. *Science*, N. S., 45: 591-592. **397.**
- . 1917a. The experimental production of hypotypical ovaries through underfeeding. A contribution to the analysis of sterility. *Biol. Bull.*, 33: 91-115. **397.**
- . 1921. The effect of undernourishment on the mammalian ovary and the sexual cycle. *J. Am. M. A.*, 77: 1646-1648. **397.**
- Loenne, F. 1918. Schwangerschaft, Geburt- und Wochenbett, Erstgebärender in Kriegs- und Friedenzeiten. *Monatschr. f. Geburtsh. u. Gyn.*, 48: 9-33. **79, 80, 129.**
- Loetsch, E. u. Lange. 1912. Ueber den "Stallmangel," eine eigenartige Rinderkrankheit im sächsischen Erzgebirge. Zur Kenntnis des Mineralstoffwechsels. *Ztschr. f. Inf. u. Hyg. d. Haustiere*, 12: 205-246. 2 Taf. (Cited by Funk '22.) **107, 140.**
- Loew, O. 1891. Ueber die physiologischen Functionen der Phosphorsäure. *Biol. Centralbl.*, 11: 269-281. (Cited by Reed '07.) **7, 8, 9, 10.**
- . 1892. Ueber die physiologischen Functionen der Calcium und Magnesiumsalze im Pflanzenorganismus. *Flora*, 75: 368-394. (Cited by Reed '07.)

Loewy, A. u. Zuntz, N. 1916. Einfluss der Kriegskost auf den Stoffwechsel. Nach Selbstbeobachtungen. Berl. klin. Wchnschr., 53: 825-829.

Loisel, G. 1901. Influence du jeûne sur la spermatogénèse. Compt. rend. Soc. de biol., Par., 53: 836. 407.

Lombroso, C. 1869. Studi clinici ed esperimentale sulla natura, causa e terapia della pellagra. Bologna, 376 pp. 2 pl. Also in Riv. clin. di Bologna, 1869, vol. 8. (Cited by Harris '19.) 187, 199.

———. 1892. Trattato profilattico e clinico della pellagra. Torino, 410 pp. 20 pl. (Cited by Harris '19.) 140, 232, 281, 342, 385.

London, E. S. 1896. (On the change in the general quantity and alkalinity of the blood in complete starvation.) (Russian.) Arch. biol. nauk., St. Petersburg., 4: 516-530. Also transl., Note sur la question du changement de la quantité générale et de l'alkalinité du sang. Arch. de sc. biol., St. Pétersb., 4: 523-537. (Also abstr. by Mühlmann '99.)

———. 1897. (The microbiometer and its application in the study of the phenomena of starvation in bacteria.) (Russian.) Arch. biol. nauk., St. Petersburg., 6: 70-80. Also transl., Le microbiomètre et son application à l'étude des phénomènes d'inanition chez les bactéries. Arch. de sc. biol., St. Pétersb., 6: 71-80. 3.

———. 1899. Contribution à l'étude des corpuscles centraux. Arch. de sc. biol., St. Pétersb., 7: 456-461. (Abstr. in Jahresb. d. Anat. etc., 1899, T. 1, pp. 30; 58-59.)

Longet, F. A. 1868-9. Traité de physiologie, 3d éd., vol. 1-3. Par. (Cited by Pernice u. Scagliosi '95a.) 172.

Looser, E. 1905. Ueber die Knochenveränderungen beim Skorbut. Jahrb. f. Kinderh., 62: 743-768. Also in Münch. med. Wchnschr., 1905, 52: 2345. (Cited by Hess '20.) 145, 151.

———. 1908. Ueber die Spätrachitis und die Beziehungen zwischen Rachitis und Osteomalacie. Mitt. a. d. Grenzgeb. d. Med. u. Chir., 18: 678-744. 2 pl. and 5 Textfig. 145.

———. 1909. Diskussion zu den Vorträgen über Rachitis und Osteomalacie. Verh. d. deut. path. Ges. Centralbl. f. allg. Path. etc., 13: 54-55; 64-65. 145.

———. 1920. Ueber Spätrachitis und Osteomalacie. Klinische, röntgenologische und pathologisch-anatomische Untersuchungen. Deut. Ztschr. f. Chir., 152: 210-357. 31 pl. 44 Textfig. 107, 109.

Looss. 1888. Ueber Degenerationserscheinungen im Thierreich, besonders bei den Wirbelthieren. Tagebl. d. 61. Versamml. deut. Naturf. u. Aerzte zu Köln, pp. 50-54.

Lopez-Lomba, J. 1923. Modifications pondérales des organes chez le pigeon au cours de l'avitaminose. Compt. rend. Acad. des sc., Par., 176: 1417-1419; 1752. 189, 234, 283, 299, 343, 354, 386, 415, 432, 444.

Lorenzen, A. 1887. Ueber den Einfluss der Entwässerung des Körpers auf die Entfettung. Flensburg, J. B. Meyer, 20 pp. 115, 259.

Lossen, J. 1910. Ueber das Verhalten des Knochenmarkes bei verschiedenen Erkrankungen des Kindesalters. Arch. f. path. Anat. etc., 200: 258-320. 137.

Loukianow—see Lukjanow.

Love, H. H. 1909. Influence of food supply on variation. Ann. Rep. Amer. Breeders Assn., 5: 357-364. 4 figs. (Abstr. in Exp. Sta. Rec., 1910, 22: 528.) 4.

Lubarsch, O. 1903. Article "Atrophie" in Eulenberg's Realenzyklopädie.

———. 1921. Zur pathologischen Anatomie der Erschöpfungs- und Unterernährungs-krankheiten. XVIII. Tagung d. deut. path. Ges. in Jena. (Selbstreferat.) Centralbl. f. allg. Path. etc., 31: 563. 71, 360, 385, 413, 442.

———. 1921a. Beiträge zur pathologischen Anatomie und Pathogenese der Unterernährungs- und Erschöpfungs-krankheiten. Beitr. z. path. Anat. etc., 69: 242-251. 125, 244, 255.

Lubimoff. 1894. Retour à l'état normal des cellules nerveuses malades. Rev. neurol., 2: 246. 183.

Lubsen, J. 1917. (State of nourishment of Amsterdam schoolchildren.) Nederl. Tijdschr. v. Geneesk., vol. 2, no. 21, Nov. 24. (Abstr. in J. Am. M. A.) 84.

- de Luca, U. 1905. Ricerche sopra le modificazioni dell'epitelio dei villi intestinali nel periodo di digiuno. *Bull. d. R. Accad. med. di Roma*, 31: 249-261. 321.
- . 1905a. Ricerche sopra le mastzellen dell'intestino nel periodo di assorbimento e nel periodo di digiuno. *Ibid.*, 31: 262-266. 1 tav. 321, 322.
- Lucas. 1824. *Experimenta circa famem*. Diss. inaug., Bonnae, 47 pp. (Cited by Falck '75.)
- . 1826. Ueber den Hunger und die übrigen Folgen der Entziehung von Speisen. *Ztschr. f. d. Anthrop., Lpz.*, 3. Heft, pp. 29-122. 53, 59, 60, 62, 65, 68, 69, 227, 249, 303, 331, 346, 348, 356, 364, 371, 390, 399.
- Luce, E. M. 1923. The size of the parathyroids of rats, and the effect of a diet deficiency of calcium. *J. Path. & Bact.*, 26: 200-206. 1 pl. 447.
- Luciani, L. 1889. *Fisiologia del digiuno*. Studi sull' uomo. Firenze. (Cf. *Arch. ital. de biol.*, 13: 347.) 72, 204, 211, 242, 462.
- . 1890. Das Hungern. Studien und Experimente am Menschen. Uebersetzung von M. O. Fraenkel. Hamburg u. Lpz., 239 pp. 2 Taf. 72, 204, 211, 242.
- e Bufalini, G. 1882. Sul decorso dell'inanizione; ricerche sperimentali. *Arch. per le sc. med., Torino.*, 5: 338-365. 1 tav. 227, 250, 274, 332, 349, 376, 462.
- Lucien, M. 1908. Considérations anatomo-pathologiques sur l'athrepsie. (Note préliminaire.) *Reun. biol. de Nancy, Compt. rend. Soc. de biol., Par.*, 64. 236-238. 227, 289, 315, 328, 363, 374, 420, 423, 428, 437, 449.
- . 1908a. Capsules surrenales et athrepsie. *Ibid.*, 64: 462-464. 420, 423, 428.
- . 1908b. Les lésions rénales dans l'athrepsie. *Ibid.*, 64: 464-466. 374.
- . 1908c. Thymus et athrepsie. *Ibid.*, 64: 559-561. 289.
- . 1908d. Le foie des athrepsiques. *Ibid.*, 64: 744-746. 328.
- Lugaro, L. e Chiozzi, L. 1897. Sulle alterazioni degli elementi nervosi nell'inanizione. *Riv. di patol. nerv. e ment.*, 2: 394-400. 5 fig. 183, 194, 204.
- Luebomudrow—see Liubomadrow.
- Lukjanow (Lukjanoff or Loukianow), S. M. 1888. (Zur Lehre von der Veränderung der Zusammensetzung der Organe und Gewebe in pathologischen Zuständen. I. Ueber den Gehalt an Wasser und festen Bestandtheilen der Organe und Gewebe hungernder Tauben im Vergleich mit normalen.) *Warschauer Universitätsnachr.*, Nos. 6-7. 68 pp. (Abstr. by Mühlmann '99.) 170, 186, 250, 280, 333, 349, 365, 377.
- . 1889. Ueber den Gehalt der Organe und Gewebe an Wasser und festen Bestandtheile bei hungernden und durstenden Tauben. *Ztschr. f. physiol. Chemie*, 13: 339-351. 134, 186, 227, 250, 274, 333, 349, 365, 377.
- . 1892. Ueber die Gallenabsonderung bei vollständiger Inanition. *Ztschr. f. physiol. Chemie*, 16: 87-142. 2 Taf. 333, 334.
- . 1895. *Elements de pathologie cellulaire*, Par. (Cited by Russo '06.)
- . 1896. (Ueber das Hungern. Oeffentl. Vorlesung.) *Arch. des Laboratoriums f. allg. Pathologie*. Warschau. (Cited by Mühlmann '99.)
- . 1897. L'inanition du noyau cellulaire. *Compt. rend. Congr. internat. de méd. de Moscou*, 1: 297-308. Also in *Rev. scientif.*, 60: 513-519; and abstr. in *Arch. de sc. biol., St. Pétersb.*, 1897, 6: 111. 335.
- . 1897a. Sur les modifications du volume des noyaux des cellules hépatiques chez la souris blanche sous l'influence de l'inanition complète et incomplète, comparativement a l'alimentation normale. I. Recherches karyométriques. II. Appréciation générale des données karyométriques. *Arch. d. sc. biol., St. Pétersb.*, 6: 81-107; 111-132. 335.
- . 1898. De l'influence du jeûne absolu sur les dimensions des noyaux de l'épithelium renal chez la souris blanche. *Ibid.*, 7: 168-176. Also in (Russian) *Arch. biol. nauk*. (Abstr. in *Jahresb. d. Anat. etc.*, 1898, T. 3, p. 275; and by Mühlmann '99.) 378.
- . 1898a. Zur Frage nach der biologischen Autonomie des Zellkerns. *Arch. f. path. Anat. etc.*, 153: 158-159. 378.
- Luksch, F. 1911. Ueber das histologische und funktionelle Verhalten der Nebennieren beim hungernden Kaninchen. *Arch. f. exp. Path. u. Pharm.*, 65: 161-163. (Cf. also *Ztschr. f. Hyg.*, Bd. 58, 1908.) 427.

- Lumière, A. 1920. Sur les accidents polynévriques et cérébelleux chez le pigeon soumis au régime du riz decortiqué. *Bull. de l'Acad. de med., Par.*, 83: 96-101. (Also in *Paris méd.*, 10: 474-ff.) 323.
- . 1920a. Sur l'anorexie chez le pigeon nourri au riz decortiqué et le rôle des vitamines dans la nutrition. *Ibid.*, 83: 310-313. 113, 312.
- . 1920b. Avitaminose et inanition. *Ibid.*, 84: 274-276. 113.
- Lunin, N. 1881. Ueber die Bedeutung der anorganischen Salze für die Ernährung des Thieres. *Ztschr. f. physiol. Chemie*, 5: 31-39. 109.
- Lusk, G. 1901. Ueber Phlorhizin-Diabetes. *Ztschr. f. Biol.*, 42: 41-44. 128.
- . 1917. The elements of the science of nutrition. 3d ed. Saunders Co., Phila. & Lond., 641 pp. 128, 135, 140, 241, 372.
- . 1921. The physiological effects of undernutrition. *Physiol. Rev.*, 1: 523-552. 129.
- Lussana, F. 1868. *Manuale di fisiologia*. (Cited by Pernice u. Scagliosi '95a.) 69.
- e Frua, C. 1856. *Sula pellagra*. Milano, 352 pp. (Cited by Harris '19.) 103.
- Lust, F. 1911. Ueber den Wassergehalt des Blutes und sein Verhalten bei den Ernährungsstörungen der Säuglinge. *Jahrb. f. Kinderh.*, 23: 85-100; 179-214. 248.
- . 1913. (In discussion following Aron '13.) 91, 135.
- Lustig, A. e Galeotti, G. 1911. *Patologia generale*. Ed. 3, vol. 2, Milano. 243.
- Lyubomudroff—see Liubomadrow.
- Lynch, K. M. 1917. The pellagrous intestine and some of its parasites. *Southern Med. J.*, 10: 286-291. (Cited by Funk '22.) 322, 342.
- Maas, O. 1904. Ueber die Wirkung der Kalkentziehung auf die Entwicklung der Kalkschwämme. *Sitzungsb. d. Ges. f. Morph. u. Physiol. im München*, 20: 4-21. 9 Fig. 33.
- . 1904a. Ueber den Aufbau des Kalkskeletts der Spongien in normalen und in  $\text{CaCO}_3$ -frei Seewasser. *Verh. d. deut. zool. Ges.*, 14. Jahrg. (Cited by Morgan '07.) 33.
- . 1906. Ueber die Einwirkung karbonatfreier und kalkfreier Salzlösungen auf erwachsene Kalkschwämme und auf Entwicklungsstadien derselben. *Arch. f. Entw. d. Org.*, 22: 581-602. 33.
- . 1907. Ueber die Wirkung des Hungers und der Kalkentziehung bei Kalkschwämmen und anderen kalkausscheidenden Organismen. *Sitzungsb. d. Ges. f. Morph. u. Physiol. im München*, 23: 82-89. 34, 57.
- . 1910. Ueber Involutionerscheinungen bei Schwämmen und ihre Bedeutung für die Auffassung des Spongienkörpers. *Festschr. f. R. Hertwig*, 3: 93-130. 2 Taf. 2 Textfig. (Abstr. in *Jahresb. d. Anat. etc.*, 1911, T. 1, pp. 243, 281.) 34.
- . 1912. Ueber die Wirkung des Hungerns und der Kalkentziehung bei Kalkschwämmen und anderen kalkausscheidenden Organismen. *Proc. 7th Internat. Zool. Congr. Boston (1907)*, pp. 503-509. (Abstr. in *Jahresb. d. Anat. etc.*, 1912, T. 2, pp. 137, 220.) 18, 47, 57.
- Maase, C. u. Zondek, H. 1917. Das Kriegsödem. *Berl. klin. Wchnschr.*, 54: 861-864. 71, 102, 170.
- . 1917a. Ueber eigenartige Oedeme. *Deut. med. Wchnschr.*, 43: 484-485. 71, 102, 254, 255.
- . 1920. Das Hungerödem. Eine klinische und ernährungsphysiologische Studie. *G. Thieme, Lpz.*, 137 pp. 17 Fig. 71, 236, 342.
- Maass, H. 1921. Zur Pathogenese der rachitischen Wachstumsstörung. *Jahrb. f. Kinderh.*, 3. F., 45: 207-229. 14 Abb. 142.
- Macallum, A. B. 1905. On the distribution of potassium in animal and vegetable cells. *J. Physiol.*, 32: 95-126. 9.
- Macbride, D. 1774. *Philos. Trans.*, Lond., p. 436. (Cited by Lucas 1826.) 53.
- MacDougal, D. T. 1903. The influence of light and darkness upon growth and development. *Mem. N. Y. Bot. Garden*, Vol. 2, 319 pp. 12, 13.
- Mackay, H. M. M. 1921. The effect on kittens of a diet deficient in animal fat. *Biochem. J.*, 15: 19-27. 107, 111, 150, 322.

- Mackensie. 1857. *Traité pratique des maladies de l'oeil*, 2: 144-ff. (Cited by Koun '03.) 211, 216.
- MacNeal, W. J. 1921. Pellagra. *Am. J. Med. Sc.*, 161: 469-501. 13 figs. 103, 130.
- Macomber, D. 1923. Defective diet as a cause of sterility. Final report of fertility studies in the albino rat. *J. Am. M. A.*, 80: 978-980. 398, 413, 414.
- Magendie. 1852. *Leçons faites au Collège de France pendant le semestre d'hiver*. 1851-1852. Par., 68 pp. (Cited by Falck '75.) 249.
- Magnan, A. 1913. Variations expérimentales en fonction du régime alimentaire. Thèse méd., Par. (Abstr. in *Centralbl. f. norm. Anat. etc.*, 1914, 11: 113.)
- Maige, A. 1923. Influence de la température sur la décroissance, par inanition du noyau, chez le haricot. *Compt. rend. Soc. de biol.*, Par., 88: 97-99. 5.
- Maillet, M. 1913. Azotémie des nourrissons. Thèse méd., Par. (Cited by Nobécourt '16.) 329, 374.
- Malassez, L. 1875. Recherches sur quelques variations, que présente la masse totale du sang. *Arch. de physiol. norm. et path.* 2. sér., 7. ann., 2: 261-280. 249.
- Maliwa, E. 1917. Bemerkungen zur "Oedemkrankheit." *Wien. klin. Wchnschr.*, 30: 1477-1479.
- Manassein, W. (Manasein, V.). 1866. Beitrag zur Frage über das Hungern. *St. Petersb.* (Cited by Dreike '95.) 316.
- . 1868. Zur Lehre von der Inanition. *Centralbl. f. d. med. Wiss.*, Berl., 6: 273-275. (Cf. also Botkin's *Arch.*, 1867-8.) 119, 137, 179, 192, 213, 227, 274, 305, 316, 331, 365, 376, 406, 422.
- . 1869. (Materials on the question of starvation.) *Russian med. dissert.*, St. Petersb., 108 pp. (Also abstr. by Mühlmann '99.) 119, 127, 137, 167, 179, 192, 212, 213, 227, 229, 230, 274, 293, 305, 316, 331, 357, 365, 376, 400, 406, 422, 428, 429, 462.
- . 1869a. Material zur Frage über das Hungern. (v. Botkin's) *Arch. d. Klin. f. inn. Krankh.*, Bd. 1. (Cited by Statkewitsch '04 and Morgulis '11.) 167.
- Manca, G. 1895. Il decorso dell'inanizione negli animali a sangue freddo. *Gior. d. r. Accad. di med. di Torino*, 3. s., 43: 23-31. (Also in *Atti d. Soc. Veneta di sc. nat.* (2) p. 293-ff, acc. to Bardier '13; and under French title in *Arch. ital. de biol.*, 23: 243-251.) 462.
- . 1895-96. Influenza dell'acqua sul decorso dell'inanizione negli animali a sangue freddo. *Atti r. Ist. Veneto di sc., lett. ed arti*, 7. s., 7: 149-158. Also in *Lavori del lab. fisiol. d. Padova*, vol. 5 and (under French title) in *Arch. ital. de biol.*, 1896, 25: 299-307.
- . 1896. Il decorso del digiuno assoluto nelle Tartarughe. *Atti Mem. Accad. Sc.*, Padova, N. S., 12: 315-334; 336-348. Tab. (Concil. bibliogr.)
- . 1896a. Influenza del peso iniziale sulla resistenza al digiuno negli animali a sangue freddo. *Bull. d. sc. med. di Bologna*, 7. s., 7: 105-125. (Also abstr. in *Arch. ital. de biol.*, 1896, 25: 426-435.)
- . 1897. Le cours du jeûne absolu chez les tortues. (Abstr. from orig. in *Atti e Mem. d. R. Accad. di sc., lett. ed arti in Padova*, fasc. 3, 1896.) *Arch. ital. de biol.*, 27: 94-102. 462.
- . 1897a. Le cours de l'inanition absolue chez les lézards. *Ibid.*, 28: 83-94. 462.
- . 1900. Ricerche chimiche intorno agli animali a sangue freddo sottoposti ad inanizione. *Arch. di Farm. e Therap.*, Palermo, 8: 276-ff; 469-ff; 9: 320-ff; 10: 49-ff. (Abstr. in *Arch. ital. de biol.*, 1901, 35: 115-131; 373-379; 37: 161-176; 1903, 39: 193-203.)
- e Casella, D. 1903. Il decorso dell'inanizione assoluta nel *Gongylus ocellatus* alla luce e nell'oscurità. *Studi sassaresi*, Sassari, 3: 17-46. (Also under French title in *Arch. ital. de biol.*, 1903, 40: 247-272.)
- e Fatta, G. 1903. Il decorso del digiuno assoluto nel *Carabus morbillosus*. *Studi Sassaresi*, Sassari, 3: 81-139. Also in *Arch. di fisiol.*, 2: 459-470. 1 tav. (Ind. med.)
- Mankowsky (Mankowski), V. 1882. (Zur Frage über das Hungern. *Histologische Untersuchung*.) *Russian dissert.*, St. Petersb. Also in *Militär-med. J.*, 1883, vols. 3 & 4. (Abstr. by Mühlmann '99.) 182, 194, 204, 235, 274, 332, 377.
- Mann, F. C. 1916. The ductless glands and hibernation. *Am. J. Physiol.*, 41: 173-188. 280, 297, 353, 398, 412, 430, 446, 455.

- & Drips, D. 1917. The spleen during hibernation. *J. Exp. Zool.*, 23: 277-285. 4 figs. **280.**
- G. 1898. Demonstration über Veränderungen im Magen während der Inanition. *Verh. d. Anat. Ges.*, 12. Versamml. in Kiel, p. 271. **307.**
- and Gage, J. G. 1912. On the changes induced in the blood by feeding: a study in cellular physiology. *Lancet*, 90th year, 2: 1069-1073. 1 pl. **244.**
- W. L., Helm, J. B. & Brown, C. J. 1920. An edema disease in Haiti. *J. Am. M. A.*, 75: 1416-1418. **71, 232, 255, 281, 342, 384.**
- Manny, F. A. 1916. Indices of nutrition and growth. *Mod. Hosp.*, 7: 425-426. (Cited by Emerson & Manny '20.) **85.**
- . 1918. A comparison of three methods of determining defective nutrition. *Arch. Pediatr.*, 35: 88-94. (Cited by Emerson & Manny '20.) **85.**
- . 1918a. Defective nutrition and growth. A selected bibliography. *Am. J. School Hyg.*, 2: 78-88.
- Marchand, F. 1902. Ueber das Hirngewicht des Menschen. *Abhandl. d. math.-phys. Kl. d. k. sächs. Ges. d. Wiss.*, Lpz., 27: 436-ff. Also in *Biol. Centralbl.*, 1902, 22: 376-382. (Cited by Matiegka '04.) **175.**
- L. et Vurpas, C. 1901. Lésions du système nerveux central dans l'inanition. *Compt. rend. Soc. de biol., Par.*, 53: 296-298. **184, 196.**
- Marchi, V. 1888. Ricerche anatomo-patologica e batteriologica sul tifo-pellagroso. *Riv. sper. di freniatr.*, 14: 341-348. (Cited by Raubitschek '15 and Harris '19.)
- Marfan, A.-B. 1894. Lésions histologiques de l'estomac dans la dyspepsie gastro-intestinale chronique des nourrissons. *Mercur. méd.*, 1er août. (Cited by Thiercelin '04.) **304.**
- . 1920. Introduction à l'étude des affections des voies digestives dans la première enfance. 2, ed., *Par.*, 152 pp. **81.**
- . 1921. Les états de dénutrition dans la première enfance. Description de l'hypothrepsie et l'athrepsie. *Nourrisson*, 9: 65-86. **122, 178, 227, 248, 273, 277, 329, 348, 374, 392, 421, 423, 428, 437.**
- . 1922. Quatre leçons sur le rachitisme. *Ibid.*, 10: 65-80; 145-167; 228-239; 289-ff. **142, 158, 298.**
- et Baudouin, A. 1909. Études anatomiques sur les os rachitiques (en trois mémoires). *J. de physiol. et de path. gén.*, 11: 651-666; 883-898; 912-921. 5 pl. **146, 147.**
- et Feuille, E. 1909. Lésions de la moelle osseuse dans le rachitisme. *Compt. rend. Soc. de biol., Par.*, 66: 862-864. **146.**
- Dorlencourt, H. et Saint Girons, F. 1914. Les pertes minérales par les selles chez un athrépsique. *Nourrisson*, 2: 1-9. Also in *Bull. Soc. de pédiatr., Par.*, 1913, 15: 494-506. (Cited by Marfan '21.)
- Marie, A. 1908. La pellagre. *Giard et Briere, Par.* **103, 104, 129, 131, 140, 170, 187, 200, 206, 215, 232, 236, 255, 281, 322, 342, 367, 385.**
- . 1910. Pellagra. Transl. by C. H. Lavinder & J. W. Babcock. State Co., Columbia, S. C., 434 pp. **103, 104, 129, 131, 140, 170, 187, 200, 206, 215, 232, 236, 255, 281, 322, 342, 367, 385.**
- P. 1894. De l'origine exogène ou endogène des lésions du cordon postérieur, étudiées comparativement dans le tabes et dans la pellagre. *Semaine méd.*, 14: 17-20. Also in *Gaz. des hôp.*; and *Bull. de la Soc. méd. des hôp.* (Cited by Raubitschek '15.) **199.**
- Marine, D. 1907. On the physiological nature of the "glandular hyperplasias" of dog's thyroids, with a detailed report of a case typical of the group. *J. Inf. Dis.*, 4: 417-425. **443.**
- & Kimball, O. P. 1921. The prevention of simple goitre in man. *J. Am. M. A.*, 77: 1068-1070. **443.**
- Marinesco, G. 1900. L'évolution et l'involution de la cellule nerveuse. *Rev. scient.*, 65: 161-168. **184.**
- . 1905. La sensibilité de la cellule nerveuse aux variations de température. *Rev. neurol.*, p. 784. Also in *Revista Stântelor Med.*, No. 3, Bucarest. (Cited by Rasmussen & Myers '16.) **185, 197, 198.**

- . 1906. Recherches sur les changements des neurofibrilles consécutifs aux différents troubles de nutrition. *Névraxe*, 8: 149-173. 12 figs. 184.
- . 1909. La cellule nerveuse. 2 vols., Par. 184, 185, 187, 196, 197, 206.
- . 1910. De la constance des lésions de l'appareil fibrillaire des cellules nerveuses dans la rage humaine et leur valeur diagnostique. *Compt. rend. Soc. de biol., Par.*, 68: 898-900.
- Marquis, C. 1892. Das Knochenmark der Amphibien in den verschiedenen Jahreszeiten. *Dissert., Dorpat*, 82 pp. (Cited by Beretta '02.)
- Marriott, W. M. 1920. Some phases of the pathology of nutrition in infancy. *Am. J. Dis. Child.*, 20: 461-485. 259.
- . 1923. Anhydremia. *Physiol. Reviews*, 3: 275-294. 115, 132, 259, 303.
- & Sisson, W. R. 1918. Variations in the lipid (fat) content of the blood of infants under certain nutritional conditions. *Am. J. Dis. Child.*, 16: 75-82.
- Marshall, F. H. A. 1910. The physiology of reproduction. Longmans, Green & Co., N. Y. & Lond. Also 1922, 2nd ed. 395.
- . 1923. Animal fecundity. II. *Discovery, Lond.*, 4: 243-244. 395.
- . J. A. 1923. Changes in tooth structure resulting from deficient diets. *J. Am. M. A.*, 81: 1665-1666. 160.
- . W. 1882. Ueber einige Lebenserscheinungen der Süßwasserpolyphen und über eine neue Form von *Hydra viridis*. *Ztschr. f. wiss. Zool.*, 37: 662-702. 1 Taf. 34, 35. de Martigny, C. (see Collard de Martigny.)
- Martin, A. A. 1907. A prolonged fast,—some experiences and findings. *Montreal Med. J.*, 36: 482. 243.
- . H. G., Loevenhart, A. S. & Bunting, C. H. 1918. The morphological changes in the tissues of the rabbit as a result of reduced oxidation. *J. Exp. Med.*, 27: 399-412. 257, 444.
- Martinotti, C. 1892. Contributo allo studio delle capsule surrenale. *Giorn. d. r. Accad. di med. di Torino, Ser. III*, 40: 299-301. 422, 428.
- . 1892a. Contribution à l'étude des capsules surrénales. *Arch. ital. de biol.*, 17: 284-286. 422, 428.
- et Tirelli, V. 1900. La microphotographie appliqué à l'étude de la structure des cellules nerveuses dans les ganglions intervertébraux d'animaux morts d'inanition. *Verh. d. anat. Ges.*, 14. Versamml., Pavia. *Anat. Anz., Ergänzungsh. z. Bd. 18*, pp. 89-96. 1 Taf. Also in *Arch. ital. de biol.*, 35: 390-406.
- . 1901. La microfotografia applicata allo studio della struttura della cellula dei gangli spinali nell'inanitione. *Ann. freniatr. e. sc. aff.*, 11: 35-66. 2 tav. Also in *Gior. d. r. Accad. di med. di Torino*, 64: 231-234. (Abstr. in *Jahresb. d. Anat. etc.*, 1901, T. 1, pp. 229; 260-261.) 204.
- Marzari. 1810. Saggio medico politico. (Cited by Harris '19.) 103.
- Maslowsky, W. 1923. (Ueber die Aenderungen in Geschlechtsdrüsen im Kindesalter beim Hungern. Russian paper, cited by Stefko '24.) 392, 406.
- Masslow, M. 1913. Ueber die biologische Bedeutung des Phosphors für den wachsenden Organismus. *Biochem. Ztschr.*, 55: 45-62; 56: 174-194. 106, 131.
- Mast, S. O. 1917. Conjugation and encystment in *Didinium* with especial reference to their significance. *J. Exp. Zool.*, 23: 335-359. 20.
- & Ibara, Y. 1923. The effect of temperature, food, and the age of the culture on the encystment of *Didinium nasutum*. *Biol. Bull.*, 45: 105-112. 20.
- Matiegka, H. 1904. Ueber die Bedeutung des Hirngewichtes beim Menschen. *Anat. Hefte, I. Abt.*, H. 73, 23: 655-659. 175.
- Matsuoka, Y. 1915. On the process of atrophy in adipose tissue and on the histogenesis of fat cells. *J. Path. & Bact.*, 20: 118-132. 3 pl. 125.
- Mattei, C. 1914. Anatomie pathologique des glandes à sécrétion interne dans l'athrepsie. Thèse de Montpellier, 228 pp. 3 pl. 263, 273, 277, 290, 305, 316, 329, 348, 374, 392, 405, 420, 423, 427, 428, 437, 446, 449, 450.
- Matthias. 1919. *Deut. med. Wchnschr.*, No. 27. (Erroneous citation by Bürger '20.) 71, 103.

- Matti, H. 1913. Physiologie und Pathologie der Thymusdrüse. *Ergeb. d. inn. Med. u. Kinderh.*, 10: 1-145. 290.
- Mattioli, L. 1910. Effeti del 'azione combinata del digiuno e del freddo sul reticolo neurofibrillare della cellula nervosa. *Riv. di patol. nerv. e ment.*, 15: 649-656. 1 tav. 197.
- Matusiewicz. 1914. Dér Körperlängen—Körpergewichts-Index bei Münchner Schulkindern. Verlag Müller u. Steinecke, München. (Cited by Pfaundler '21a.) 85, 86.
- Maupas, E. 1888. Recherches expérimentales sur la multiplication des infusoires ciliés. *Arch. de zool. expér. et gen.*, ser. 2, 6: 165-277. 17, 19.
- . 1889. La rajeunissement karyogamique chez les ciliés. *Ibid.*, 7: 149-517. 17.
- . 1900. Modes et formes de reproduction chez les Nématodes. *Ibid.* (Not found in vol. 8 as cited by O. Schultze '03.) 46.
- Maurel, E. 1904. Influence du régime sec sur le poids de l'animal et sur les quantités d'aliments ingérés. *Compt. rend. Soc. de biol., Par.*, 57: 325-328. 115, 116.
- . 1904a. Conclusions générales des expériences sur le régime sec. Considerations pratiques. *Ibid.*, 57: 455-456. 115, 116.
- Maver, M. B. 1920. Nutritional edema and "war dropsy." *J. Am. M. A.*, 74: 934-941. 71, 102, 215, 232, 236, 255, 384.
- Maximow, A. u. Korowin, J. 1900. Pathologie des Hungerns. *Russische Literatur, 1895-1898. Ergeb. d. allg. Path., etc.*, (1898), 5: 702-704.
- Maxwell, J. P. 1923. Osteomalacia in China. *China Med. J.*, 35: 625-642. 15 figs. 145.
- Mayeda, R. 1890. Ueber die Kaliberverhältnisse der quergestreiften Muskelfasern. *Ztschr. f. Biol.*, 27: 119-152. 2 Taf. 167.
- Mayer, A. 1900. Essai sur la soif; ses causes et son mécanisme. Thèse méd., *Par.* (1899-1900, No. 563), 168 pp.
- Rathery, F. et Schaeffer, G. 1910. Sur l'aspect et les variations des granulations ou mitochondries de la cellule hépatique. *Compt. rend. Soc. de biol., Par.*, 68: 427-429. 337.
- et Schaeffer, G. 1914. Recherches sur la variations de la teneur des tissus en lipoïdes et en eau au cours de l'alimentation absolue. *J. de physiol. et de path. gén.*, 16: 203-211.
- A. G. 1914. The law governing the loss of weight in starving *Cassiopea*. *Papers, Tortugas Lab., Carnegie Inst. Washington*, 6: 55-82. 1 pl. 40, 73.
- Maynard, F. P. 1909. Preliminary note on increased intraocular tension met with in cases of epidemic dropsy. *Indian Med. Gaz.*, 44: 373. (Cited by Maver '20.) 215.
- McCarrison, R. 1919. The pathogenesis of deficiency disease. I. *Indian J. Med. Res.*, 6: 275-355. (Also abstr. in *Brit. Med. J.*, 1919, 1: 177-178.) 171, 189, 233, 283, 298, 311, 322, 343, 386, 397, 409, 415, 429, 432, 444.
- . 1919a. The pathogenesis of deficiency disease. II. Effects of deprivation of "B" accessory food factors. *Ibid.*, 6: 550-556. 189, 283, 298, 354, 432, 455.
- . 1919b. Involution of the thymus in birds. *Ibid.*, 6: 557-559. 281, 297, 298, 386.
- . 1919c. The pathogenesis of deficiency disease. III. Influence of dietaries deficient in accessory food factors on the intestine. *Ibid.*, 7: 167-187. 298.
- . 1919d. The pathogenesis of deficiency disease. IV. Influence of scorbutic diet on the adrenal glands. *Ibid.*, 7: 188-194. (Also abstr. in *Brit. Med. J.*, 1919, 2: 200.) 433.
- . 1919e. The pathogenesis of deficiency disease. V. Histopathology. *Ibid.*, 7: 269-278. 298, 386.
- . 1919f. The pathogenesis of deficiency disease. VI. The influence of a scorbutic diet on the bladder. *Ibid.*, 7: 279-282.
- . 1919g. The pathogenesis of deficiency disease. VII. The effects of auto-claved rice dietaries on the gastro-intestinal tract of monkeys. *Ibid.*, 7: 283-307.

- . 1919h. The pathogenesis of deficiency disease. VIII. The general effect of deficient dietaries on monkeys. *Ibid.*, 7: 308-341.
- . 1919i. The pathogenesis of deficiency disease. IX. On the occurrence of recently developed cancer of the stomach in a monkey fed on food deficient in vitamins. *Ibid.*, 7: 342-345.
- . 1920. The pathogenesis of deficiency disease. X. The effects of some food deficiencies and excesses on the thyroid gland. *Ibid.*, 7: 633-647. 432, 444.
- . 1920a. Dietetic deficiency and endocrine activity with special reference to deficiency oedemas. *Brit. Med. J.*, 2: 236-239. 298, 430, 445, 455.
- . 1920b. The genesis of oedema in beriberi. *Proc. Roy. Soc. Lond.*, "B," 91: 103-110.
- . 1921. Studies in deficiency disease. Oxford Med. Publ., Lond., 270 pp. 78, 102, 111, 113, 140, 189, 207, 228, 232, 267, 281, 283, 297, 298, 311, 322, 340, 343, 353, 354, 360, 367, 368, 384, 386, 397, 408, 415, 428, 429, 430, 431, 432, 433, 440, 444, 445, 447, 455.
- . 1922. Simple goiter. *Brit. Med. J.*, 1: 636-637. 443.
- . 1923. Pathogenesis of deficiency disease. XIV. On the occurrence of ophthalmia in pigeons fed exclusively on parboiled rice and on its prevention by the addition of soil to the food. *Ind. J. Med. Res.*, 11: 323-335. 218.
- McClendon, J. F. 1910. On the effect of external conditions on the reproduction of *Daphnia*. *Amer. Naturalist*, 44: 404-411. 29, 58.
- . 1920. Nutrition and public health with special reference to vitamins. *Am. J. Med. Sc.*, 159: 477-497.
- . 1921. A consideration of the diet of infants in relation to the physical and mental status of the next generation. *Am. J. Clin. Med.*, 28: 521-524.
- . 1922. Are iodides foods? *Science, N. S.*, 55: 358-361. 443.
- . 1922a. The diagnostic value of phosphate metabolism in experimental rickets. *Proc. Soc. Exp. Biol. & Med.*, 19: 412-413. 141.
- . 1922b. Calcium phosphate metabolism in the diagnosis of rickets. *Am. J. Physiol.*, 61: 373-379. 141.
- , Cole, W. C. C., Engstrand, O. & Middlekauff, J. E. 1919. The effects of malt and malt extracts on scurvy and the alkaline reserve of the blood. *J. Biol. Chem.*, 40: 243-257. 154.
- & Shuck, C. 1923. The presence of antiophthalmic vitamin and the absence of antirachitic vitamin in dried spinach. *Proc. Soc. Exp. Biol. & Med.*, 20: 288.
- & Williams, A. 1923. Simple goiter as a result of iodine deficiency. *J. Am. M. A.*, 80: 600-601. 1 fig. 443.
- McCollum, E. V. 1918. The "vitamin" hypothesis and diseases referable to faulty diet. *J. Am. M. A.*, 71: 937-941.
- . 1922. The newer knowledge of nutrition. 2nd ed. Macmillan Co., N. Y., 449 pp. 102, 106, 110, 148.
- . 1923. Pathologic effects of lack of vitamin A and of antirachitic vitamin. *J. Am. M. A.*, 81: 894-899. 107.
- & Davis, M. 1913. The necessity of certain lipins in the diet during growth. *J. Biol. Chem.*, 15: 167-175. 104, 110, 111.
- . 1914. Further observations on the physiological properties of the lipins of the egg-yolk. *Proc. Soc. Exp. Biol. & Med.*, 11: 101-102. 111.
- . 1915. The essential factors in the diet during growth. *J. Biol. Chem.*, 23: 231-246. 111.
- . 1915a. The influence of the composition and amount of the mineral content of the ration on growth and reproduction. *Ibid.*, 21: 615-643. 105.
- , Halpin, J. G. & Driescher, A. H. 1912. Synthesis of lecithin in the hen and the character of lecithins produced. *Ibid.*, 13: 219-224. 104.
- , Mendel, L. B., Sherman, H. C., Shipley, P. G., Holt, L. E. & Hess, A. F. 1922. Some aspects of the physiology and pathology of nutrition. *J. Am. M. A.*, 78: 1566-1568. 110.

- & Pitz, W. 1917. The "vitamin" hypothesis and deficiency diseases. A study of experimental scurvy. *J. Biol. Chem.*, 31: 229-253.
- & Simmonds, N. 1917. A biological analysis of pellagra-producing diets. I. The dietary properties of mixtures of maize kernel and bean. *Ibid.*, 32: 29-61. **103, 111.**
- . 1918. The nursing mother as a factor of safety in the nutrition of the young. *Am. J. Physiol.*, 46: 275-313. **111, 131, 217.**
- & Becker, J. E. 1922. A type of ophthalmia caused by unsatisfactory relations in the inorganic portion of the diet. Ophthalmia not due to starvation for fat-soluble A and not curable by its administration. *J. Biol. Chem.*, 53: 313-322. **107.**
- & Shipley, P. G. 1922. Experimental rickets. XXI. The experimental demonstration of the existence of a vitamin which promotes calcium deposition. *Ibid.*, 53: 293-312. Also abstr. in *Johns Hopkins Hosp. Bull.*, 33: 229. **107.**
- Kinney, E. M. & Grieves, C. J. 1922. Relation of nutrition to tooth development and tooth preservation. *Johns Hopkins Hosp. Bull.*, 33: 202-215. 19 figs. **159.**
- Shipley, P. G. & Park, E. A. 1922. Studies on experimental rickets. XVII. Effects of diets deficient in calcium and in fat-soluble A in modifying histologic structure of bones. *Am. J. Hyg.*, 2: 97-106. **109, 131, 148, 282.**
- & Parsons, H. T. 1920. The etiology of rickets. *Proc. Am. Soc. Biol. Chem.*, XIV. *J. Biol. Chem.*, 41: xxxi.
- Shipley, P. G. & Park, E. A. 1921. Studies on experimental rickets. I. The production of rachitis and similar diseases in the rat by deficient diets. *Ibid.*, 45: 333-348. 2 pl. **148.**
- Shipley, P. G. & Park, E. A. 1921. Studies on experimental rickets. VI. The effects on growing rats of diets deficient in calcium. *Am. J. Hyg.*, 1: 492-510. 5 pl. **131, 148, 282, 298, 398, 413.**
- . 1921a. Studies on experimental rickets. VIII. The production of rickets by diets low in phosphorus and fat-soluble A. *J. Biol. Chem.*, 47: 507-529. 4 pl. **148.**
- . 1922. Studies on experimental rickets XV. The effect of starvation on the healing of rickets. *Johns Hopkins Med. Bull.*, 33: 31-33. **109, 148.**
- McCrudden, F. H. 1912. The nutrition and growth of bone. *Trans. XV Internat. Congr. on Hyg. & Demogr.*, Washington, pp. 424-429.
- . 1913. Die Bedeutung des Calciums für das Wachstum. *Deut. Arch. f. klin. Med.*, 110: 90-100. Also repr. in studies of the Rockefeller Inst., 19: 409-419. **105.**
- McHargue, J. S. 1922. The rôle of manganese in plants. *Science*, 61: 85. **10.**
- McIntosh, W. A. 1918. A histological study of the fat contained in the mucosa of the alimentary tract of moderately starved cats. *Am. J. Physiol.*, 46: 570-583. 6 figs. **321.**
- Mead, A. D. 1900. Growth and food supply in starfish. *Amer. Naturalist*, 34: 17-23. **53, 57, 59.**
- Meckel, J. F. 1810. Zusätze zu den Vorlesungen über vergleichende Anatomie von G. Cuvier. 4T. Lpz. (Cited by Hammar '06.) **286.**
- . 1820. Handbuch der menschliche Anatomie. Bd. IV, pp. 456-457. Halle u. Berl. (Cited by Hammar '06.) **286.**
- Medwedjew (Medvedjev), J. 1882. Zur Lehre vom Fasten, St. Petersburg. (Abstr. by Mühlmann '99 and Morgulis '23.) **83.**
- Meier, C. 1921. Ein neuer, durch Durstschädigung hervorgerufener Symptomenkomplex beim Neugeborenen und Säugling. *Monatschr. f. Kinderh.*, 19: 470-477. **115.**
- Meigs, E. B. 1922. Milk secretion as related to diet. *Physiol. Reviews*, 2: 204-237. **131.**
- Mellanby, E. 1919. An experimental investigation on rickets. *Lancet, Lond.*, 196: 407-412. (Cf. also *ibid.*, 1918, 1: 407; and *Proc. Soc. Physiol.*, *J. Physiol.*, 1919, 52: liii.) **107, 148.**
- . 1920. Accessory food factors (vitamins) in the feeding of infants. *Lancet*, 1: 856-862.

- . 1921. Experimental rickets. Med. Res. Council, Spec. Rep. Ser., No. 61. Lond., 78 pp. 129 figs. **107, 109, 147, 148.**
- . 1922. Some common defects of diet and their pathological significance. Brit. Med. J., pp. 790-791; 831-832. **110, 443.**
- & Mellanby, M. 1921. The experimental production of thyroid hyperplasia in dogs. J. Physiol., 55: vii-viii. **442.**
- M. 1918. The influence of diet on teeth formation. Lancet. Lond., 2: 767-770. (Abstr. in J. Am. M. A.) **159.**
- . 1921. Diet and teeth. Brit. J. Dent. Sc., 64: 70-81. **159.**
- Mendel, L. B. 1908. Der Einfluss der Nahrung auf die chemische Zusammensetzung des Tierkörpers. Biochem. Ztschr., 11: 281-293.
- . 1912. The rôle of proteins in growth. Trans. XV Internat. Congr. on Hyg. & Demogr., Sec. II., pp. 1-10.
- . 1914. Viewpoints in the study of growth. Biochem. Bull., 3: 156-176. **101.**
- . 1915. Nutrition and growth. J. Am. M. A., 64: 1539-1547. 5 charts. **101.**
- . 1917. Abnormalities of growth. Am. J. Med. Sc., 153: 1-20. **89, 101.**
- . 1920. The fat-soluble vitamin. N. Y. State Med. J., 20: 212-217. **112, 218, 385.**
- & Judson, S. E. 1916. Some interrelations between diet, growth and the chemical composition of the body. Proc. Nat. Acad. Sc., 2: 692-694. **89, 101, 140.**
- Menzies, W. F. 1920. Oedema as a symptom in so-called food deficiency diseases. Lancet, Lond., 198: 350. **71, 232, 431.**
- Merkel, H. 1914. Gerichtsärztliche Gesichtspunkte und Verfahren bei der Beurteilung der Leichen von Neugeborenen und Kindern. In Brüning u. Schwalbe's Handb. d. allg. Path. u. d. path. Anat. d. Kindesalters. Bd. 1, Abt. 2. Kap. 10, p. 953. Wiesbaden.
- Merzbacher, L. 1903. Untersuchungen an winterschlafenden Fledermäusen. II. Mitt. Die Nervendegeneration während des Winterschlafes. Die Beziehungen zwischen Temperatur und Winterschlaf. Arch. f. d. ges. Physiol., 100: 568-585. **205.**
- von Mettenheimer, H. 1898. Zum Verhalten der Thymusdrüse in Gesundheit und Krankheit. Jahrb. f. Kinderh., 46: 55-94. **287.**
- Metzner, R. 1890. Ueber die Beziehungen der Granula zum Fettansatz. Arch. f. Anat. u. Physiol., Anat. Abt., pp. 82-96. 2 Taf. **125.**
- Meyer(s),<sup>1</sup> A. W. 1917. Morphological effects of prolonged inanition. J. Med. Res. 36: 51-77. 3 pl. **71, 96, 120, 122, 136, 137, 166, 167, 181, 194, 204, 211, 224, 229, 262, 271, 277, 304, 314, 326, 347, 356, 362, 372, 404, 419, 436, 445, 449.**
- Meyer, H. 1849. Ueber den Bau rachitischer Knochen. Arch. f. Anat., Physiol. u. wiss. Med., p. 432. (Cited by Pommer '85.) **145.**
- K. 1905. Die klinische Bedeutung der Eosinophilie. Dissert., Berl., 106 pp. **242.**
- L. F. 1913. Ueber den Wasserbedarf des Säuglings. Ztschr. f. Kinderh., 5: 1-30. **115.**
- u. Japha, A. 1919. Ueber den Einfluss der Ernährung auf das Blut bei Kindern. Deut. med. Wchnschr., 45: 1345-1351. **248.**
- Meyerstein, A. 1922. Anatomische Untersuchungen zur Frage der akzessorischen Nährstoffe. Arch. f. path. Anat. etc., 239: 350-362. 6 Abb. **189, 233, 283, 343, 385, 399, 414.**
- Meynier, E. 1906. Influenza dell'inanizione sulla struttura della ghiandola mammaria funzionante. Riv. clin. pediatri., 4: 881-895. 1 tav. **128.**
- . 1908. Influenza dell'inanizione sulla struttura della ghiandola mammaria. Lavori dell'Ist. di Anat. patol. di Torino. (Abstr. in Centralbl. f. allg. Path., 1909, 20: 760.) **128.**
- Miescher, F. 1880. Schweizer. Literatursammlung zur internat. Fischereiausstellung in Berlin. (Cited by Ohlmüller '82.) **164, 168, 397, 412.**

<sup>1</sup> Misspelled "Meyers" in original article.

- . 1897. Der Hunger des Rheinlachs. Histochemische und physiologische Arbeiten. Lpz., 2: 116-327. 77, 164, 168, 275, 310, 397, 412.
- Miescher-Ruesch. 1880. Statische und biologische Beiträge zur Kenntnis vom Leben des Rheinlachs im Süßwasser. Internat. Fischerei-Ausstellung zu Berlin. Metzger u. Wittig, Lpz. (Cited by Gulland '98.) 310.
- Miles, W. R. 1919. The sex expression of men living on a lowered nutritional level. J. Nerv. & Ment. Dis., 49: 208-224. (Abstr. in J. Am. M. A.) 415.
- Miller, H. G. 1923. Potassium in animal nutrition. II. Potassium in relation to growth in young rats. J. Biol. Chem., 55: 61-78. 31 charts. 105.
- . S. P. 1922. Effects of various types of inanition upon the mitochondria in the gastro-intestinal epithelium and in the pancreas of the albino rat. Anat. Rec., 23: 205-210. 309, 320, 353.
- . 1923. The effects of inanition upon the stomach and intestines of albino rats underfed from birth for various periods. Unpublished thesis for Ph. D. degree, Univ. of Minn., Minneapolis. 308, 309, 319, 320.
- . W. D. 1887. Der Einfluss der Nahrung auf die Zähne. Deut. Monatschr. f. Zahnh., 5: 1-8. (Abstr. in Jahresb. d. Anat. etc., 1888, p. 634.) 157.
- Milne-Edwards. 1861. Expériences sur la nutrition des os. Compt. rend. Acad. des sc., Par., 52: 1327-ff. (Cited by Schabad '10.) 141.
- Minet, J. 1907. Contribution à l'étude du sang dans l'athrespie. Numération des globules et richesse du sang en hémoglobine. Leucocytose digestive. Formule hémoleucocytaire. Thèse de Lille, 111 pp. (Cited by Nobécourt '16.) 247.
- Mingazzini, P. 1900. Cambiamenti morfologici dell'epitelio intestinale durante l'assorbimento delle sostanze alimentari. Nota I. Rend. d. r. Accad. d. Lincei, Ser. 5, vol. 9, fasc. 1. (Cited by Biscossi '08.) 321.
- . 1900a. Cambiamenti morfologici dell'epitelio intestinale durante l'assorbimento delle sostanze alimentari. Nota II. Ricerche Lab. di Anat. norm. di Roma, 8: 41-64. 1 tav. (Abstr. in Jahresb. d. Anat. etc., 1900, T. 3, pp. 253; 280-281. 317, 321.
- Minot, C. S. 1891. Senescence and rejuvenescence. First paper: On the weight of guinea pigs. J. Physiol., 12: 97-153. 80, 94.
- Missirolì, A. 1910. La tiroide negli animali a digiuno ed in quelli rialimentati. Patologica, 2: 38-42. (Cited by Rondoni e Montagnani '15; see also next title.) 438.
- . 1911. La thyreoide chez les aminaux à jeun et chez les aminaux réalimentés. Arch. ital. de biol., 55: 115-118. 438.
- . 1912. Sulla funzione tiroidea. Patologica, 4: 253-254. 438.
- Mitchell, D. 1919. Malnutrition and health education. Pedagog. Seminary, 26: 1-26. 84.
- . P. C. 1911. Article "Sex" in the Encyclop. Britannica, 11th ed., vol. 24. 80.
- Mitscherlich, E. A. 1920. Das Liebig'sche Gesetz vom Minimum und das Wirkungsgesetz der Wachstumsfactoren. Naturwiss., 8: 85-88. (Bot. Abstr., 1920, 6: 123.) 14.
- Miwa, S. u. Stoeltzner, W. 1898. Ueber die bei jungen Hunden durch kalkarme Fütterung entstehende Knochenerkrankung. Beitr. z. path. Anat. etc., 24: 578-595. 2 Taf. 109, 147.
- Miyoshi, M. 1896. Physiologische Studien über Ciliaten. Bot. Mag., Tokio, No. 112, 7 pp., June. (Abstr. in Bot. Centralbl., 1896, 68: 287-288.) 19.
- Modinos, P. 1916. Une nouvelle théorie sur l'étiologie de la pellagre et son traitement. Bull. Soc. méd. d. hôp. de Par., 3. s., 40: 440-443. (Cited by Funk '22.) 431.
- Moehl, E. 1922. Beobachtungen über die Folgen der Futternot bei unsern Haustieren während der Kriegszeit. Vet.-med. Dissert., Bern, 31 pp. 120, 128, 253, 308, 397, 401.
- Moенckeberg, J. G. 1912. Die Pathologie der Gewebe im Kindesalter. In Brüning u, Schwalbe's Handb. d. allg. Path. u. d. path. Anat. d. Kindesalters, Bd. 1, Abt. 1, Kap. 3. pp. 56-154. 125, 169, 182, 230, 290, 374.
- Moessmer. 1916. Ueber "Kriegsneugeborene." Zentralbl. f. Gyn., 40: 684-686. 79.
- Moglia. 1910. Sul significato funzionale del pigmenti nei gangli nervosi nei Molluschi gastropodi. Arch. zool., 4: 317-334. (Cited by Legendre '13.) 54.

- Moldenhauer, A. 1899. Sulle fine alterazioni della milza e delle glandole linfatiche nell'athrepsia. Atti d. III. Congr. pediatr. ital. (1898), Torino, 3: 94-98. 263, 277.
- Moleschott. 1859. Physiologie der Nahrungsmittel. 2. Aufl., Giessen. (Cited by Rosenstern '11.) 70.
- Molisch, H. 1895. Die Ernährung der Algen. I. Abh. Sitzungsber. d. Akad. Wien. math.-nat. Kl., Bd. 104, Abt. 1, p. 783-ff. Also *ibid.*, 1896, 105: 633. (Cited by Reed '07.) 8.
- Molliard et Coupin. 1903. Sur les formes tératologiques du *Sterigmatocystis nigra* privé de potassium. Compt. rend. Acad. des sc., Par., 136: 1695. (Cited by Reed '07.) 9.
- Momm. 1916. Hat die eiweiss- und fettarme Nahrung einen Einfluss auf die Entwicklung der Frucht? Zentralbl. f. Gyn., 40: 545-550. 79.
- . 1920. Die durch die Hungerblockade herabgesetzte Stillfähigkeit der deutschen Frau. Münch. med. Wchnschr., 67: 783-784. 129.
- Montessoro, B. 1912. L'azione del digiuno e dell'estratto secco di tiroide sulla struttura dell'epitelio del tubo seminfero del topo. Arch. de biol., 27: 35-62. 1 pl. 408.
- e Schlatter, B. 1911. Sull'origine del grasso nei tubi seminfero del topo (*Mus decumanus* var. *alb.*). Bull. Accad. Giornia sc. nat., Catania, ser. 2, fasc. 15, pp. 28-33. 1 tav. (Cited in Jahresb. d. Anat. etc., 1912, T. 3, p. 604.) 408.
- Montessori, M. 1911. Antropologia pedagogica. Milano.
- Monti, A. 1889. Ubersichtliche Zusammenstellung der Wachstumsverhältnisse der Kinder. Arch. f. Kinderh., 10: 401-429. 81.
- . 1895. Sulle alterazioni del sistema nervoso nell'inanizione. Rif. med., Napoli, 11: 362; 375-ff. (Cited by Barbacci '99.) 183.
- . 1895a. Sur les altérations du système nerveux dans l'inanition. Arch. ital. de biol., 24: 347-360. 183.
- . 1898. Contributions a l'histologie pathologique de la cellule nerveuse. *Ibid.* 29: 307-314. (From orig. in Rend. R. Ist. Lomb. Sc. e Lett., ser. 2, vol. 31, fasc. 5, 1898.)
- R. 1903. Le funzioni di secrezione e di assorbimento intestinale studiate negli animali ibernanti. Mem. R. Ist. Lomb. Sc. e Lett., Milano, 34 pp., 2 pl. (Abstr. in Jahresb. d. Anat. etc., 1903, T. 2, p. 112.) 322.
- . 1905. Le leggi del rinnovamento dell'organismo studiate negli animali ibernanti. *Ibid.*, 38: 714-719.
- R. e Monti, A. 1900. Su l'epitelio renale delle marmotte durante il sonno. Verh. d. anat. Ges. XIV Versamml., Pavia, pp. 82-87. 383.
- . 1903. Les glandes gastriques des marmottes durant la léthargie hivernale et l'activité estivale. Arch. ital. de biol., 39: 248-252. 311.
- Moore, B., Roaf, H. E. & Knowles, R. E. 1908. The effects of variations in the inorganic salts and the reactivity of the external medium upon the nutrition, growth and cell division in plants and animals. Biochem. J., 3: 279-312. 4 pl. 5, 11.
- W. 1892. Abstract of an address on famine. Indian Med. Gaz., Calcutta, 27: 196-199.
- Morat, J. P. 1901. Réserve adipeuse de nature hivernale dans les ganglions spinaux de la grenouille. Compt. rend. Soc. de biol., Par., 53: 473-474. 204.
- Morelli, C. 1855 (1856?). La pellagra nei suoi rapporti medici e sociali. 279 pp. Firenze. (Cited by Harris '19.) 103, 342.
- Moreschi, C. 1909. Beziehungen zwischen Ernährung und Tumorwachstum. Ztschr. f. Immunitätsforsch. u. exper. Therap., 1. Theil, 2: 651-675. (Cited by Rous '11.) 459.
- Morgagni, J. B. 1761. De sedibus et causis morborum, etc. Lib. III, Epist. 28, Art. 5, 6. Venetiis. 241, 249.
- Morgan, T. H. 1901. Growth and regeneration in *Planaria lugubris*. Arch. f. Entw. d. Org., 13: 179-212. 14 figs. 41.
- . 1907. Experimental zoology. Chapt. 16. Macmillan Co., N. Y.
- Morgulis, S. 1911. Studies of inanition in its bearing upon the problem of growth. I. Arch. f. Entw. d. Org., 32: 169-268. 3 Taf. 92, 94, 121, 318, 338, 352.
- . 1912. Studien über Inanition in ihrer Bedeutung für das Wachstumsproblem. II. Experimente an *Triton cristatus*. *Ibid.*, 34: 618-679.

- . 1912a. The effect of inanition and a return to normal diet upon the organic substance, salts and water content in *Diemictylus viridescens*. Verh. 8. Internat. Zool. Congr., Graz. (1910), pp. 636-638.
- . 1913. The influence of protracted and intermittent fasting upon growth. Am. Naturalist, 47: 477-487. 94.
- . 1915. Studies on fasting flounders. J. Biol. Chem., 20: 37-46. 462.
- . 1918. Studies on the nutrition of fish. Experiments on brook trout. *Ibid.*, 36: 391-413. 462.
- . 1923. Fasting and undernutrition. A biological and sociological study of inanition. E. P. Dutton & Co., N. Y., 407 pp. 15 figs. 59, 70, 73, 77, 83, 257, 317, 372, 407, 460.
- Howe, P. E. & Hawk, P. B. 1915. Studies on tissues of fasting animals. Biol. Bull., 28: 397-406. 1 pl. 169, 307, 338, 358, 380, 395, 409.
- Mori, M. 1904. Ueber den sog. Hikan (xerosis conjunctivae infantum ev. Keratomalacie). (II Mitteilung.) Jahrb. f. Kinderh., 59: 175-ff. 220.
- S. 1922. Primary changes in eyes of rats which result from deficiency of fat soluble A in diet. J. Am. M. A., 79: 197-200. 7 figs. 218.
- . 1923. The pathological anatomy of ophthalmia produced by diets containing fat-soluble A, but unfavorable contents of certain inorganic elements. Am. J. Hyg., Balt., 3: 99-102. 219.
- Morikawa, Y. 1920. Ueber die pathologischen Veränderungen der Nebennieren bei experimenteller Barlowscher Krankheit, nebst Gewichten einiger endokrinen Drüsen bei derselben. Osaka Igakkwai, 19: 9-ff. (Abstr. in Endocrinol., 1920, 4: 615.) 433.
- Morini, F. 1885. Ancora sulla questione della sessualità nelle Ustilaginee. Mem. Accad. Sc. Bo'ogna, 6: 283-290. (Cited by Thomson '88.) 4.
- Morozoff (Morozov), N. N. 1897. (On the effect of fasting for a short time—incomplete starvation—upon the morphological composition of the blood in man.) (Russian.) Vrach, St. Petersburg., 18: 1081-1085. 254.
- Morpurgo, B. 1888. Sul processo fisiologico di neoformazione cellulare durante la inanizione acuta dell'organismo. Arch. per le sc. med., 12: 395-418. 121, 264, 278, 302, 306, 332, 349, 357, 393, 400, 406.
- . 1889. Sur le processus physiologique de neoformation cellulaire durant l'inanition aigue de l'organisme. Arch. ital. de biol., 11: 118-133. 121, 167, 264, 278, 302, 306, 317, 332, 349, 357, 377, 393, 400, 406.
- . 1889a. Ueber den physiologischen Zellneubildungsprocess während der acuten Inanition des Organismus. Beitr. z. path. Anat. etc., 4: 313-334. 121, 167, 264, 306, 317, 332, 349, 357, 377, 393, 400, 406.
- . 1889b. Sur la nature des atrophie par inanition aiguë chez les animaux à sang chaud. Compt. rend. d. trav. d'anat., etc. XIII Congr. de l'assoc. méd. ital., Padoue. Arch. ital. de biol., 12: 333-338. 168, 231, 332, 349, 377.
- . 1890. Della neoproduzione di elementi cellulari nei tessuti di animali nutriti dopo un lungo digiuno. Arch. per le sc. med., 14: 29-62. 167, 264, 278, 306, 317, 333, 357, 377, 400, 406.
- . 1898. Ueber die karyometrischen Untersuchungen bei Inanitionszuständen. Arch. f. path. Anat. etc., 152: 550-552. (Also in Atti d. r. Accad. d. fisiocrit. in Siena, 1898, 4. s., 10: 253-255.)
- . 1898a. Ueber die postembryonale Entwicklung der quergestreiften Muskeln von weissen Ratten. Anat. Anz., 15: 200-206. 169.
- . 1909. Beobachtungen an Serienschnitten von osteomalacischen und rachitischen Knochen. Centralbl. f. allg. Path. etc. Bd. 20. Verh. d. deut. path. Ges., 13: 51-54. 146.
- Morse, P. F. 1916. The general pathology of pellagra, with special reference to findings in the thyroid and adrenals. J. Lab. & Clin. Med., 1: 217-233. 20 figs. 431, 442.
- Mosse, M. 1906. Ueber Leberzellenveränderungen nephrektomierter und hungernder Tiere; ein Beitrag zur Lehre von der Azidose. Ztschr. f. klin. Med., 60: 373-376. 1 Taf. (Also in Berl. klin. Wchnschr., 43: 990.) 336.

- Mosso, A. 1887. De la transformation des globules rouges en leucocytes. Arch. ital. de biol., 8: 252-316. 250.
- Moszeik, O. 1888. Microscopische Untersuchungen über den Glycogenansatz in der Froschleber. Arch. f. d. ges. Physiol., 42: 556-581. 1 Taf. 333, 341.
- Motrochin. (Cited by Bardier '13.) 393.
- Mott, F. W. 1913. The histological changes in the nervous system of Dr. Box cases of pellagra. Brit. Med. J., 2: 4-5, 3 pl. Also in Trans. Soc. Trop. Med. Hyg., 1913, 6: 156.) 188, 200.
- Mottram, V. H. 1907. Changes in fat content of liver cells during hunger. (Abstr.) Proc. Physiol. Soc. Lond., J. Physiol., 1907, 36: viii. 337.
- . 1909. Fatty infiltration of the liver in hunger. *Ibid.*, 38: 281-314. 2 pl. 337.
- . 1909a. Fettinfiltration der Leber, durch Hunger verursacht. Ztschr. f. Biol., 52: 280-281. 337.
- J. C., Cramer, W. & Drew, A. H. 1922. Vitamins, exposure to radium and intestinal fat absorption. Brit. J. Exp. Path., 3: 179-181. 1 pl. 323.
- Moulton, C. R. 1920. Biochemical changes in the flesh of beef animals during under-feeding. J. Biol. Chem., 43: 67-78. 1 fig. (Also abstr. in Science, 1920, N. S., 52: 390.) 169, 241, 253, 340.
- Trowbridge, P. F. & Haigh, L. D. 1921. Studies in animal nutrition. I. Changes in form and weight on different planes of nutrition. Univ. of Mo. Coll. of Agr. Exp. Sta. Res. Bull. No. 43, 111 pp. 90, 96, 135.
- ————. 1922. Studien über tierische Ernährung. I. Form- und Gewichtsveränderungen bei verschiedenen Fütterungsnormen. Biedermann's Zentralbl., 51: 192-193. (Abstr. in Ber. üb. d. ges. Physiol. etc., 1922, 15: 57-58.) 90, 180, 193.
- ————. 1922a. Studies in animal nutrition. II. Changes in proportions of carcass and offal on different planes of nutrition. Univ. of Mo. Coll. of Agr. Exp. Sta. Res. Bull. No. 54, 76 pp. 170, 193, 228, 276, 297, 303, 308, 320, 340, 353, 366, 381, 440.
- ————. 1922b. Studies in animal nutrition. III. Changes in chemical composition on different planes of nutrition. *Ibid.*, Res. Bull. No. 55, 88 pp. 193, 381.
- Mouriquand, G. 1921. Indications cliniques et diététiques tirées de l'étude expérimentale du scorbut. Arch. internat. de physiol., 18: 92-102. 259.
- . 1923. Notes sur le rachitisme et la nutrition osseuse. Par. méd., 13: 406-410. 147.
- Mourre, C. 1904. Sur la variation des corpuscles de Nissl dans diverses conditions physiologiques. Compt. rend. Soc. de biol., Par., 56: 907-908. 196.
- Muehlmann, M. 1899. Russische Litteratur über die Pathologie des Hungerns. Zusammenfassendes Referat. Centralbl. f. allg. Path. etc., 10: 160-220.
- . 1910. Untersuchungen über das lipoide Pigment der Nervenzellen. Ist das Nervenpigment ein Abnutzungsprodukt der Zelle? Arch. f. path. Anat. etc., 202: 153-160. 1 Fig. 184.
- Mueller. *Historia vermium*, vol. 2 (p. 12). (Cited by Lucas 1826.) 53.
- F. 1897. Allgemeine Pathologie der Ernährung, in von Leyden's Handb. d. Ernährungstherapie, 1: 156-ff. (Cited by Hirsch '99.) 98.
- K. 1890. Die Sekretionsvorgänge im Pancreas bei *Salamandra maculata*. Dissert., Halle a. S., 33 pp. (Cited by Kulisch '91.) 349.
- . 1911. Beobachtung über Reduktionsvorgänge bei Spongilliden nebst Bemerkungen zu deren äusserer Morphologie und Biologie. Zool. Anz., 37: 114-121. 3 Abb. 34.
- W. 1883. Die Massenverhältnisse des menschlichen Herzens. L. Voss, Hamb. u. Lpz., 220 pp. (Cited by Krieger '20.) 223, 228.
- Munk, I. 1891. Ueber die Folgen langer fortgesetzter eiweissarmer Nahrung. Arch. f. Physiol., pp. 338-341. 100.

- . 1893. Untersuchungen an zwei hungernden Menschen. Arch. f. path. Anat. etc., Bd. 131, Suppl., pp. 1-228. 140.
- . 1894. Beiträge zur Stoffwechsel- und Ernährungslehre. Arch. f. d. ges. Physiol., 58: 309-408.
- Murray, I. 1923. The thyroid gland in experimental rickets. Brit. J. Exp. Path., 4: 335-339. 6 figs. 442.
- M. B. 1924. Child life investigations. The effect of maternal social conditions and nutrition upon birth-weight and birth-length. Med. Research Council, Lond., Spec. Rep. Ser., No. 81, 34 pp., 2 charts. 79.
- Myers, J. A. 1919. Studies on the mammary gland. V. The effects of inanition on the developing mammary glands in male and female albino rats from birth to ten weeks of age. Amer. J. Dis. Child., 17: 311-328. 16 figs. (Also abstr. in Proc. Am. Assn. Anat., Anat. Rec., 16: 159.) 128.
- Naegele, H. F. J. 1872. Lehrbuch der Geburtshilfe. 8 Aufl., 842 pp. Mainz. (Cited by Reeb '05.)
- Naegeli, O. 1897. Zur pathologischen Anatomie und zum Wesen des Morbus Barlow. Centralbl. f. allg. Path. etc., 8: 687-694. (Cited by Hart '12.) 151.
- . 1908. Blutkrankheiten und Blutdiagnostik. Also 2. Aufl., Veit & Co., Lpz., 1912. 719 pp. 20 Taf. (Abstr. in Ergeb. d. allg. Path. etc., 1911, 15: 543.) 259, 289.
- Nagayo, M. 1923. Beriberi and rice neuritis. J. Am. M. A., 81: 1435-1437. 112, 207, 233, 257, 268, 283, 343, 367, 386, 432.
- Nalepa, A. 1902. Grundriss der Naturgeschichte des Tierreiches, Wien. (S. 112.) (Cited by Kammerer '12.) 462.
- Napp, O. 1905. Ueber den Fettgehalt der Nebenniere. Arch. f. path. Anat. etc., 182: 314-326. 418, 423.
- Nasse, H. 1850. Einfluss der Nahrung auf das Blut. Marburg. 99 pp. 250.
- Nathan, M. 1920. Le rachitisme est-il une maladie par carence? Presse méd., 28: 577-579. 107.
- Needham, J. G. 1897. The digestive epithelium of dragon-fly nymphs. Zool. Bull., Boston, 1: 103-113. 59, 60.
- Neiva, A. 1910. Beiträge zur Biologie der *Conorhinus megistus*, Burm. Memorias de Institute Oswaldo Cruz, 2: 206-212. (Cited by Riley & Johannsen '15.) 60.
- Nelson, V. E. & Lamb, A. R. 1920. The effect of vitamin deficiency on various species of animals. I. The production of xerophthalmia in the rabbit. Am. J. Physiol., 51: 530-535. (Also abstr. in Science, 1920, N. S., 52: 393.) 218.
- . 1920a. Further studies on the effect of a deficiency of fat-soluble vitamin. (Abstr.) Science, N. S., 52: 566.
- & Heller, V. G. 1922. The vitamin requirements of various species of animals. II. The production and cure of xerophthalmia in the suckling. Am. J. Dis. Child., 23: 518-520. 1 fig. 218.
- Nemzer (Nemser), M. G. 1899. Sur le question de savoir comment les nucléines se comportent dans l'inanition. Arch. d. sc. biol. de St. Pétersb., 7: 221-232. Also in Russian, Arch. biol. nauk. etc., 7: 221-232. 317, 335, 378.
- Neumann, E. 1868. Ueber die Bedeutung des Knochenmarkes für die Blutbildung. Arch. f. Heilk., Bd. 9. (Cited by Jackson '04.) 125.
- . 1882. (Zur histologischen Structur des Knochenmarkes.) Inaug. Dissert., Warschau. (Abstr. by Hoyer in Jahresb. d. Anat. etc., 1882, pp. 54; 60-63.) 126.
- Neurath, R. 1924. (Rickets and the nervous system.) Klin. Wchnschr., 3: 337-339. (Abstr. J. Am. M. A., 1924, 82: 1155.) 188.
- Newman, G. 1915-16. Annual Report of the Chief Medical Officer, Board of Educ. (England and Wales), p. 32. Also *Ibid.*, 1917-18, p. 126. (Cited by Roberts '23.) 84.
- Nicholls, L. 1912. Tropical pellagra. Jour. Trop. Med. & Hyg., 15: 241-245. (Cited by Raubitschek '15.) 103, 232, 233, 236, 281, 342, 367, 385, 431.
- . 1913. The pathological changes in pellagra and the production of the disease in lower animals. Jour. Hyg., 13: 149-161. 2 pl. 103, 281, 342, 431.

- Nicolaëff, L. 1923. Influence de l'inanition sur la morphologie des organes infantiles. *Presse med.*, Par., 31: 1007-1009. 2 figs. 71, 83, 120, 122, 136, 139, 165, 178, 182, 227, 230, 273, 278, 291, 305, 316, 329, 348, 363, 374, 392, 400, 406, 421, 437, 458.
- Nicolas, A. 1890. Sur la constitution du protoplasma des cellules épithéliales des villosités de l'intestin grêle et sur l'état de ces cellules pendant l'absorption des graisses. *Bull. d. séances de la Soc. de sc. de Nancy*, 2: 54-58. (Abstr. in *Jahresb. d. Anat. etc.*, 1890, pp. 321; 329-330.) 321.
- Nikolaïdes (Nicolaidés), R. 1889. Ueber die mikroskopischen Erscheinungen der Pankreaszellen bei der Secretion. *Centralbl. f. Physiol.*, No. 25, pp. 686-687. (Abstr. in *Jahresh. d. Anat. etc.*, 1889, pp. 322, 323-324.) 349.
- . 1899. Ueber den Fettgehalt der Drüsen im Hungerzustande und über seine Bedeutung. *Arch. f. Physiol.*, Lpz., pp. 518-524. 1 pl. 124, 317, 335, 351, 358.
- u. Savas, C. 1895. Ueber Fettgranula in den Pylorusdrüsen des Magens und in den Brunner'schen Drüsen. *Centralbl. f. Physiol.*, 9: 278-280. 306.
- Niles, G. M. 1916. Pellagra; an American problem. 2nd ed. Saunders Co., Phila. & Lond., 261 pp. 103.
- Nirenstein, E. 1910. Ueber Fettverdauung und Fettspeicherung bei Infusorien. *Ztschr. f. allg. Physiol.*, 10: 137-149. 1 Taf. 17, 22.
- Nobbe, F., Schroeder, J. u. Erdmann, R. 1871. Ueber die organische Leistung des Kalium in der Pflanze. *Landw. Versuchsst.*, 13: 399-423. 8.
- Nobécourt, P. 1916. Des hypotrophies et des cachexies des nourrissons. *Étiologie. Physiologie pathologique. Anatomie pathologique. Pathogénie. Arch. de méd. des enf.*, 19: 113-136; 169-205; 234-259; 301-316. 81, 87, 120, 169, 178, 230, 241, 248, 273, 277, 291, 305, 316, 329, 348, 363, 374, 392, 420, 437, 446.
- et Maillet, M. 1914. Étude des hémocopies chez les nourrissons. *Bull. de la Soc. de pédiatr. de Par.*, 16: 285-298. (Cited by Nobécourt '16.) 241, 248.
- Tixier, L. et Maillet. 1913-15. Hématologie et altérations ostéo-médullaires dans la maladie de Barlow. *Compt. rend. Assoc. de pédiatr.*, p. 123-f. (Cited by Hess '20.) 258.
- Noé, J. 1900. La réparation compensatrice après la jeûne. *Compt. rend. Soc. de biol.*, Par., 52: 755-757. 94.
- . 1901. Variations de résistance du hérisson à l'inanition. *Ibid.*, 53: 1000-1010.
- . 1902. Rapport comparatif du poids des organes au poids total chez le hérisson à l'état normal et après l'inanition. *Ibid.*, 54: 1106-1108.
- . 1903. Influence de la croissance sur la résistance à l'inanition. *Ibid.*, 55: 601-603.
- Noël, R. 1923. Recherches histo-physiologiques sur la cellule hépatique des mammifères. *Arch. d'anat. micr.*, 19: 1-158. 8 pl. 340.
- Noll, A. 1902. Ueber die Bedeutung der Gianuzzi'schen Halbmonde. *Anat. Anz.*, 21: 139-142. Also 1902a, *Arch. f. Physiol.*, Suppl. B, pp. 166-202. 358.
- F. (Personal communication, cited by O. Schultze, '03, p. 220.) 4.
- von Noorden, C. 1907. *Metabolism; physiology and pathology, with its application to practical medicine. Vol. 2. The pathology of metabolism.* Anglo-Amer. ed. by I. W. Hall. W. T. Keener & Co., Chicago.
- Northrop, J. H. 1917. The effect of the prolongation of the period of growth on the total duration of life. *J. Biol. Chem.*, 32: 123-126. 62.
- Nothnagel. 1903. *Krankheiten des Darms und Peritoneums.* Wien. (Cited by Tugendreich '04 and Mönckeberg '12.) 315.
- Nothwang, F. 1891. Die Folgen der Wasserentziehung. *Arch. f. Hyg.*, 14: 272-302. Also *Dissert.*, Marburg, 1891, 33 pp. (Abstr. in *Physiol. Jahresb.*, 1892 and by Tobler '10.) 115, 172, 303.
- Novaro, P. 1920. Ricerche calorimetriche comparative sul digiuno e sull'avitaminosi. *Nota II. Dell'avitaminosi. Pathologica*, 12: 133-156. 113.
- . 1920a. Tessuto testicolare ed avitaminosi. *Gaz. degli Osp.*, Milano, 41: 424. (Abstr.) 415.

- Nusbaum, J. u. Oxner, M. 1912. Studien über die Wirkung des Hungerns auf den Organismus der Nemertinen. I. Arch. f. Entw. d. Org., 34: 386-443. 3 Taf. 45, 46, 204.
- Nussbaum, M. 1880. Zur Differenzierung des Geschlechtes im Thierreich. Arch. f. mikr. Anat., 18: 1-121. 393, 407.
- . 1887. Geschlechtsentwicklung bei Polypen. Verh. d. Nat. Ver. Bonn, Jahrg. 49. (Cited by Schultz '06.) 35.
- . 1893. Die Geschlechtsentwicklung bei Polypen. Sitzungsber. der Niederrhein. Ges. f. Natur- u. Heilk. zu Bonn (27. Feb., 1892), 29: 13; 14; 40-41. (Cited by R. Hertwig '06 and O. Schultze '03.) 28, 35.
- . 1897. Die Entstehung des Geschlechts bei *Hydatina senta*. Arch. f. mikr. Anat., 49: 227-308. 28, 57.
- . 1898. Zur Parthenogenese bei den Schmetterlingen. *Ibid.*, 53: 444-480.
- . 1906. Ueber den Einfluss der Jahreszeit, des Alters und der Ernährung auf die Form der Hoden und Hodenzellen der Batrachier. *Ibid.*, 68: 1-121. 407, 412.
- . 1906a. Fortgesetzte Untersuchungen über den Einfluss des Hungers auf die Entwicklung der männlichen Geschlechtsorgane der *Rana fusca*. Anat. Anz., 29: 315-316. 407, 412.
- . 1909. Hoden und Brunstorgane des braunen Landfrosches (*Rana fusca*). Arch. f. d. ges. Physiol., 126: 520-577. 407.
- . 1914. Die experimentelle Morphologie, in Lehrb. d. Biol. f. Hochschulen, von Nussbaum, Karsten u. Weber, 2. Aufl., Lpz. (Kap. 13, pp. 113-115.) 135, 395, 407.
- Oberndorfer. 1918. Pathologisch-anatomische Erfahrungen über innere Krankheiten im Felde. Münch. med. Wchnschr., 65: 1154-1156; 1181-1191. (cf. also 1919, No. 7, p. 196 ff.) 71, 232, 236, 281, 342, 384, 442.
- Ochotin (Okhotin), I. A. 1885. (Pathological-anatomical changes in rabbits during inanition.) Russian thesis, St. Petersburg., 69 pp. Also in Med. pribav. k. morsk. sborniku, St. Petersburg., 1885, pp. 41-48. (Also abstr. by Statkewitsch '94 and Muhlmann '99.) 73, 167, 194, 230, 332, 377.
- . 1886. (On the effect of incomplete starvation.) (Russian.) Med. pribav. k. morsk. sborniku. St. Petersburg., pp. 82-90; 166-180. 167, 183, 193, 194, 230, 332, 377.
- . 1886a. Congr. de la Soc. d. méd. russe. (Cited by Beretta '02.)
- Ogata, T., Kawakito, S. & Oka, C. 1917. Polished rice disease of birds. Tokio Med. News, pp. 2154-2157. Also in Trop. Dis. Bull., 1920, 16: 394. (Cited by Hoffman '22.)
- Ohlemann. 1899. Tod durch Verhungern? Ztschr. f. Med.-Beamte, Berl., 12: 38-42.
- Ohlmüller, W. 1882. Ueber die Abnahme der einzelnen Organe bei an Atrophie gestorbenen Kindern. Inaug. Dissert., München. Also in Ztschr. f. Biol., 1882, 18: 78-103. 119, 122, 135, 165, 172, 211, 226, 273, 314, 328, 332, 349, 357, 362, 373, 405.
- Okhotin—see Ochotin.
- Okintschitz (Okinchits), E. 1893. (Alteration of the morphological composition of the blood of rabbits in complete starvation and subsequent refeeding.) (Russian.) Arch. lab. obst. pathol. f. Imp. Varshav. Univ., 1: 1-18. (Index-cat., S. G. L.) 251.
- . 1893a. Ueber die Zahlenverhältnisse verschiedener Arten weisser Blutkörperchen bei vollständiger Inanition und bei nachträglicher Auffütterung. (Versuche an Kaninchen.) Arch. f. exp. Path. u. Pharmak., 31: 383-397. 251.
- Okuneff, N. 1922. Zur Morphologie der lipoiden Substanzen im Hungerzustande. Beitr. z. path. Anat. etc., 71: 99-114. 253, 280, 297, 340, 354, 381, 412, 427, 440.
- . 1923. Studien über Zellveränderungen im Hungerzustande. (Das Chondriom.) Arch. f. mikr. Anat., 97: 187-203. 1 Taf. 280, 341, 354, 381, 384, 412.
- Olin, R. M. 1924. Iodin deficiency and prevalence of simple goiter in Michigan. J. Am. M. A., 82: 1328-1332. 444.
- Ono, S. I. 1920. Cytological reinvestigations on the somatic cells of *Ascaris*, with special reference to mitochondria. Proc. Anat. & Anthrop. Assn. of China. Conference in Peking, Feb. 1920. (Abstr.) Printed by Shanghai Times, pp. 23-25. 46.
- . 1920a. Effect of starvation and refeeding upon the mitochondria and other cytoplasmic contents. *Ibid.*, pp. 25-26. 320.

- Opie, E. L. 1904. The occurrence of cells with eosinophile granulation and their relation to nutrition. *Am. J. Med. Sc., N. S.*, 127: 217-239. 136, 242, 252, 278, 318, 366.
- Opitz, E. 1924. Ueber Hungerkrankheiten der Schwangeren (Inanition graviditatis). *Zentralbl. f. Gyn.*, 48: 1-9.
- H. 1913. Ueber Wachstum und Entwicklung untergewichtiger ausgetragener Neugeborener. *Dissert., Breslau (Berl., 1913)*, 39 pp. Also in *Monatschr. f. Kinderh.*, Bd. 13, Nr. 3. 91, 97.
- K. 1918. Die Stillfähigkeit im Kriege. *Deut. med. Wchnschr.*, 44: 437-438. 129.
- Oppenheimer, K. u. Landauer, W. 1911. Ueber den Ernährungszustand von Münchner Volksschülern. *Münch. med. Wchnschr.*, pp. 2218-2220. 85.
- Orth, J. 1893. *Lehrbuch der pathologische Anatomie*, Bd. 2. 418, 423.
- Osborne, T. B. & Mendel, L. B. (*et al.*). 1911. Feeding experiments with isolated food substances. *Carnegie Inst. Washington, Publ. No. 156, Parts I and II.* 101, 110, 129, 140, 186.
- ————. 1911a. The rôle of different proteins in nutrition and growth. *Science, N. S.*, 34: 722-732. 101, 186.
- ————. 1912. Feeding experiments with fat-free mixtures. *J. Biol. Chem.*, 12: 81-89. 104, 110.
- ————. 1912a. Maintenance experiments with isolated proteins. *Ibid.*, 13: 237-276. 101.
- ————. 1912b. Beobachtungen über Wachstum bei Fütterungsversuchen mit isolierten Nahrungssubstanzen. *Ztschr. f. physiol. Chem.*, 80: 307-370. 101.
- ————. 1913. The relation of growth to the chemical constituents of the diet. *J. Biol. Chem.*, 15: 311-326. 111.
- ————. 1914. Amino-acids in nutrition and growth. *Ibid.*, 17: 325-349. 101.
- ————. 1914a. The suppression of growth and the capacity to grow. *Ibid.*, 18: 95-106. 95.
- ————. 1915. The comparative nutritive value of certain proteins in growth and the problem of the protein minimum. *Ibid.*, 20: 351-378. 101.
- ————. 1915a. The resumption of growth after long continued failure to grow. *Ibid.*, 23: 439-454. 95, 101.
- ————. 1916. Acceleration of growth after retardation. *Am. J. Physiol.*, 40: 16-20.
- ————. 1916a. The amino-acid minimum for maintenance and growth, as exemplified by further experiments with lysine and tryptophane. *J. Biol. Chem.*, 25: 1-12. 129.
- ————. 1916b. The effect of the amino-acid content of the diet on the growth of chickens. *Ibid.*, 26: 293-300. 1 pl. 101, 129.
- ————. 1917. The effect of retardation of growth upon the breeding period and duration of life of rats. *Science, N. S.*, 45: 294-295. 101, 396.
- ————. 1917a. The rôle of vitamins in the diet. *J. Biol. Chem.*, 31: 149-163. 111, 112.
- ————. 1917b. Nutritive factors in animal tissues. I. *Ibid.*, 32: 309-323.
- ————. 1917c. Incidence of phosphatic urinary calculi in rats fed on experimental rations. *J. Am. M. A.*, 69: 32-33. 385.
- ————. 1918. Nutritive factors in animal tissues. II. *J. Biol. Chem.*, 34: 17-27.
- ————. 1918a. The inorganic elements in nutrition. *Ibid.*, 34: 131-139. 105.
- ————. 1918b. The choice between adequate and inadequate diets, as made by rats. *Ibid.*, 35: 19-27.
- ————. 1918c. Continuation and extension work on vegetable proteins. *Year Book of the Carnegie Inst. of Washington*, pp. 302-310. 414.

- \_\_\_\_\_ . 1920. Milk as a source of water-soluble vitamin. *J. Biol. Chem.*, 41: 515-523.
- \_\_\_\_\_ . 1920a. Growth on diets poor in true fats. *Ibid.*, 45: 145-152. 104.
- \_\_\_\_\_ . 1921. A critique of experiments with diets free from fat-soluble vitamin. *Ibid.*, 45: 277-288. 111, 112, 218.
- \_\_\_\_\_ . 1921a. Ophthalmia and diet. *J. Am. M. A.*, 76: 905-908.
- \_\_\_\_\_ . 1921b. Does growth require preformed carbohydrate in the diet? *Proc. Soc. Exp. Biol. & Med.*, 18: 136-137. 104.
- \_\_\_\_\_ . 1921c. Growth on diets containing more than ninety per cent of protein. *Ibid.*, 18: 167-168. 104.
- \_\_\_\_\_ . 1921d. Feeding experiments with mixtures of foodstuffs in unusual proportions. *Proc. Nat. Acad. Sc.*, 7: 157-162. 104.
- O'Shea, H. V. 1918. Scurvy. *Practitioner*, 101: 217; 283. (Cited by Hess '20.) 221.
- Osiander, F. B. 1820. *Handbuch der Entbindungskunst*. 4 vols. Tübingen. (Cited by Reeb '05.) 79.
- Osterud, H. L. 1923. Postnatal changes in weight and structure of the reproductive tract in the female albino rat. *Papers from the Mayo Foundation and the Medical School, Univ. of Minn.* Saunders Co., Phila., 2: 218-232. 401.
- Ostwald. 1908. In *Vortr. u. Aufsätze über Entw.* Herausg. v. W. Roux, H. 5. (Cited by Robertson '15.) 80.
- Ott, M. D. 1924. Changes in the weights of the various organs and parts of the leopard frog (*Rana pipiens*) at different stages of inanition. *Am. J. Anat.* Also (abstr.) in *Proc. Am. Assn. Anat.*, 1923, *Anat. Rec.*, 25: 111-112. 70, 118, 135, 164, 179, 192, 213, 228, 276, 302, 309, 341, 366, 381, 397, 398, 401, 412, 470.
- Oxner, M. 1911. Analyse biologique d'une série d'expériences concernant l'avènement de la maturité sexuelle, la régénération et l'inanition chez les Nemertiens, *Lineus ruber* (Müll.) et *Lineus lacteus* (Rathke). *Compt. rend. Acad. des sc., Par.*, 153: 1168-1171. 45.
- Padua, R. G. 1919. Cystolithiasis among Filipinos in association with dietetic deficiency. *Philip. J. Sc.*, 14: 481-499. 386.
- Pagano, R. 1906. Contributo sperimentale sulla patogenesi dell'atrofia infantile. *Pediatria*, 14: 641-657. 318.
- Pagliani, L. 1879. Lo sviluppo umano per età, sesso, condizione sociale ed etnica studiato nel peso, statura, circonferenza toracica, capacità vitale e forza muscolare. *Gior. d. r. Soc. ital. d'igiene*, Milano, 1: 357-382; 453-491; 589-ff. 83, 97.
- Paira-Mall, L. 1900. Ueber die Verdauung bei Vögeln; ein Beitrag zur vergleichenden Physiologie der Verdauung. *Arch. f. d. ges. Physiol.*, 80: 600-627. (Also med. Inaug. Dissert., München, 1900.) 310.
- Palladin, V. I. 1918. *Plant physiology*. Authorized Engl. ed., based on the German transl. of the 6th Russian, and on the 7th Russian ed. Ed. by B. E. Livingston, Blakiston & Co., Phila., 320 pp. Also 2d Amer. ed., 1923. 2, 6, 8, 12, 13.
- Palmer, L. S. & Hoffman, C. T. 1922. Biochemical properties of the blood of pigeons in polyneuritis and starvation. *Proc. Soc. Exp. Biol. & Med.*, 20: 118-119. 250.
- \_\_\_\_\_ & Kempster, H. L. 1919. Relation of plant carotinoids to growth, fecundity and reproduction of fowls. *J. Biol. Chem.*, 39: 299-312.
- Paltauf. 1917. *Sitz. d. K. u. K. Ges. d. Aerzte in Wien vom 26. Okt.*; ref. im *Wien. klin. Wehnschr.*, Nr. 46, pp. 1470-1471. 71, 186, 232, 281, 342, 384, 430, 442.
- Panella, A. 1906. Il nucleone e l'acqua del cervello in animali a digiuno. *Arch. di farm. sper. e sc. affini*, 5: 70-76. 184.
- Paneth, J. 1888. Ueber die secernierenden Zellen des Dünndarmepithels. *Arch. f. mikr. Anat.*, 31: 113-191. 3 Taf. 317.
- Panum, P. L. 1864. Experimentelle Untersuchungen über die Veränderungen der Mengenverhältnisse des Blutes und seiner Bestandtheile durch die Inanition. *Arch. f. path. Anat. etc.*, 29: 241-296. 2 Taf. 249.

- Papanicolaou, G. N. & Stockard, C. R. 1920. Effects of underfeeding on ovulation and the oestrus rhythm in guinea pigs. *Proc. Soc. Exp. Biol. & Med.*, 17: 143-144. 397, 401
- . 1922. Experimental results bearing on the etiology of cystic growths in the ovary and uterus of the guinea pig. *Ibid.*, 19: 402-403. 397, 401.
- Pappenheim, A. 1901. Beobachtungen über das Verhalten des Knochenmarkes beim Winterschlaf in besonderem Hinblick auf die Vorgänge der Blutbildung. *Kurze Mitt. Ztschr. f. klin. Med.*, 43: 363-376. 137, 253, 276.
- Pappenheimer, A. M. 1914. Further experiments upon the effects of extirpation of the thymus in rats, with special reference to the alleged production of rachitic lesions. *J. Exp. Med.*, 20: 477-498. 4 pl. 107.
- . 1922. Experimental rickets in rats. VI. The anatomical changes which accompany healing of experimental rat rickets, under the influence of cod liver oil or its active derivatives. *Ibid.*, 36: 335-355. 9 pl. 147.
- McCann, G. F., Zucker, T. F. and Hess, A. F. 1921. The effect of various modifications of a diet producing rickets in rats. *Proc. Soc. Exp. Biol. & Med.*, 18: 267-270. 148.
- . 1922. Experimental rickets in rats. IV. Effect of varying inorganic constituents of rickets producing diet. *J. Exp. Med.*, 35: 421-446. 148.
- . 1922a. Experimental rickets in rats. V. Effect of varying organic constituents. *Ibid.*, 35: 447-466.
- & Minor, J. 1921. Hyperplasia of parathyroids in human rickets. *J. Med. Res.*, 42: 391-404.
- Parhon, R. et Papinian, J. 1905. Sur les altérations des neurofibrilles dans la pellagre. *Compt. rend. Soc. de biol., Par.*, 58: 360. Also in *Semaine méd.*, No. 10. (Cited by Raubitschek '15 and Harris '19.) 187, 200.
- Park, E. A. 1923. The etiology of rickets. *Physiol. Reviews*, 3: 106-163. 108.
- . 1923a. Certain factors causing the deposition of lime salts in bone. *Dental Cosmos*, 65: 176-185. 9 figs. 158.
- & Howland, J. 1921. Dangers to life of severe involvement of the thorax in rickets. *Johns Hopkins Hosp. Bull.*, 32: 101-109. 142.
- Shipley, P. G., McCollum, E. V. & Simmonds, N. 1922. Is there more than one kind of rickets? *Proc. Soc. Exp. Biol. & Med.*, 19: 149-154. 148.
- F. S. 1918. War edema (Kriegsoedem). *J. Am. M. A.*, 70: 1826-1827. 71, 102, 232.
- Parker, G. H. 1917. The fur-seals of the Pribilof Islands. *Scient. Monthly*, 4: 385-409. 77.
- Parrot, J. 1868. Sur la stéatose viscerale par inanition chez le nouveau-né. *Compt. rend. Acad. de sc., Par.*, 67: 412-414. (Also in *Arch. de Physiol.*, 1868.) 182, 194, 195, 229, 328, 362.
- . 1874. Des maladies des enfants; atrepsie. *France méd., Par.*, 21: 409; 441; 481; 513; 537; 593; 626; 650. (*Ind. cat., S. G. L.*) 328.
- . 1877. Clinique des nouveau-nés. *L'athrepsie*. G. Masson, Par., 450 pp. 13 pl. 81, 123, 182, 194, 247, 304, 314, 328, 362, 373.
- . 1882. Poids de l'encéphale comparé avec le poids du coeur. *Bull. de la Soc. d'anthropol., Par.* (Cited by Fayolle '10.) 176.
- Parsons, H. T. 1920. The antiscorbutic content of certain body tissues of the rat. The persistence of the antiscorbutic substance in the liver of the rat after long intervals on a scorbutic diet. *J. Biol. Chem.*, 44: 587-602. 113.
- Paschoutine (Paschutin), J. A. 1885. Contribution à l'étude de la métamorphose chez les animaux soumis à une alimentation insuffisante suivie d'une alimentation normale. (Russian.) Thèse de St. Pétersb. (Cited by Bardier '13 and Morgulis '23.)
- Paschutin (Pashutin), W. (V). 1881. (Vorlesungen über allgemeine Pathologie. II. Theil.) (Russian.) *St. Petersb.*, pp. 9-150. (Abstr. by Mühlmann '99.)
- . 1902. (A course in general and experimental pathology-pathological physiology.) (Russian.) Vol. 2, Part 1, 1726 pp. M. Merkusheff, St. Petersb. 242.

Pasini, A. 1903. Sul processo di atrofia del tessuto adiposo sottocutaneo nel dimagrimento. *Sperimentale*, 57:571-583. 2 fig. 125.

Passer (Cited by Falck '75.)

Paternò, G. I. 1902. Studio clinico sperimentale dell'atrepsia del Parrot. *Pediatrics*, 10: 548-573. (Also abstr. in *Centralbl. f. Kinderh.*, 1903, 8: 288-289.)

———. 1903. (Untersuchungen über die pathologische Anatomie der Parrotschen Athrepsie.) *Ibid.*, Vol. 11, No. 2. (Cited from abstr. in *Centralbl. f. Kinderh.*, 1903, 8: 288-289.)

Paton, D. N. 1898. Report of investigations on the life history of the salmon in fresh water. Glasgow, 176 pp. 77, 164, 168, 310, 397, 412.

———. 1903. The influence of diet in pregnancy on the weight of the offspring. *Lancet*, 81st yr., 2: 21-22. 77, 78.

——— & Stockman, R. 1889. Observations on the metabolism of man during starvation. *Proc. Roy. Soc. Edinb.*, 16: 121-131. 72.

——— & Watson, A. 1921. Etiology of rickets; an experimental investigation. *Brit. J. Exp. Path.*, 2: 75-94. 2 pl. Also abstr. in *Brit. Med. J.*, 1921, 1: 594. 107.

Pearl, R. 1906. Variations in *Chilomonas* under favorable and unfavorable conditions. *Biometrika*, 5: 53-72. 18.

——— & Bacon, A. L. 1922. Biometrical studies in pathology. I. The quantitative relations of certain viscera in tuberculosis. *Johns Hopkins Hosp. Rep.*, 21: 157-230. Also abstr. in *Proc. Nat. Acad. Sc., Balt.*, 1922, 8: 125-128. 225, 272.

——— & Parker, S. L. 1924. Experimental studies on the duration of life. X. The duration of life of *Drosophila melanogaster* in the complete absence of food. *Amer. Nat.*, 58: 193-218. 6 figs. 62.

Peckham, F. E. 1920. Many orthopedic deformities due to calcium deficiency; a direct result of sterilized and pasteurized food. *J. Am. M. A.*, 75: 1317-1320. 142.

Peiper, H. 1922. Ueber den Lipoidgehalt der Nebennierenrinde des Meerschweinchens bei experimentellem Skorbut. *Klin. Wchnschr.*, 1: 1263-1264. 433.

Peiser, J. 1906. Ueber den Einfluss des Winterschlafes auf die Schilddrüse. *Ztschr. f. Biol.*, (N. F., Bd. 30), 48: 482-488. 441.

———. 1921. Ueber objektive Beurteilung des kindlichen Ernährungszustandes. *Jahrb. f. Kinderh.*, 3. F., 95: 195-206. (Abstr. in *J. Am. M. A.*) 122.

Pellegrin, J. 1901. Durée de la vie et perte de poids chez les ophiidiens en inanition. *Bull. Soc. philomat. de Par.*, 1899-1900, 9. S., 2: 112-116. Also in *Compt. rend. Soc. de biol., Par.*, 1901, 53: 119-120. 75, 462.

Pellegrini, R. 1916. (Effects of fasting on the suprarenals.) *Atti d. r. Ist. Veneto*, 72: 781-ff. (Abstr. from "Chem. Abstr." in *Endocrinol.*, 1917, 1: 354.) 427.

———. 1920. Contributo alla conoscenza della patologia del prigioniero di guerra. *Nota II. Giorn. di med. mil.*, 68: 32-56. (Cf. also *Boll. d. Soc. med. di Parma*, 1919, 2. s., 12: 67.) (Cited by Castaldi '22.) 419, 428.

Peller, S. 1917. Die Masse der Neugeborenen und die Kriegsernährung der Schwangeren. *Deut. med. Wchnschr.*, 43: 178-180. 79.

Penard, E. 1905. Observations sur les amibes à pellicule. *Arch. f. Protistenk.*, 6: 175-206. 18.

Penny, F. 1909. Notes on a thirty days' fast. *Brit. Med. J.*, 1: 1414-1416. 72, 243.

Pepere, A. 1906. Le ghiandole paratiroidee. *Ricerche anatomiche e sperimentali*. Torino, 326 pp. 5 tav. Also abstr. in *Arch. ital. de biol.*, 1907, 48: 67-93. 445.

Pérez, C. 1903. Sur la résorption phagocytaire des ovules par les cellules folliculaires, sous l'influence du jeûne chez le Triton. *Ann. Inst. Pasteur*, pp. 617-630. 1 pl. and 4 figs. Also abstr. in *Compt. rend. Soc. de biol., Par.*, 55: 716-718. 5 figs. 393.

Peri, A. 1892. Sulle alterazioni del sistema nervoso centrale e periferico indotte dalla inanizione acuta. *Sperimentale*, Mem. orig., 46: 286-305. (For abstract, see next title.) 195.

———. 1893. Sur les altérations du système nerveux central et périphérique produites par l'inanition aiguë. *Résumé. Arch. ital. de biol.*, 18: 193-203. 183, 195, 205.

- Peritz, G. 1911. Der Infantilismus. *Ergeb. d. inn. Med. u. Kinderh.*, 17: 405-486. 15 Abb.
- Perls. (Cited by Falck '75.)
- Pernice, B. e Scagliosi, G. 1893. Sugli effetti della privazione dell'acqua negli animali. *Rif. med.*, Napoli, 9: 461-463. Also in *Atti d. 11. Cong. med. internaz.*, Roma, 2: 215-218. (Cited by Pernice & Scagliosi '95.) 202.
- . 1895. Sulle alterazioni istologiche del sistema nervoso negli animali privati dell'acqua. *Pisani, Palermo*, 16: 173-180. (Cited by Barbacci '99 and Marinesco '09; see also next title.) 190, 202, 208, 221.
- . 1895a. Ueber die Wirkung der Wasserentziehung auf Tiere. *Experimentaluntersuchung. Arch. f. path. Anat. etc.*, 199: 155-184. 2 Taf. 115, 132, 155, 172, 190, 202, 208, 209, 221, 235, 237, 259, 268, 284, 302, 312, 323, 344, 355, 368, 387, 399, 401, 416.
- Perrando, G. G. 1902. Sulla struttura della tiroide dei néonati in varie condizioni anatomo-patologiche. *Studi Sassaesi*, 2: 1-115. 437.
- Pestagalli, G. 1850. Studi sull' inanizioni, desunti dell'opera del Chossat e da altri recenti lavori. *Gaz. med. ital. lomb.*, Milano, 2. s., 3: 10-12; 17-18.
- Peters, R. A. 1920. Nutrition of the protozoa. The growth of *Paramoecium* in a sterile culture medium. Preliminary communication. *Proc. Physiol. Soc., Lond. J. Physiol.*, 53: cviii-cix; 54: 1. 19.
- . 1921. The substances needed for the growth of a pure culture of *Colpidium colpoda*. *J. Physiol.*, 55: 1-32. 19.
- Petrow (Petrov or Petroff), V. A. 1883. (Zur Frage über das Hungern. Drei Variationen einer Form des sogenannten unvollständigen Hungerns.) (Russian.) *Protok. d. Konferenzsitz. d. K. mil. med. Akad.*, pp. 141-174. (Abstr. by Mühlmann '99.) 73, 74.
- . 1886. (Starvation in different periods of animal growth.) (Russian.) *Russk. Med.*, St. Petersburg, 11: 615-616; 632-633; 649.
- . W. (Pyotroff, V. S.) 1897. (Pathologisch-anatomische Veränderungen der Ovarien (von Kaninchen und Hunden) bei vollständigem Hunger und nachfolgender Auf-fütterung. *Exper. Untersuchung a. d. path.-anat. Inst. d. Prof. K. Winogradow.* (Russian.) *Dissert.*, St. Petersburg. (Abstr. by Mühlmann '99.) 393.
- Pfaundler, M. 1916. Körpermass-Studien an Kindern. Sonderabdruck a. d. *Ztschr. f. Kinderh.*, Bd. 14, 148 pp. 8 pl. Verlag J. Springer, Berl. 83, 85, 87.
- . 1919. Ueber Körpermasse von Münchener Schulkindern während des Krieges. *Münch. med. Wchnschr.*, 66: 859-862. 85.
- . 1921. Ueber die Indices der Körperfülle und über "Unterernährung." *Ztschr. f. Kinderh.*, 29: 217-244. 87.
- . 1922. Pathological changes of the blood and blood-forming organs. In *Feer's Textbook of Pediatrics*, English transl. by Sedgwick & Scherer. Sec. II, pp. 156-225. Lippincott Co., Phila. & Lond. 158, 188, 267, 282, 283, 342.
- Pfeiffer, L. 1887. Ueber den Fettgehalt des Körpers und verschiedener Theile desselben bei mageren u d fetten Thieren. *Ztschr. f. Biol. (N. F.)*, Bd. 5), 23: 340-380. 118, 134, 164, 170, 186, 227, 333.
- Pfützner, W. 1886. Zur pathologischen Anatomie des Zellkerns. *Arch. f. path. Anat. etc.*, 103: 273-300. 458.
- Pflüger, E. (Cited by Weber '02.) 77.
- Pick, L. 1920. Ueber einige Kriegsfolgen bei Augenleiden. *Deut. med. Wchnschr.*, 46: 44-45. 211.
- Pictet, A. 1905. Influence de l'alimentation et de l'humidité sur la variation des papillons. *Mém. Soc. phys. et d'hist. nat.*, Genève, 35: 46-127. 63.
- . 1905a. Des variations des papillons provenant des changements d'alimentations de leurs chenilles et de l'humidité. *Compt. rend. 6me Congr. internat. Zool.*, Berne pp. 408-507. 63.
- Pignet. 1900. Valeur numérique de l'homme. Nouveau mode d'appréciation de la force physique exprimée par un nombre tiré de la comparaison des trois mensurations: taille, périmètre et poids. *Arch. med. d'Angers*, 4: 345-361; 406-411; 453-461. 86.

von Pirquet, C. 1916. Sitzhöhe und Körpergewicht. (System der Ernährung. II.) Ztschr. f. Kinderh., 14: 211-288. 4 Fig. 85.

Pitz, W. 1918. Experimental scurvy. III. Influence of meat and various salts upon the development of scurvy. J. Biol. Chem., 36: 439-466.

Placzek, S. 1898. Ueber Veränderungen der Nervensubstanz beim Hungertode. Preuss. Med.-Beamten-Ver. Off. Ber., Berl., 15: 110-112. Also (Autoreferat) in Ztschr. f. Med.-Beamte, Berl., 11: 614. 193.

———. 1899. Rückenmarksveränderungen beim Hungertode des Menschen. Vrtl.-jschr. f. ger. Med., Berl., 3. F., 18: 101-106. 193, 196.

———. 1899a. Ueber Veränderungen des Nervensystems beim Hungertode. *Ibid.*, 17: 274-281. Also abstr. in Centralbl. f. Nervenheilk. u. Psychiatr., 1899, No. 115, pp. 485-486.

von Planta, A. (Cited by Geddes & Thompson '01.) 65.

Plateau, F. 1878. Recherches sur les phénomènes de la digestion et sur la structure de l'appareil digestif chez les Myriapodes de Belgique. Mém. de l'Acad. r. de Belgique. Vol. 42. (Cited by Childs '21.) 59.

Ploetz, A. J. 1890. Die Vorgänge in den Froschhoden unter dem Einfluss der Jahreszeit. Arch. f. Anat. u. Physiol., Physiol. Abt., Suppl., pp. 1-32. 2 Taf. 412.

———. (Cited by Geddes & Thompson '01.) 80.

Podhradský, J. 1923. Das Wachstum beim absoluten Hungern. Arch. f. Entw. d. Org., 52: 532-549. 30 Diagr. 77, 90, 135, 137.

Poňarkov (Poyarkoff), E. L. 1913. L'influence du jeûne sur le travail des glandes sexuelles du chien. Communication préliminaire. Compt. rend. Soc. de biol., Par., 74: 141-143. 408.

Pok, J. 1917. Ueber Kriegsamorrhoe. Zentralbl. f. Gyn., 41: 483-487. 391, 392, 399, 400.

Polanyi, M. 1911. Untersuchungen über die Veränderungen der physikalischen und chemischen Eigenschaften des Blutserums während des Hungerns. Biochem. Ztschr., 34: 192-204. (Ind. Med.)

Poletaew (Poletayeff), P. N. 1893. Sur la composition morphologique du sang dans inanition par abstinence complète et incomplète. (French and Russian.) Arch. de sc. biol. (Arch. biol. nauk), St. Petersb., 2: 794-901. 250, 251.

———. 1894. (Die morphologische Zusammensetzung des Blutes beim vollständigen und unvollständigen Hungern der Hunde.) (Russian.) Thèse, St. Petersb., 97 pp. (Abstr. by Mühlmann '99 and Bardier '13.) 250, 251.

———. 1895. Sulla composizione morfologica del sangue nell'inanizione per astinenza completa e incompleta. Riv. internaz. d'ig., Roma, 6: 129-134. 250.

Policard, A. 1909. Notes histophysiologiques sur la cellule hépatique. I. Les formations filamenteuses de la cellule hépatique de la grenouille; modifications pendant la digestion. Compt. rend. Soc. de biol., Par., 66: 352-354. 337.

———. 1909a. Notes histophysiologiques sur la cellule hépatique. II. Sur certaines formations colorables par l'hématoxyline ferrique dans la cellule hépatique des mammifères. *Ibid.*, 66: 465-467. 337.

———. 1910. Faits et hypothèses concernant la physiologie de la cellule intestinale. *Ibid.*, 68: 8-10. 321.

Polimanti, O. 1904. Sulle variazioni di peso delle marmotte (*Arctomys marmotta*) in ibernazione. Bull. d. r. Accad. med. di Roma, 30: 227-261. 1 ch. 70.

———. 1905. Sur les variations de poids des marmottes (*Arctomys marmotta*) en hibernation. Arch. ital. de biol., 42: 341-367. 1 pl. 70.

———. 1909-10. Il letargo. Atti Soc. ligust. sc. nat., Genova, 20: 34-47; 117-135; 21: 161-224 225-369. (Cited by Rasmussen '16.) 70.

———. 1913. Il letargo. Tipogr. del Senato di G. Bardi, 684 pp. 70, 254.

Poljakoff, P. 1888. Ueber eine neue Art von fettbildenden Organen im lockeren Bindegewebe. Arch. f. mikr. Anat., 32: 123-182. 3 Taf. (Also in Russ. Med., 1888, No. 4.) 125, 235.

- . 1895. Beiträge zur mikroskopischen Anatomie und Physiologie des lockeren Bindegewebes. *Ibid.*, 45: 574-592. 1 Taf. 125.
- de Pommer. 1828. Suc gastrique, effets de l'abstinence des alimens. *Méd.-chir. Ztg.*, vol. 1, No. 4. (Abstr. in *Arch. gén. de méd., Par.*, 1828, 18: 558.) 305.
- Pommer, G. 1885. Untersuchungen über Osteomalacie und Rachitis, nebst Beiträgen zur Kenntniss der Knochenmarkresorption und Apposition in verschiedenen Altersperioden und der durchbohrenden Gefässe. F. C. W. Vogel, Lpz., 506 pp. 7 Taf. 145, 146.
- . 1909. Diskussion zu den Vorträgen über Rachitis und Osteomalacie. *Centralbl. f. allg. path., etc. Verh. d. deut. path. Ges.*, 13: 55, 62, 13.
- Ponomarew, A. A. 1914. Ueber den Ursprung der Fettsubstanzen in der Nebennierenrinde. *Beitr. z. path. Anat. etc.*, 59: 349-370. 1 Taf. 424.
- Popel, W. (V. L.). 1896. Sur les variations de la densité du sang dans le jeûne absolu, simple ou compliqué de la ligature des uréters. (French and Russian.) *Arch. d. sc. biol. (Arch. biol. nauk.) St. Petersb.*, 4: 354-376. 251.
- Popoff, M. 1907. Depression der Protozoenzelle und der Geschlechtszellen der Metazoen. In R. Hertwig's Festband. *Arch. f. Protistenk., Suppl. I.*, pp. 43-82. 17.
- . 1910. Ein Beitrag zur Chromidialfrage. Nach Untersuchungen an Musciden. *Festschr. zum 60. Geburtstag von R. Hertwig*, 1: 19-48. 3 Taf. u. 2 Fig. G. Fischer, Jena. 61.
- Popovici-Bazosanu, A. 1910. Relation entre la taille de l'adulte et la quantité de nourriture absorbée par les larves chez l'*Osmia rufa* et l'*Osmia cornuta*. *Compt. rend. Soc. de biol., Par.*, 68: 480-481. 65.
- Popow (Popov, Popoff), L. (V.). 1885. (Addition to Dr. Ruppert's article: "Case of stricture of the esophagus" and examples; a few notes on the process of hunger in general.) (Russian.) *Investig. and notes of the Therap. Clinic, Hosp. Warsaw Imp. Univ.*, ed. by L. V. Popov, Warsaw, pp. 65-112. (Also abstr. under German title by Mühlmann '99 and Bardier '13.) 181, 194, 230, 325, 332, 371.
- . 1885a. Ein Fall von Pylorusstenose, *Klin. Samml. d. Warschauer Universitätsklinik*, unter Red. von Prof. L. Popow, Warschau. (Abstr. by Statkewitsch '94.) 166, 181, 332, 371.
- . N. 1882. (Material zum Studium der acuten Myelitis toxischen Ursprungs.) *Russian Dissert., St. Petersb.* (Cited by Statkewitsch '94.) 181.
- Porter, A. 1878. Notes on the post-mortem appearances in cases of famine-stricken natives. *Doctor, Lond.*, 8: 61-ff.
- . 1885-'87. Notes on famine diseases. *Dublin J. Med. Sc.*, 1885, 3. s., 80: 361-ff; 1886, 82: 275-ff; 357-ff; 472-ff; 505-ff; 1887, 83: 134-ff; 253-ff. (See also under next title.) 174.
- . 1886. Dropsy in famine. *Ind. Med. Gaz., Calcutta*, 21: 195, 227. (Ind. cat., S. G. L.)
- . 1887. Death from starvation. *Dublin J. Med. Sc.*, 3. s., 84: 106-112. (Ind. cat. S. G. L.)
- . 1889. The diseases of the Madras famine of 1877-78. *Gov't. Press, Madras*, 262 pp. 9 pl. 71, 88, 120, 128, 174, 224, 229, 240, 262, 271, 277, 302, 304, 313, 325, 346, 362, 371, 391, 399.
- . W. T. 1893. Untersuchungen der Schulkinder in Bezug auf die physischen Grundlagen ihrer geistigen Entwicklung. *Verh. d. Berl. Ges. f. Anthrop., Ztschr. f. Ethnol.*, 25: 337-354. (Cf. also *Trans. St. Louis Acad. Sc.*)
- Portier, P. 1920. Modifications du testicule des oiseaux sous l'influence de la carence. *Compt. rend. Acad. des sc., Par.*, 170: 755-757. 415.
- . 1920a. Régénération du testicule chez le pigeon carencé. *Ibid.*, 170: 1339-1341. 415.
- Pouchet, G. et Chabry, L. 1889. L'eau de mer artificielle comme agent tératogénique. *J. de l'anat. et de la physiol.*, 25: 298-307. 4 figs. 48.
- . 1889a. Sur le développement des larves d'oursin dans l'eau de mer privée de chaux. *Compt. rend. Soc. de biol., Par.*, 41: 17-20. 48.

- . 1889b. De la production des larves monstreuses d'oursin, par privation de chaux. *Compt. rend. Acad. de sc., Par.*, 108: 196-198. **48.**
- Poulton, E. B. 1893. On the sexes of larvae emerging from the successively laid eggs of *Smerinthus populi*. *Trans. Entom. Soc. Lond.*, pp. 451-456. **29, 63.**
- Powers, J. H. 1903. The causes of acceleration and retardation in the metamorphosis of *Amblystoma tigrinum*. A preliminary report. *Amer. Nat.*, 36: 385-410. **77.**
- Prandtl, H. 1906. Die Konjugation von *Didinium nasutum*. *Arch. f. Protistenk.*, 7: 220-258. **17, 20.**
- Prantl, K. 1881. Beobachtungen über die Ernährung der Farnprothallien und die Vertheilung der Sexualorgane. *Bot. Ztg.*, 39: 753. (Cited by Reed '07 and O. Schultze '03.) **11.**
- Pratje, A. 1921. *Noctiluca miliaris* Suriray. Beiträge zur Morphologie, Physiologie und Cytologie. I. Morphologie und Physiologie. Beobachtungen an der lebenden Zelle. *Arch. f. Protistenk.*, 42: 1-98. 5 Taf. u. 9 Textfig. **18.**
- Preble, E. 1917. Starvation. In *Ref. Handb. of the Medical Sciences*, 3d ed., N. Y., 7: 925-926.
- Prince, M. A. 1921. Note sur la mortalité et la "maladie des oedemes" a l'aisle de Hoerd (Bas-Rhin) pendant la guerre. *Encephale*, 28r., 16: 526-532. **71, 102, 188, 232, 281, 342, 384.**
- Prinzing, F. 1916. Epidemics resulting from wars. Oxford Univ. Press, 340 pp. **71.**
- Pritchard, E. 1919. The causation and treatment of rickets. *Brit. Med. J.*, 2: 627-629.
- Prochownick, L. 1889. Ein Versuch zum Erstaze der künstlichen Frühgeburt. *Zentralbl. f. Gyn.*, 13: 577-581. (Cited by Reed '95.) **79, 104.**
- . 1901. Ueber Ernährungskuren in der Schwangerschaft. *Therap. Monatsh.*, 15: 387-403; 446-463. (Cited by Tobler & Bessau.) **79, 104.**
- . 1917. Ueber Ernährungskuren in der Schwangerschaft. *Ibid.*, 41: 785-794. (Also in *Therap. Monatsh.*, 1901, 15: 387-403; 446-463.) **79, 104.**
- Prugavin, A. S. 1906. Starving peasantry. (Russian, 1898-'99.) (Cited by Morgulis '23.) **216.**
- Prunelle. 1811. Recherches sur les phénomènes et sur les causes du sommeil hivernal de quelques mammifères. *Ann. du Museum*. (Cited by Baroncini e Beretta '01.) **253.**
- Przibram, H. 1907. Equilibrium of animal form. *J. Exp. Zool.*, 5: 259-264. **59.**
- Puetter, A. 1911. Vergleichende Physiologie. G. Fischer, Jena, 721 pp. **27, 47.**
- Pugliese, A. 1904. Studi sulla rialimentazione. Nota 1. Il peso del fegato e la funzione glicogenetica del fegato e dei muscoli nei primi giorni della rialimentazione. *Bull. di sc. med. di Bologna*, Anno 75, ser. 7, 4: 135-148. **336.**
- . 1905. Cambiamenti morfologici dell'epitelio delle ghiandole digestive e dei villi intestinali nei primi giorni della rialimentazione. *Ibid.*, Anno 76, ser. 8, 5: 267-284. 1 tav. (See also next title.) **321, 336, 352, 358.**
- . 1905a. Changements morphologiques de l'épithélium des glandes digestives et des villosités intestinales dans les premiers jours de la réalimentation. *Arch. ital. de biol.*, 44: 49-65. 1 pl. **321, 352, 358.**
- Puglisi-Allegra, S. 1900 (?). Sulle alterazioni del sistema nervosa nel inanizione. *Atti d. r. Accad. Peloritana*. Anno 15, 16 pp. (Cited by Legendre '09.) **184.**
- Punnett, R. C. 1906. Sex determination in *Hydatina*, with some remarks on parthenogenesis. *Proc. Roy. Soc. Lond.*, Ser. B, 223-230. 1 pl. (Cited by Shull '10 and Green '19.) **57.**
- Pyotroff, V. S. (Petroff, W.) 1897. (Pathologo-anatomical alterations of the ovaries of rabbits and dogs during complete starvation and refeeding.) Russian thesis, St. Petersburg, 48 pp. (Ind. cat., S. G. L.) **393.**
- Quattrochi, S. 1901. Alterazioni del tubo gastroenterico di cagnolini resi atrofici per insufficiente, cattiva, o irregolare alimentazione. *Studio sperimentale*. *Pediatria*, Napoli, 9: 49-64. **165, 275, 307, 318, 335.**
- Querton, L. 1898. Le sommeil hivernal et les modifications des neurones cérébraux. *Trav. de Lab. de l'Inst. Solvay*, Bruxelles, T. 2, F. 1, 2, 58 pp. 4 tab. **185, 197.**

- Quest, R. 1905. Ueber extreme Körpergewichtsabnahmen bei Kindern der ersten zwei Lebensjahre. *Monatschr. f. Kinderh.*, 3: 453-464. **82, 97.**
- . 1906. Ueber den Einfluss der Ernährung auf die Erregbarkeit des Nervensystems im Säuglingsalter. *Wien. klin. Wchnschr.*, 19: 830-833. **109, 131, 188.**
- Quincke, H. 1882. Ueber die Wärmeregulation beim Murmelthier. *Arch. f. exp. Path. u. Pharm.*, 15: 1-21. 1 Taf. **253.**
- Quinquaud, C. E. 1885. Sur la dénutrition expérimentale. *Compt. rend. Acad. des sc.*, Par., 101: 1166-1177.
- Rabe, F. 1910. Experimentelle Untersuchungen über den Gehalt des Knorpels an Fett und Glycogen. *Beitr. z. allg. Path. etc.*, 48: 554-575. **137, 338.**
- Rabl, C. 1885. Ueber Zelltheilung. *Morph. Jahrb.*, 10: 287. **121, 302.**
- Rabnow, L. J. 1916. Entwicklung der Neugeborenen des zweiten Kriegsjahres. *Deut. med. Wchnschr.*, 42: 1388. **79.**
- Raimondi, R. 1917. Contribution à l'étude des nourrissons atrophiques, hypotrophiques et dystrophiques. *Presse méd.*, Par., 25: 14-17. **81.**
- Ramond, F. 1908. Sur l'état clair des cellules hépatiques. *Presse méd.*, Par., p. 779. **336.**
- Ramsey, W. R. 1908. The simple atrophy of infants and its relation to food. *St. Paul Med. J.*, 10: 676-684.
- & Alley, A. A. 1918. Observations on the nutrition and growth of newborn infants; an analysis of 300 clinical charts. *Am. J. Dis. Child.*, 15: 408-412. **81.**
- Ranke, H. 1884. Ein Saugposter in der menschlichen Backe. *Arch. f. path. Anat. etc.*, 97: 527-547. **123.**
- Ranvier, L. 1885. Les membranes muqueuses et le système glandulaire. Le foie. *J. de microgr.* Nos. 1-12. 9: 6-ff, 55-ff, 103-ff, 155-ff, 194-ff, 240-ff, 287-ff, 334-ff, 389-ff, 438-ff, 480-ff. **332.**
- Rasmussen, A. T. 1916. The corpuscles, hemoglobin content, and specific gravity of the blood during hibernation in the woodchuck (*Marmota monax*). *Am. J. Physiol.*, 41: 464-482.
- . 1916a. Theories of hibernation. *Amer. Nat.*, 50: 609-625. **254.**
- . 1917. Seasonal changes in the interstitial cells of the testis in the woodchuck (*Marmota monax*). *Am. J. Anat.*, 22: 475-515. 1 chart, 3 pl. **412.**
- . 1918. Cyclic changes in the interstitial cells of the ovary and testis in the woodchuck (*Marmota monax*). *Endocrinol.*, 2: 353-404. 4 pl. **398, 412.**
- . 1919. The mitochondria in nerve cells during hibernation and inanition in the woodchuck (*Marmota monax*). *J. Comp. Neurol.*, 31: 37-49. **185, 198, 204.**
- . 1921. The hypophysis cerebri of the woodchuck (*Marmota monax*) with special reference to hibernation and inanition. *Endocrinol.*, 5: 33-66. 5 figs. **455.**
- . 1922. The glandular status of brown multilocular adipose tissue. *Ibid.*, 6: 760-770. **126.**
- . 1923. The so-called hibernating gland. *J. Morph.*, 38: 147-205. 8 pl. **126.**
- & Myers, J. A. 1916. Absence of chromatolytic change in the central nervous system of the woodchuck (*Marmota monax*) during hibernation. *J. Comp. Neurol.*, 26: 391-401. 2 pl. **185, 198.**
- & Rasmussen, G. B. 1917. The volume of the blood during hibernation and other periods of the year in the woodchuck (*Marmota monax*). *Am. J. Physiol.*, 44: 132-148. **254.**
- Rathery, F. 1909. État granuleux de la cellule hépatique normale. Ses rapports avec la teneur en glycogène de la cellule hépatique. *Compt. rend. Soc. de biol.*, Par., 65: 469-471. **336, 337.**
- . 1909a. La cellule hépatique normale de l'état granuleux. Son importance dans l'interprétation exacte des alterations anatomo-pathologiques du foie. *Arch. de méd. exp. et d'anat. path.*, 21: 50-63. 4 figs. **337.**
- et Terroine, E. F. 1913. Mitochondries et graisse décelable histologiquement dans la cellule hépatique, au cours de régimes variés. *Compt. rend. Soc. de biol.*, Par., 75: 47-49. **338.**

- Rau, P. & Rau, N. 1912. Longevity in saturniid moths: An experimental study. *J. Exp. Zool.*, 12: 179-204. 62.
- Raubitschek, H. 1915. Pathologie, Entstehungsweise und Ursache der Pellagra. *Ergeb. d. allg. Path. etc.*, 18: 662-786. 103, 130, 140, 170, 187, 200, 206, 232, 236, 281, 322, 342, 354, 367, 385, 398, 401, 413, 431, 442.
- von Raumer, E. 1883. Kalk und Magnesia in der Pflanze. *Landw. Versuchsst.*, 29: 253-280. 8, 9.
- Raymond, P. 1889. Les altérations cutanées de la pellagre. *Ann. de dermat. et de syphil.*, 2. ser., 10: 627-ff. (Cited by Raubitschek '15.) 130.
- Reach, F. 1919. Kriegsödem und endokrine Hodenfunktion. *Wien. klin. Wchnschr.*, 31: 1249-1250. 413.
- Reaumur. 1742. *Histoire des insectes*. 6: 268-? (Cited by Lucas 1826, but not found on page cited.) 65.
- von Recklinghausen, F. 1910. Untersuchungen über Rachitis und Osteomalacie. G. Fischer, Jena, 574 pp. 41 Taf. 135, 145.
- Redi, F. 1684. *Traité des animaux vivants*. Florence. (Cited by Chossat '43.)
- . 1708. *Animal. vivent. etc.* Amsterdam. (Cited by Bardier '13.)
- . 1729. *Nobil. Aretini opusc., pars tertia, sive de animalibus vivis quae in corporibus animalium vivorum reperiuntur, observationes*. Lugd. Bat. (Cited by Lucas 1826.)
- . 1741. *Degli animali negli animali viventi*. Édit. de Venise. (Cited by Manca '95a.)
- . 1778. *Osservazioni intorno agli animali viventi che si trovano negli animali viventi*. In *Opere di Francesco Redi, gentiluomo Aretino etc.* Seconda edizione Napoletana corretta e migliorata. Tom. II. Napoli. (pp. 53-55). (Cited by Falck '75.)
- Reeb, M. 1905. Ueber den Einfluss der Ernährung der Muttertiere auf die Entwicklung ihrer Früchte. *Beitr. z. Geburtsh. u. Gyn.*, 9: 395-412. 78, 401.
- Reed, H. S. 1907. The value of certain nutritive elements to the plant cell. *Ann. Bot.*, 21: 501-543. 2 figs. 5, 6, 7, 8, 9, 10.
- Reese, A. M. 1913. The histology of the enteron of the alligator while hibernating and while feeding. (Abstr.) *Science, N. S.*, 37: 267. 302, 311.
- . 1913a. The histology of the enteron of the Florida alligator. *Anat. Rec.*, 7: 105-130. 302, 311.
- Reeve, H. 1809. *An essay on the torpidity of animals*. Lond., 152 pp. (Cited by Rasmussen '16a.)
- Regnault, F. 1899. Le crâne rachitique. *Rev. mens. des mal. de l'enf., Dec.* (Abstr. in *Jahrb. f. Kinderh.*, 1900, 51: 598.) 142.
- Reichel. 1921. Ueber Osteopathie. *Münch. med. Wchnschr.*, 68: 1242-1244.
- Reicher, K. 1909. Zur Kenntniss der prä-mortalen Stickstoffsteigerung. *Ztschr. f. exp. Path. u. Therap.*, 5: 750-760. 241.
- Reijenge, J. 1896. Die Prochowicksche Diätkur etc. *Dissert., Freiburg*, 64 pp. (Cited by Reeb '05.) 78.
- Reimers, P. u. Boye. 1905. Ein Beitrag zur Lehre von der Rachitis. *Centralbl. f. inn. Med.*, 26: 953-962. (Cited by Schabad '10.) 147.
- Reinke, F. 1906. Die Beziehungen des Lymphdruckes zu den Erscheinungen der Regeneration und des Wachstums. *Arch. f. mikr. Anat.*, 68: 252-278. 186, 198.
- Reisinger. 1820. Die künstliche Frühgeburt etc. Augsburg, 360 pp. (Cited by Reeb '05.) 78.
- Reiss, E. 1921. Die Reizlosigkeit der Kriegskost als Krankheitsursache. *Therap. Monatshefte*, 35: 765-772. 229, 244, 311.
- Rennie, J. 1909. On the relation of the islets of Langerhans to the alveoli of the pancreas. *Internat. Monatschr. f. Anat. u. Physiol.*, 26: 197-205. 345, 352.
- Report on pellagra among Turkish prisoners of war. Alexandria, Dec. 31, 1918. (Cited by McCarrison '21.) (*Cf. J. Roy. Army Corps, Lond.*, 1919, 33: 445; 508; 1920, 34: 70; 173; 272.)

- Repreff, A. 1893. (Effects of starvation upon the human organism.) (Russian.) *Izviest. Imp. Tomsk. Univ.*, 5: 323-339.
- Retan, G. M. 1920. The measure and development of nutrition in childhood. *Arch. of Pediatr.*, 37: 32-39. 5 charts. 85.
- Retterer, E. 1902. Sur les circonstances dans lesquelles on obtient la disparition des hématies du ganglion lymphatique ou leur stase dans les sinus de l'organe (glande hémolympatique). *Compt. rend. Soc. de Biol., Par.*, 54: 33-37. 261, 264.
- . 1902a. Sur les modifications que détermine l'abstinence dans les ganglions lymphatiques. *Ibid.*, 54: 101-103. 265.
- . 1902b. Structure et fonctions des ganglions lymphatiques dans l'espèce humaine. *Ibid.*, 54: 103-107. 263.
- . 1913. Evolution et hématisation dans les ilots de Langerhans. *J. de l'anat. et de physiol.*, 49: 489-505. 345, 353.
- Retzius, G. 1881. Studien über die Zelltheilung. Stockholm u. Lpz. (Cited by Morgulis '23.)
- Reuter, K. 1903. Ein Beitrag zur Frage der Darmresorption. *Anat. Hefte*, H. 66 pp. 121-144. 4 Taf. 321.
- Reynal, J. 1911. L'hypoalimentation chez le nourrisson. Thèse méd., Montpellier, No. 116, 1910-11.
- Reyne, L. 1881. De la crise hématique dans les maladies aiguës à défervescence brusque. Thèse, Par., No. 393, 83 pp. (Cited by Hayem '89.) 250.
- Reynolds, E. & Macomber, D. 1921. Defective diet as a cause of sterility. A study based on feeding experiments with rats. *J. Am. M. A.*, 77: 169-175. 11 figs. 398, 413, 414.
- . 1921a. Certain dietary factors in the causation of sterility in rats. *Am. J. Obst. & Gyn.*, 2: 379-394. 14 figs. 398, 413, 414.
- Rezza, A. 1912. Beitrag zur pathologischen Anatomie der Pellagrapsychosen. *Ztschr. f. d. ges. Neur. u. Psychiatr., Orig.*, 12: 1-30. 2 pl. (Cited by Raubitschek '15 and Harris '19.) 200.
- Ribbert, H. 1909. Lehrbuch der allgemeinen Pathologie und pathologischen Anatomie. 3. Aufl., Lpz. (Cited by Mönckeberg '12.) 145.
- . 1912. Pathologie. In *Handbuch der Naturwissenschaften*, 7: 525-555.
- . 1913. Beitrag zur Rachitis. *Deut. med. Wchnschr.*, 39: 8-10. 146.
- Richet, C. 1886. Du coefficient de dénutrition. *Compt. rend. Soc. de biol., Par.*, 38: 623-627.
- . 1889. L'inanition chez les animaux. *Rev. scient., Par.*, 43: 641-647; 711-715.
- . 1889a. L'inanition chez l'homme. *Ibid.*, 43: 801-804; 44: 106-112.
- . 1893. L'inanition. In *Richet's Physiol. trav. du lab. de physiol. Par.*, 2: 267-325. (Cited by Rosenstern '11.)
- . 1906. Expériences sur les alternances du jeûne et d'alimentation chez les lapins. *Compt. rend. Soc. de biol., Par.*, 61: 546-548.
- . 1920. (Fasting records. Cited by *J. Am. M. A.*, Oct. 30, 1920 from *Vie médicale*.)
- . C. Jr. et Mignard, M. 1919. Le syndrome d'hypotrepisie chez les prisonniers français repatrié d'Allemagne. *Bull. de l'Acad. de Méd., Par.*, 81: 481-486. 120, 136, 342.
- Richter, J. 1917. Einfluss des Krieges auf die Geburtshilfe. *Zentralbl. f. Gyn.*, 41: 761-769. 79, 80.
- . P. F. 1906. Stoffwechsel und Stoffwechsel-krankheiten. Berl., 389 pp. (Cited by Barker '16.) 82.
- Ricklin, E. 1879. Des altérations de la moelle des os longs dans leurs rapports avec les états cachectiques. *Gaz. méd. de Par.*, pp. 177-178; 225-226; 237-238. 125, 136.
- Rieber, O. W. 1905. Ueber die Leukocyten bei der Säuglingsatrophie nebst eigener Leukocytenzählungen an zwei atrophischen Kindern. *Dissert. med., Freiburg i. Br.* 247.
- Rietschel, H. 1908. Ueber Mehle und Mehlfütterungen bei Säuglingen und ihre Beziehungen zum Stoffwechsel. *Deut. med. Wchnschr.*, 34: 826-830.

- Rievel, H. 1907. Knochenpathologie der Tiere. *Ergeb. d. allg. Path. etc.*, Bd. 11, 2. Abt., pp. 590-708. **145.**
- Rignano, E. 1911. Upon the inheritance of acquired characters. Engl. transl. by B. C. H. Harvey, Chicago. **3.**
- Riley & Johannsen. 1915. Handbook of medical entomology. 349 pp. Comstock Co., Ithaca, N. Y. **60.**
- Rindfleisch. 1868. *Jahrbuch d. patholog. Geweb.*, 3: 383-ff. (Cited by Statkewitsch '94.) **331.**
- Ritter, C. 1920. Ueber Epithelkörperchenbefunde bei Rachitis und anderen Knochenerkrankungen. *Frankf. Ztschr. f. Path.*, 24: 137-176. 8 Abb. **446, 447.**
- Riva, E. 1905. Lesioni del reticolo neurofibrillare della cellula nervosa nell'inanizione sperimentale studiata con i metodi del Donaggio. 1. Nota. *Riv. sper. freniatr.*, 31: 245-250. **184, 197, 204.**
- . 1905a. Sulla presenza di corpuscoli all'interno delle cellule nervose spinali nell'inanizione sperimentale. *Ibid.*, 31: 251-255.
- . 1907. Lésions du réseau neurofibrillaire de la cellule nerveuse, dans l'inanition expérimentale étudiées avec les méthodes de Donaggio. *Arch. ital de biol.*, 46: 437-447. 1 pl. (From orig. in *Riv. sper. freniatr.*, 1906, 32: 400-409. 1 tav.) **184, 197, 204.**
- . 1907a. Lésions primaires des fibres nerveuses spinales produites par diverses conditions expérimentales et examinées avec la méthode de Donaggio pour les dégénérescences. *Ibid.*, 48: 156. (From orig. in *Riv. sper. freniatr.*, T. 32, 1907.)
- Roaf, H. E. 1920. A contribution to the pathology of pellagra. *J. Roy. Army Med. Corps*, 34: 534-538 (*Physiol. Abstr.*, 1921, 5: 577-578). **431.**
- Robb, E. F., Medes, G., McClendon, J. F., Graham, M. & Murphy, I. J. 1921. A study of scurvy and its bearing on the preservation of the teeth. *J. Dent. Res.*, 3: 39-61. 5 figs. **161, 433.**
- Roberts, D. 1907. Underfeeding and its associated ills. *Boston Med. & Surg. J.*, 157: 692-695.
- L. 1923. What is malnutrition? U. S. Dept. Labor, Children's Bureau, Publ. No. 59, 20 pp. Govt. Printing Office, Washington. **87.**
- S. R. 1912. Pellagra. H. Kimpton, Lond., & C. V. Mosby, St. Louis, 272 pp. 1 pl. **130, 140, 200, 311.**
- . 1920. Types and treatment of pellagra. *J. Am. M. A.*, 75: 21-25. **103.**
- Robertson, T. B. 1913. Studies in the blood relationship of animals as displayed in the composition of the serum proteins. I. A comparison of the sera of the horse, rabbit, rat and ox with respect to their content of various proteins in the normal and fasting condition. *J. Biol. Chem.*, 13: 325-340. **241.**
- . 1914. The postnatal loss of weight in infants and the compensatory overgrowth which succeeds it. Preliminary communication. *Proc. Soc. Exp. Biol. & Med.*, 12: 66. **81.**
- . 1915. Studies on the growth of man. II. The postnatal loss of weight in infants and the compensatory overgrowth which succeeds it. *Am. J. Physiol.*, 37: 74-85. **81, 94.**
- . 1923. Growth and development. In *Abt's Pediatrics*, 1: 445-519. Saunders & Co., Phila. **81, 87, 95.**
- . 1923a. The chemical basis of growth and senescence. 389 pp. J. B. Lippincott Co., Phila. & Lond. **460.**
- W. 1899. Normal and pathological histology of the nerve cell. *Brain*, 22: 203-327. 14 figs. **185, 196.**
- Robolotti. 1865. Studi sulla pellagra. *Gaz. Med. Ital. Ven.*, pp. 1, 9, 17, 25, 33, 45, 53, 69, 81, 91. (Cited by Harris '19.) **103.**
- de Rochas, A. 1902. Les longs jeûnes. *Ann. d. sc. psych., Par.*, 12: 65-96. 2 figs. **69.**
- Rodgers, J. E. D. 1877. Report of post-mortem examination and on the cause of death of Harriet Staunton, aged 35. (The Penge case.) *Brit. Med. J.*, 2: 604.

- Roehmann, F. 1903. Allg. med. Centr.-Ztg., 72: 14. **109.**  
 ———. 1916. Ueber künstliche Ernährung und Vitamine. Berl., 150 pp. 19 Fig. u. 2 Taf. **107, 109.**
- Roessle, R. 1919. Allgemeine Pathologie und pathologische Anatomie. Bedeutung und Ergebnisse der Kriegspathologie. Jahreskurse f. arztl. Fortbildung, 10: 19–ff. **71, 224, 326, 347, 372, 419, 436, 449.**
- Roger, H. 1907. Le variations de l'eau dans l'organisme des inanitiés. Presse méd., Par., 15: 673–675. **170, 186, 252, 280, 336, 366, 379, 404.**  
 ——— et Josué. 1900. Des modifications histologiques de la moelle osseuse dans l'inanition. Compt. rend. Soc. de biol., Par., 52: 417–419. **136, 137.**  
 ———. 1900a. Des modifications chimiques de la moelle dans l'inanition. *Ibid.*, 52: 419–421.
- Rohrer, F. 1908. Eine neue Formel zur Bestimmung der Körperfülle. Korr. Bl. d. deutsch. Ges. f. Anthrop., Ethnol. u. Urgesch., Jahrg. 39, Nr. 1–2. (Cited by Guttmann '22.) **85, 86.**  
 ———. 1921. Der Index der Körperfülle als Mass des Ernährungszustandes. Münch. med. Wechschr., 68: 580–582. **85.**
- Rokitansky, C. 1854. A manual of pathological anatomy. vol. 1. Transl. by W. E. Swaihe, Sydenham Soc., Lond., (pp. 49 ff.) **134, 163, 174, 181, 204, 240.**
- Roloff, F. 1866. Ueber Osteomalacie und Rachitis. Arch. f. path. Anat., etc., 37: 433–503. **77, 144.**  
 ———. 1875. Ueber Osteomalacie und Rachitis. Arch. f. wiss. u. prakt. Tierheilk., 1: 189–220. (Cf. also *ibid.*, 1879, 5: 152–ff.) **144.**
- Rolph, W. H. 1884. Biologische Probleme. Lpz., 238 pp. **16, 393.**
- Rondoni, P. 1911. Ricerche e consider. sul maldismo sperimentale. Ricerche di biologia dedicate al Prof. A. Lustig, Firenze, p. 299. (Cited by Rondoni e Montagnani '15.)  
 ———. 1915. Ricerche sulla alimentazione maldica con speciale riguardo alla eziologia della pellagra. Sperimentale, 69: 723–798. (Cited by Harris '19.) **103, 431, 442.**  
 ———. 1919. Remarks on the pathogenesis of deficiency diseases and on pellagra. Brit. Med. J., pp. 542–544. **103, 281, 342, 431.**  
 ———. 1922. Zur Frage des Einflusses der Ernährung auf die Blutdrüsen und insbesondere auf den Adrenalingehalt der Nebennieren. Ztschr. f. d. ges. exp. Med., 29: 197–199. **354, 431, 433, 442, 445.**  
 ——— e Montagnani, M. 1915. Lesioni istologiche nel maldismo, nel digiuno e nello scorbuto sperimentale. Sperimentale, 69: 659–696. **103, 234, 280, 281, 342, 366, 380, 409, 424, 427, 429, 431, 438.**
- Ronsse, I. et Van Wilder, H. 1903. Variations du nombre des globules rouges et du taux de l'hémoglobine au cours de l'inanition chez le lapin. Arch. internat. de pharmacod., Brux. et Par., 11: 301–312. **251.**
- Root, F. M. 1914. Reproduction and reactions to food in the suctorian, *Podophyra collini* (n. sp.). Arch. f. Protistenk., 35: 164–196. 11 figs. **20.**
- Rosemann, R. 1911. Beiträge zur Physiologie der Verdauung. III Mittheilung. Die Magensaftsekretion bei Verminderung des Chlorvorrates des Körpers. Arch. f. d. ges. Physiol., 142: 208–234.
- Rosenbach (Rozenbakh), P. I. 1883. (Effect of starvation on the nerve centers.) Russian thesis, St. Petersburg., 105 pp. 4 figs. and 1 pl. **182, 194, 204, 462.**  
 ———. 1884. (Effect of hunger on the nerve centers.) (Russian.) Vet. Vestnik, Kharkov, 3: 17–26. (Abstr. by Beeli '08.) **182, 194, 204.**  
 ———. 1884a. Ueber die Bedeutung der Vacuolenbildung in den Nervenzellen. Neurol. Centralbl., 3: 54–56. **183.**  
 ———. 1884b. Des allures du système nerveux dans l'inanition. Soc. de psychiatr. et des mal. nerv. de Berl., 14. juillet. (Cited by Marchand et Vurpas '01.)  
 ———. 1884c. Das Nervensystem im Hungerzustande. Centralbl. f. Nervenheilk. 7: 33–34. (Abstr. of Rosenbach '83?) **183.**

- Rosenfeld, G. 1886. Die Gefahren der Entfettungskuren. F. Enke, Stuttgart, 32 pp. **115, 388.**
- Rosenheim, T. 1891. Ueber den gesundheitsschädigenden Einfluss eiweissarmer Nahrung. Arch. f. Physiol., pp. 341-344. **100, 322, 341.**
- Rosenstern, I. 1911. Ueber Inanition im Säuglingsalter. Ergeb. d. inn. Med. u. Kinderh., Berl., 7: 332-404. **69, 70, 81, 82, 97, 120, 248.**
- Ross, S. G. 1921. Nutritional keratomalacia in infants, with report of four cases. Am. J. Dis. Child., 22: 232-243. **220.**
- Rossi, E. 1898. Alterazioni degli elementi cellulari nervosi nella pellagra. Ann. di freniatr., pp. 331-334. (Cf. also *ibid.*, pp. 91-97 and 1899, pp. 182-196.) (Cited by Harris '19.) **187, 199, 206.**
- . O. 1910. Nuove ricerche sui fenomeni di rigenerazione che si svolgono nel midollo spinale. Rigenerazione negli animali ibernanti. Riv. patol. nerv. e ment., 15: 201-210. 1 tav. e 3 figg. **198.**
- . 1910a. Nouvelles recherches sur les phénomènes de régénération qui s'accomplissent dans la moelle épinière. Régénération chez les animaux hibernants. Arch. ital. de biol., 54: 30-40. **198.**
- . 1913. Klinischer und anatomo-pathologischer Beitrag zur Kenntniss des sogenannten Pellagratyphus. J. f. Psychol. u. Neurol., 20: 1-23 2 pl. (Cited by Harris '19.) **442, 455.**
- Rothschild, M. A. 1915. Zur Physiologie des Cholesterinstoffwechsels. V. Der Cholesteringehalt des Blutes und einiger Organe im Hungerzustand. Beitr. z. path. Anat., etc., 60: 227-231. **241, 338, 425.**
- Rous, P. 1911. Tumor growth in underfed hosts. Proc. Soc. Exp. Biol. & Med., 8: 128-130. (Also reprinted in Studies of the Rockefeller Inst., N. Y., 14: 22-fl.) **459.**
- & McMaster, P. D. 1924. The liver requirement of the fasting organism. J. Exp. Med., 39: 425-445. 1 pl. 2 text figs. **122, 341.**
- Roux, W. 1881. Der Kampf der Theile, Lpz.
- . 1887. Ueber die Selbstregulation der morphologischen Länge der Skelettmuskeln. Jen. Ztschr. f. Naturw., 16: 420-424.
- . 1895. Einleitung. Arch. f. Entw. d. Org., 1: 1-42.
- . 1895a. Gesammelte Anhandlungen über Entwicklungsmechanik der Organismen. 1: 236, 400, 642, 658; 2: 224.
- . 1901. Ueber Selbstregulation der Lebewesen. Arch. f. Entw. d. Org., 13: 610-650.
- Rowntree, L. G. 1922. The water balance of the body. Physiol. Reviews, 2: 116-169. **94, 114.**
- Rubner, M. 1903. In v. Leyden's Handb. d. Ernährungstherapie, p. 53-fl. (Cited by Lusk '17.)
- . 1908. Das Wachstumsproblem und die Lebensdauer des Menschen und einiger Säugethiere etc. Sitz.-Ber. d. k. preuss. Akad. d. Wiss., pp. 32-47. (Also in Wien. med. Wchnschr., 58: 546-551; 619-623; 679-684.)
- . 1909. Grundlagen einer Theorie des Wachstums der Zelle nach Ernährungsversuchen am Hefe. *Ibid.*, pp. 164-179.
- . 1909a. Kraft und Stoff im Haushalte der Natur. Lpz. (S. 116-117.) Akad. Verlagsges., 181 pp.
- . 1918. Der Einfluss der Kriegsverhältnisse auf den Gesundheitszustand im Deutschen Reich. Ein Bericht aus dem Jahre 1917 als Beitrag zur Wirkung der Hungerblockade. Münch. med. Wchnschr., Suppl. zu Nr. 8, p. 229. (Cited by Lusk '21.)
- . 1919. Abstract of report of Professor Rubner made in the Reichsgesundheitsrat, Dec. 20, 1917. Milit. Surgeon, 45: 237-247; 405-413. (Cf. also J. Am. M. A., 1919, 73: 168.) **79, 120, 204, 254, 314, 326, 372, 392, 398, 400, 405.**
- . 1920. Die physiologische Bedeutung des Stickstoffs. Naturforschervers., Nauheim. (Cited by Lusk '21.) (Cf. also Münch. med. Wchnschr., 1920, 67: 1216; Wien. klin. Wchnschr., 1920, 33: 957; Wien. med. Wchnschr., 1920, 70: 1976.) **229, 398, 400.**

- . 1920a. Ueber die Frage des Kalkmangels in der Kost. *Vrtljschr. d. ger. Med.*, 60: 1-26. 141.
- Rubow, V. 1905. Ueber den Lecithingehalt des Herzens unter normalen Verhältnissen, im Hungerzustande und bei der fettigen Degeneration. *Arch. f. exp. Path. u. Pharm.*, 52: 173-204. (Also as Danish Dissert., 1903.) 170, 231, 378.
- . 1920. (Effect on the blood of restriction of fluids.) *Hospitalstidende* (Copenhagen), 63: 305-ff. (Abstr. *J. Am. M. A.*, Aug. 14, 1920.) 259.
- Ruden. 1922. Ueber den Einfluss der Konstitution auf die Zahnentwicklung. *Deut. Zahnärztl. Wchnschr.*, 25: 335-337; 347-350; 361-364. (Abstr. in *Anat. Ber.*, 1922, 1: 24-25.) 158.
- Rudolski. 1893. (Ueber die Schwangerschaft der Thiere bei ungenügender Ernährung des Organismus.) Thèse, St. Petersburg., 144 pp. (Abstr. by Mühlmann '99 and Bardier '13.) 77, 78.
- Ruffer, M. A. R. 1921. *Studies in the paleopathology of Egypt.* U. of Chicago Press, 372 pp. 108.
- Rufz. 1834. *Recherches sur le rachitisme chez les enfants.* *Gaz. méd. de Par.*, 2. ser., 2: 65-70. 145.
- Ruge, C. 1916. Ueber den Einfluss der Kriegsernährung auf Fruchtentwicklung und Laktation. *Zentralbl. f. Gyn.*, 40: 680-684. 79, 80, 129.
- Ruhrah, J. 1903. The relation of the thymus gland to marasmus. *Brit. Med. J.*, 2: 455-456. 287.
- Rulot, H. 1901. Note sur l'hibernation des chauve-souris. *Arch. de biol.*, 18: 365-375. (Also in *Bull. de l'Acad. de Belg.*, 1901, pp. 17-20.) 70, 462.
- Rumbaur, W. 1922. Augenkrankungen bei Enten infolge von Avitaminose. *Klin. Monatsbl. f. Augenheilk.*, Stuttgart, 68: 744-749. 218.
- Rumpf und Luce. 1900. Zur Klinik und pathologischen Anatomie der Beri-Beri-Krankheit. *Deut. Ztschr. f. Nervenheilk.*, 18: 63-98. 171, 189, 200, 206.
- Runnström, J. 1912. Sur l'appareil excréteur chez la larve de *Strongylocentrotus lividus*. *Bull. de l'Inst. Oceanographique*. (Monaco.) No. 240, 14 pp. 9 figs. 52.
- . 1912a. L'effet de l'inanition sur la larve de l'oursin. *Ibid.*, No. 245, Sept. 52.
- Russell, H. L. & Morrison, F. B. 1919. *Service to Wisconsin.* Univ. Wisc., Agr. Exp. Sta. Bull. No. 302 (p. 54). 105.
- Russo, A. 1906. Sull' origine dei mitochondri e sulla formazione del deutoplasma nell'oocite di alcun mammiferi. *Atti d. R. Accad. d. Lincei*, 16: 292-296. (Abstr. in *Jahresb. d. Anat. etc.*, 1907, T. 1, pp. 46, 61-62.) 394.
- . 1906a. Modificazioni sperimentali dell'elemento epitheliale dell'ovaia dei mammiferi (da servire come base per la determinazione artificiale del sesso femminile e per la interpretazione della legge di Mendel sulla prevalenza degli ibridi). *Ibid.*, Anno 303, ser. 5, Mem. d. cl. di sc. fis., mat. e nat., Roma, 6: 315-384. 5 tav. 394.
- . 1909. Sulla cromolisi delle cellule della granulosa durante il digiuno e sul suo significato nella differenziazione sessuale delle ova dei mammiferi. Nota II. *Atti d. Accad. Gioenia Sc. Nat.*, Catania. Anno 86, ser. 5, T. 2. 2 fig. e 4 tav. (Cited in *Jahresb. d. Anat.*, etc., 1911, T. 2, pp. 3, 23.) 394.
- . 1910. Sui prodotti del diverso tipo di metabolismo osservato nelle uova di coniglia e sul loro valore per il problema della sessualità. *Arch. di fisiol.*, 8: 530-536. 2 fig. e 2 tav. (Abstr. in *Jahresb. d. Anat. etc.*, 1910 T. 1, pp. 3, 23.) 394.
- . 1910a. I mitochondri ed i globuli vitellini dell'oocite di coniglia in stato normale ed in condizione sperimentali. Nota I. *Ist. Anat. e Fisiol. compar.*, Catania. 4 fig. e 1 tav. (Cited by Russo '10c.) 394.
- . 1910b. Le modificazioni sperimentali dell'ovaia nei mammiferi e le cause della differenziazione del sesso. *Natura*, 1: 41-62. (Cited by *Jahresb. d. Anat. etc.*, 1910, T. 2, pp. 3, 23.) 394.
- . 1910c. Sui mutamenti che subiscono i mitochondri ed i materiali deutoplasmici dell'oocite di coniglia in diversi periodi di inanizione. *Arch. f. Zellforsch.*, 5: 173-181. 1 Taf. u. 3 Fig. 394.

———. 1912. Aumento dei granuli protoplasmatici nell'ooite delle coniglie iniettate con lecitina, loro diminuzione nelle coniglie digiunanti e loro natura lipoide e mitochondriale. *Ibid.*, 8: 203-216. 9 Fig. **394**.

———. C. 1892. Emoglobinuria sperimentale da inanizione. *Gaz. di clin.*, Napoli, 3: 417-418. **378**.

Ruzicka, V. 1917. Beschleunigung der Häutung durch Hunger. Ein Beitrag zum Studium des morphologischen Metabolismus und der Verjüngungsfrage. *Arch. f. Entw. d. Org.*, 42: 671-704. 1 Taf. u. 2 Textfig. **121**.

Rywosch. (Cited, without ref., by Geddes & Thomson '01.) **41**.

Sabrazes, J. 1902. Perte de poids considérable par diverses espèces du genre *Helix* mises à jeûneur. *Actes Soc. Linn. de Bordeaux* (6. ser., T. 7) 57: 88. **54**.

Sacerdotti, C. 1894. Sulla ipertrofia compensatoria dei reni nella inanizione. *Gior. d. r. Accad. di med. di Torino*, 3. ser., 42: 534-536. **378, 380**.

———. 1898. Sul grasso delle cartilagini. *Atti r. Accad. sc.*, Torino, 34: 984-1003. 1 tav. Also in *Gazz. med.*, Torino, No. 49, p. 97. (Abstr. in *Jahresb. d. Anat. etc.*, 1899, T. 1, pp. 174, 179-180.) **137**.

———. 1900. Ueber das Knorpelfett. *Arch. f. path. Anat.*, etc. 159: 152-173. 2 Taf. **137**.

von Sachs, J. 1887. Lectures on the physiology of plants. English transl. by H. M. Ward. Oxford, 836 pp. **12**.

Sachsaler, A. 1903. Ueber den Regenerationsvorgang von Hornhautsubstanzverlusten bei allgemeiner Ernährungsstörung (*Atrophia infantum*). *Ztschr. f. Augenh.*, Berl., 9: 395-408. 1 Taf. **122**.

Sagot. (Date?). Influence de l'état hygrométrique sur la végétation. *Bull. Bot. Soc. France*, 26: 57. (Cited by Thomson '88.) **6**.

Salkind, J. 1915. Contributions histologiques à la biologie comparée du thymus. *Arch. de zool. exp.*, 55: 81-322. 3 pl. **295**.

Salvioli, I. e Sacchetto, I. 1921. Ricerche sul metabolismo dei lipoidi e dei grassi nelle cellule epatiche di animali digiunanti od avvelanati con fosforo. *Gaz. d. osp.*, Milano, 42: 828-830. Also in *Lavoro*, 1921, 229-230. (Chem. Abstr., 1922, 16: 3970.) **340**.

Samuel, S. 1879. *Handbuch der allgemeinen Pathologie*, etc. Enke, Stuttgart, 947 pp. (Cited by Monti '95a.) **121**.

———. 1885. Die histogenetische Energie und Symmetrie des Gewebswachstums. *Arch. f. path. Anat. etc.*, 101: 389-429. **121**.

Sanfelice, F. 1889. Genesi dei corpuscoli rossi nel midollo delle ossa dei vertebrati. *Boll. della Soc. dei Nat. in Napoli*, Anno 3, fasc. 2. Also in *Arch. ital. de biol.*, 1890, 13: 45-54. (Cited by Beretta '02.) **137**.

Sanford, E. W. 1918. Experiments on the physiology of digestion in the Blattidæ. *J. Exp. Zool.*, 25: 355-411. 21 figs. **60**.

Santoro-Silipigni, G. 1901. Alcuni appunti sulla resistenza al digiuno. *Boll. Soc. zool. ital.* (2). 2: 172-175; (Concil. Bibl.)

Saricinielli, F. 1903. La milza nella rachitide. *Pediatria*, 2. s., 1: 221-234. (Abstr. in *Arch. f. Kinderh.*, 1904, 39: 185.) **283**.

Sasuchin, P. N. 1900. Die Rachitismilz. *Jahrb. f. Kinderh.*, 51: 297-307. 1 Taf. **282**.

Sato, T. u. Nambu, K. 1908. Zur Pathologie und Anatomie des Skorbutus. *Arch. f. path. Anat. etc.*, 194: 151-187. **132, 171, 189, 202, 208, 234, 236, 237, 258, 268, 284, 302, 312, 323, 343, 355, 386**.

Sauer, H. 1895. Neue Untersuchungen über das Nierenepithel und sein Verhalten bei der Harnabsonderung. *Arch. f. mikr. Anat.*, 46: 109-146. 1 Taf. **383**.

———. 1920. Ein Fall von Hungerosteomalazie und Tetanie. *Deut. med. Wchnschr.*, 46: 45-47. **136**.

de Saussure, T. 1804. *Recherches chimiques sur la végétation*. Par., 327 pp. **8**.

Sawidowitsch, W. 1914. Einfluss von Ernährung und Erkrankungen auf das Wachstum des Gehirnes im 1. Lebensjahre. *Med. Diss.*, Berl., 31 pp. **178**.

- Scammon, R. E. 1919. On the development and finer structure of the corpus adiposum buccae. *Anat. Rec.*, 15: 267-286. 9 figs. 123.
- Schabad, J. A. 1910. Zur Bedeutung des Kalkes in der Pathologie der Rachitis. *Arch. f. Kinderh.*, 52: 47-106. 146, 174.
- Schaeffer. 1898. Wie lange kann der Mensch hungern? *Therap. Monatsh.*, Berl., 12: 190-193. 69.
- O. 1896. Ueber die Schwankungen der Gewichtsverhältnisse von Säuglingen in den ersten 14 Lebenstagen und die Ursachen diesen Schwankungen. *Arch. f. Gyn.*, 52: 282-313. 81.
- R. 1902. Der Einfluss der Diät und der Lebensweise Schwangerer auf die Frucht und auf die Niederkunft. Kritischer Bericht über einige wichtigere Arbeiten. *Monatschr. f. Geburtsh. u. Gyn.*, 15: 571-579. 78.
- Schaffer, J. 1908. Das thyreo-thymische System des Maulwurfs und der Spitzmaus. I. Morphologie und Histologie. *Wien. Akad. Anz.*, math.-naturw. Kl., Nr. 27, Dec. 17. (Abstr. in *Jahresb. d. Anat. etc.*, 1908, T. 3, pp. 422, 437-441.) 297.
- K. 1897. Ueber Nervenzellenveränderungen während der Inanition. *Neurol. Centralbl.*, 16: 832-837. 196.
- Schaudinn, F. 1899. Generationswechsel von *Trichosphaerium Sieboldii*. Anhang zu den *Abhandl. d. Berl. Akad.*, p. 1-ff. (Abstr. by Biedermann '10.) 16, 17.
- Schaumann, H. 1909. Weitere Beiträge zur Aetiologie der Beri-Beri. *Deut. med. Wchnschr.*, p. 783.
- . 1915. Neuere für die Physiologie und Pathologie der Ernährung wichtige Forschungsergebnisse und deren Bedeutung für die Praxis. *Therap. Monatsh.*, 29: 152-166.
- Schauta, F. 1917. Die Frau von 50 Jahren. Krieg und Geburtshilfe. M. Perles, Wien u. Lpz., 77 pp. (Cited by *Index Med. and P. Schmidt* '18.) 79.
- Scheffer, Th. 1852. *De animalium, aqua iis adempta, nutritione*. Dissert., Marburg, 35 pp. (Cited by Pernice u. Scagliosi '95a and Tobler '10.) 132, 172.
- Schelle, H. 1910. Bakteriologische und pathologisch-anatomische Studien bei Ernährungsstörungen der Säuglinge, besonders der chronischen unter dem Bilde der Pädatrie verlaufenden Formen. Thieme, Lpz., 79 pp. 4 Taf. u. 3 Fig. 252, 263, 277, 304, 315, 329, 347, 374.
- Schenk, S. L. (undated). *Elementi di istologia normali dell'uomo*. Trad. del. Monti e Golgi. *Bibl. med. contemp. Antica Casa Editrice, F. Vallardi, Milano*, 356 pp.
- Scherer. 1913. Ueber Skorbut in Deutsch Südwestafrika. *Arch. f. Schiffs- u. Tropenhyg.*, 17: 191-203. (Cited by Funk '22.) 343.
- Scheube, B. 1894. Die Beri-beri-Krankheit. Eine geographisch-medicinische Studie. 220 pp. 2 Taf. G. Fischer, Jena. (Cited by Rumpf u. Luce '00.) 171.
- Schewiakoff, W. 1894. Ueber die Natur der sogenannten Exkretkörner der Infusorien. *Ztschr. f. Wiss. Zool.*, 57: 32-56. 1 Taf. 24.
- Schick, B. 1915. Zur Frage der physiologischen Körpergewichtsabnahme des Neugeborenen. *Ztschr. f. Kinderh., Orig.*, 13: 257-281. 81.
- u. Wagner, R. 1923. Ueber eine Verdauungsstörung jenseit des Säuglingsalters. (*Atrophia pluriglandularis digestiva*.) II Mitteilung. *Ztschr. f. Kinderh.*, 35: 263-274. 5 Fig.
- Schidachi, T. 1908. Ueber die Atrophie des subkutanen Fettgewebes. *Arch. f. Derm. u. Syph.*, 90: 97-130. 125.
- Schiele, A. 1880. Das Glycogen in normalen und pathologischen Epithelien. *Inaug. Dissert.*, Bern. 20 pp.
- . 1907. *Wchnschr. f. Therap. u. Hyg. d. Auges*, 11: 101-ff. (Cited by Blegvad '24.) 211, 216.
- Schiff, A. 1917. Zur Pathologie der Oedemkrankheit. *Wien. med. Wchnschr.*, No. 48. (Cited by Maver '20.) 71, 102.
- Schilf, F. 1922. Die quantitativen Beziehungen der Nebennieren zum übrigen Körper. *Ztschr. f. d. ges. Anat. II Abth. Ztschr. f. Konstitutionsl.*, 8: 507-544. 2 Textabb. 419.

Schindler, E. 1919. Ueber die Irisfarbe des Säuglings. Ein Beitrag zur Symptomatologie der Ernährungsstörung im Säuglingsalter. *Ztschr. f. Kinderh.*, 90: 153-160. **212, 248.**

Schittenhelm, A. u. Schlecht, H. 1918. Ueber Oedemkrankheit mit hypotonischer Bradykardie. *Berl. klin. Wchnschr.*, No. 48. pp. 1138-1142. **71, 311, 342, 354, 367, 384, 430.**

———. 1919. Ueber die Oedemkrankheit. Springer, Berl. Also in *Ztschr. f. d. ges. exp. Med.*, 9: 1-103. **102, 215, 232, 236, 255, 267, 342, 384, 430.**

Schlesinger, E. 1903. Die Anemie und Leukocytose bei der Pädatrie und Gastroenteritis. *Arch. f. Kinderh.*, 37: 321-346. **247.**

———. 1920. Wachstum, Gewicht und Konstitution der Kinder und der herangewachsenen Jugend während des Krieges. *Ztschr. f. Schulgesundheitspfl.*, 33: 37-45. Also in *Münch. med. Wchnschr.*, 1919, 66: 662-664. (Abstr. in *Ber. d. ges. Physiol.*, 1920, 2: 530.) **84, 136, 406.**

——— H. 1919. Zur Klinik der Hungerosteomalazie und ihrer Beziehungen zur Tetanie. *Wien. klin. Wchnschr.*, 32: 336-ff. *Cf. also ibid.*, pp. 245; 929. (Abstr. in *Endocrinol.*, 1919, 3: 536-537.)

Schloss, E. 1910. Zur Pathologie des Wachstums im Säuglingsalter. *Jahrb. f. Kinderh.*, 72: 575-598. (Also reprint, Berl., 1911.) **91.**

Schmaus, H. u. Albrecht, E. 1899 (?). Zur funktionellen Struktur der Leberzelle. *Festschr. z. 70. Geburtstag von Carl v. Kupffer*. Jena. pp. 325-338. 1 Taf. (Cited in *Jahresb. d. Anat.*, etc., 1899, T. 2, pp. 95; 112; 279.) **335.**

Schmidt, A. 1917. Unterernährung, Magerkeit und krankhafte Abmagerung. *Deut. med. Wchnschr.*, 43: 417-420.

——— C. 1882. Ueber Kernveränderung in den Secretionszellen. *Dissert.* Breslau. **306.**

——— M. B. 1909. Referat über Rachitis und Osteomalacie. *Verh. d. Deut. path. Ges.*, 13: 3-20. 1 Fig. In *Centralbl. f. allg. Path. etc.*, Erg. z. Bd. 20. **145, 146.**

———. 1912. Ueber die Organe des Eisenstoffwechsels und die Blutbildung bei Eisenmangel. *Verh. d. Deut. path. Ges.* 15. Tagung, Strassburg. (Also *ibid.*, 1914, 17. **256.**

Tagung, p. 156-ff.) (Abstr. by *Jahresb. d. Anat. etc.*, 1912, and Hofmeister '18.)

———. 1913. Der Bewegungsapparat. In *Aschoff's Pathologische Anatomie*, 3. Aufl., Bd. 2. (Also *ibid.*, 5. Aufl., Jena, 1921.) **142, 146, 147, 151.**

——— P. 1918. Ueber den Einfluss der Kriegsernährung auf das Körpergewicht der Neugeborenen. *Monatschr. f. Geburtsh. u. Gyn.*, 47: 390-405. **79.**

Schmorl, G. 1899. Ueber Störung des Knochenwachstums bei Barlow'scher Krankheit. *Centralbl. f. allg. Path. etc.* Also in *Verh. d. Deut. path. Ges.*, München (Berl., 1900), pp. 258-259. (Cited by Hess '20.) **151.**

———. 1901. Zur pathologischen Anatomie der Barlow'schen Krankheit. *Centralbl. f. allg. Path. etc.*, Bd. 30. (Cited by Hess '20.) **151.**

———. 1906. Ueber die Knorpelverkalkung bei beginnender und heilender Rachitis. *Verh. d. deut. path. Ges.* (1905), *Centralbl. f. allg. Path. etc.*, Erg. z. 16. Bd., pp. 248-260. 4 Taf. **145, 146, 147.**

———. 1907. Ueber die Pathogenese der bei Morbus Barlow auftretenden Knochenveränderungen. *Jahrb. f. Kinderh.*, 65: 50-63. **151, 153.**

———. 1909. Ueber die Beziehungen der Knorpelmarkkanäle zu der bei Rachitis sich findenden Störung der enchondralen Ossifikation. *Verh. d. Deut. path. Ges.*, 13: 40-48. 2 Taf. *Centralbl. f. allg. Path. etc.*, Bd. 20. **146, 147.**

———. 1909a. *Ibid.* (in Diskussion). **108.**

———. 1909b. Die pathologische Anatomie der rachitischen Knochenerkrankung, mit besonderer Berücksichtigung ihrer Histologie und Pathogenese. *Ergeb. d. inn. Med. u. Kinderh.*, 4: 403-454. 6 Taf. u. 12 Fig. **145.**

———. 1913. Ueber die Beeinflussung des Knochenwachstums durch phosphorarme Ernährung. *Arch. f. exp. Path. etc.*, 73: 313-346. **142, 153.**

- Schnyder, K. 1914. Pathologisch-anatomisch Untersuchungen bei experimenteller Beriberi (Reispolyneuritis). Arch. f. Verdauungskrankh., 20: 147-178. 200, 207, 233, 234, 343, 386.
- Schoedel, J. u. Nauwerk, C. 1900. Untersuchungen über die Möller-Barlow'sche Krankheit. G. Fischer, Jena, 159 pp. (Cited by Hess '20.) 151, 153, 208, 234, 433.
- Schoendorff, B. 1897. Ueber den Einfluss der Schilddrüse auf den Stoffwechsel. Arch. f. d. ges. Physiol., 67: 395-442. 134.
- . 1913. Spezielle Physiologie des tierischen Stoffwechsels. In Handb. d. Naturwiss., 9: 707-726. Jena. 72.
- Schoene, K. 1906. Beiträge zur Kenntniss der Laubmoossporen und zur Biologie der Laubmoosrhizoiden. Flora, 96: 276-321. 10, 11.
- Schridde, H. 1913. Thymus. In Aschoff's Pathologische Anatomie. 3. Aufl. (Also 5. Aufl., 1921.) Verlag G. Fischer, Jena. 290.
- . 1914. Der angeborene Status thymolymphaticus. Münch. med. Wchnschr., 61: 2160-2164. 290.
- Schuchardt, B. 1847. Quaedam de effectu, quem privatio singularum partium nutrimentum constituentium exercet in organismum ejusque partes. Inaug. Dissert., Marburgi, 53 pp. 115, 132, 154, 172, 189, 213, 221, 234, 305, 323, 344, 355, 368, 387.
- Schukow. 1895. Ueber die Wirkung des Hungers von neugeborenen Tieren auf die Entwicklung ihres Centralnervensystems. Vorl. Mitteil. (Abstr. by Maximow u. Korowin, in Ergeb. d. allg. Path. etc., (1898), 1900, p. 704.) 179, 185.
- Schultz, C. H. 1843. Ueber den Zustand des Blutes in einem verhungerten Proteus, sowie in verhungerten Katzen und Kaninchen. Beitr. z. physiol. u. path. Chem. u. Mikr., Berl., 1: 567-571. 249.
- . E. 1902. Aus dem Gebiete der Regeneration. II. Ueber die Regeneration der Turbellarien. Ztschr. f. wiss. Zool., 72: 1-30. 42.
- . 1904. Ueber Reduktion. I. Ueber Hungererscheinungen bei *Planaria lactea*. Arch. f. Entw. d. Org., 18: 555-575. 1 Taf. 42, 204.
- . 1904a. Ueber Regenerationsweisen. Biol. Centralbl., 24: 310-317. 42.
- . 1906. Ueber Reduktionen. II. Ueber Hungererscheinungen bei *Hydra fusca* L. Arch. f. Entw. d. Org., 21: 703-726. 1 Taf. 28, 35, 36, 37, 38.
- . 1907. Ueber Reduktionen. III. Die Reduktion und Regeneration des abgeschnittenen Kiemenkorbs von *Clavellina lepadiformis*. *Ibid.*, 24: 503-523. 1 Taf. 66.
- . 1908. Ueber umkehrbare Entwicklungsprozessen und ihre Bedeutung für die Theorie der Vererbung. Roux's Vortr. u. Aufsätze über Entw. d. Org., H. 4. Lpz. 48 S. 42.
- . 1908a. Ueber ontogenetische und phylogenetische Rückbildungen. Biol. Centralbl., 28: 673-678; 705-710. 42.
- . 1908b. Ueber Reduktionen. IV. Ueber Hunger bei *Asterias rubens* und *Mytilus* bald nach der Metamorphose. Arch. f. Entw. d. Org., 25: 401-406. 53, 57.
- Schultze, F. F. 1836. De planarium vivendi ratione et structura penitori nonnulla. Diss. inaug., Berol. (Cited by Stoppenbrink '05.) 41.
- . O. 1888. Ueber den Einfluss des Hungers auf die Zellkerne. Sitzb. d. phys.-med. Ges. in Würzburg. pp. 140-147. Also abstr. in Fortschr. d. Med., Berl., 1889, 7: 48. 121.
- . 1903. Zur Frage von den geschlechtsbildenden Ursachen. Arch. f. mikr. Anat., 63: 197-257. 3, 4, 29.
- Schultzen, O. 1863. Beitrag zur Lehre vom Stoffwechsel bei Inanition. Arch. f. Anat., Physiol. etc., pp. 31-40. 122, 128, 166, 223, 270, 303, 313, 325, 371.
- . O. (G.). 1862. De inanitione; accedit observatio et exploratio microscopico-chemica. Diss. inaug., Berol. 31 pp. 122, 128, 166, 270, 303, 313, 325, 371.
- Schulz, F. N. 1896. Ueber den Fettgehalt des Blutes beim Hunger. Arch. f. d. ges. Physiol., 65: 299-307. 241.
- . 1897. Ueber die Verteilung von Fett und Eiweiss beim magern Tiere, zugleich ein Beitrag zur Methode der Fettbestimmung. *Ibid.*, 66: 145-166. (Cited by Voit '05b.) 241.

- Mangold, E., Stübel, H. u. Hempel, E. 1906. Beiträge zur Kenntnis des Stoffwechsels bei unzureichender Ernährung. *Ibid.*, 114: 419-430; 431-438; 439-461; 462-486.
- P. 1912. Wachstum und osmotischer Druck bei Hunden. *Ztschr. f. Kinderh.*, 3: 251-255; 495-500. **102, 140, 241.**
- R. 1884. Zur Vacuolenbildung in den Ganglienzellen des Rückenmarkes. *Neurol. Centralbl.*, 3: 121-124. **194.**
- Schalbe, G. 1890. Ueber die Kaliberverhältnisse der quergestreiften Muskelfasern der Wirbeltiere. *Deut. med. Wchnschr.*, 16: 795. **167.**
- Schwartz, E. 1914. Die Lehre von der allgemeinen und örtlichen "Eosinophilie." *Ergeb. d. allg. Path. etc.*, 17: 137-789. **244.**
- Schweitzer, B. 1917. Kriegsamennorrhöe. *Münch. med. Wchnschr.*, 64: 551-553. **391, 400.**
- Schwerz, F. 1911. Untersuchungen ueber das Wachstum des Menschen. *Arch. f. Anthrop.*, n. F., 10: 1-38.
- Schwinge, W. 1898. Untersuchungen über den Hämoglobingehalt und die Zahl der roten und weissen Blutkörperchen in den verschiedenen Lebensaltern unter physiologischen Bedingungen. *Arch. f. d. ges. Physiol.*, 73: 299-338. 2 Taf. **242.**
- Sedlmair, A. C. 1899. Ueber die Abnahme der Organe, insbesondere der Knochen, beim Hunger. *Ztschr. f. Biol. (n. F. Bd. 19)*, 37: 25-58. **118, 134, 164, 179, 192, 213, 228, 249, 307, 333, 351, 365, 378.**
- Sée. 1866. Leçons de pathologie expérimentale. Des anémies par alimentation insuffisante; inanitions. *Gaz. d. hôp., Par.*, 39: 321-323. **249.**
- Seefelder, R. 1919. Ueber den Einfluss des Krieges auf die Augenkrankheiten in der Heimat. *Wien. klin. Wchnschr.*, 32: 1245-1250. **211, 220.**
- von Seeland. 1887. Ueber die Nachwirkung der Nahrungsentziehung auf die Ernährung. *Biol. Centralbl.*, 7: 145-148; 184-192; 214-224; 246-256; 271-281. **94.**
- . 1888. (Ueber den Einfluss der Nahrungsentziehung auf die nachfolgende Ernährung.) *Russ. Med. (Abstr. by Mühlmann '99.)* **70.**
- Seeliger. 1923. Spaltbildungen in den Knochen und schleichende Frakturen bei den sogenannten Hungerknochenerkrankungen. *Arch. f. klin. Chir.*, 122: 588-602. 4 Textabb. **136.**
- von Segesser, V. 1914. Die Hungerkuren. Physiologisches; Methodik; Erfolge; Misserfolge. Dresden. 148 pp.
- Seibold, F. M. J. 1827. Die englische Krankheit. *Inaug.-Abhandl. Würzburg.* 34 pp. 2 Taf. **109, 142, 143, 158, 170, 188, 267, 282, 298, 342, 354, 367.**
- Seidenmann, M. 1893. Beitrag zur Mikrophysiologie der Schleimdrüsen. *J. Internat. f. Anat. u. Physiol.*, 10: 599-613. 1 pl. **357.**
- Semper, K. 1881. Animal life, as affected by conditions of existence. *Internat. Sc. Ser., N. Y.* Vol. 30, 472 pp. **38, 53, 62.**
- Senator, H. 1887. Bericht über die Ergebnisse des an Cetti ausgeführten Hungerversuches; über das Verhalten der Organe und des Stoffwechsels im allgemeinen. *Berl. klin. Wchnschr.*, 24: 425-428. **242.**
- u. Müller, F. 1893. Untersuchungen an zwei hungernden Menschen. *Arch. f. path. Anat. etc.*, Bd. 131, Suppl. (Cf. also in *Charité-Annalen*, 1885, p. 317.)
- Seydel, C. 1894. Ein Zeichen des Erschöpfungstodes durch mangelhafte Ernährung bei jungen Kinder. *Vrtljschr. f. Med., Berl.*, 3. F., 7: 226-232. **287.**
- Sherman, H. C. 1911. Chemistry of food and nutrition. *N. Y.* (p. 265). **106.**
- . 1918. Fundamental requirements of human nutrition. *Proc. Inst. of Med., Chicago*, 2: 33-49. Also *Harvey Soc. Lecture*, Jan. 12, 1918.
- & Pappenheimer, A. M. 1921. Experimental rickets in rats. I. A diet producing rickets in white rats, and its prevention by the addition of an inorganic salt. *J. Exp. Med.*, 34: 189-198. 8 pl. **107, 109, 148.**
- Rouse, M. E., Allen, B. & Woods, E. 1921. Growth and reproduction upon simplified food supply. *I. J. Biol. Chem.*, 46: 503-519.
- & Smith, S. L. 1922. The vitamins. *Amer. Chem. Soc. Monogr. Ser. Chem. Catalog Co., N. Y.*, 273 pp. 20 figs. **13, 110.**

- Shiple, P. G. 1922. Faulty diet and its relation to the structure of bone. *J. Am. M. A.*, 79: 1563-1564. 148.
- McCollum, E. V. & Simmonds, N. 1921. Studies on experimental rickets. IX. Lesions in the bones of rats suffering from uncomplicated beri-beri. *J. Biol. Chem.*, 49: 399-410. 8 figs. 112, 150.
- Park, E. A., McCollum, E. V. & Simmonds, N. 1921. Studies on experimental rickets. III. Effects of diets low in phosphorus and fat-soluble A: the phosphate ion in its prevention. *Johns Hopkins Hosp. Bull.*, 32: 160-166. 12 figs. 112, 131, 148, 150, 159, 215, 282, 298.
- ————. 1921a. Studies on experimental rickets. VII. The relative effectiveness of cod liver oil as contrasted with butter fat for protecting the body against insufficient calcium in the presence of a normal phosphorus supply. *Am. J. Hyg., Balt.*, 1: 512-525. 4 pl. 148.
- ————. 1922. Is there more than one kind of rickets? *Am. J. Dis. Child.*, 23: 91-106. 11 figs. 148.
- & Kinney, E. M. 1922. Studies on experimental rickets. XX. Effects of strontium administration on histologic structure of growing bone. *Johns Hopkins Hosp. Bull.*, 33: 216-220. 148.
- & Parsons, H. T. 1920. Studies on experimental rickets. II. The effect of cod liver oil administered to rats with experimental rickets. *J. Biol. Chem.*, 45: 343-348.
- Powers, G. F., McCollum, E. V. & Simmonds. 1921. The prevention of the development of rickets in rats by sunlight. *Proc. Soc. Exp. Biol. & Med.*, 19: 43-47.
- Shull, A. F. 1910. Studies in the life cycle of *Hydatina senta*. I. Artificial control of the transition from the parthenogenetic to the sexual method of reproduction. *J. Exp. Zool.*, 8: 311-354. 28, 58.
- . 1911. Studies in the life cycle of *Hydatina senta*. II. The rôle of temperature, of the chemical composition of the medium, and of the internal factors upon the ratio of the parthenogenetic to sexual forms. *Ibid.*, 10: 118-165. 28, 58.
- von Siebold, A. E. 1806. *Annalen der klin. Entbindungsanstalt. Würzburg.* (Cited by Reeb '05.) 79.
- . C. T. E. (Cited by Geddes & Thomson '01.) 65.
- . 1863. *Die Süßwasserfische von Mitteleuropa.* Lpz. (S. 246.) (Cited by Nussbaum '14.) 77.
- Siegel, P. W. 1917. Zur Kriegsamennorrhöe. *Zentralbl. f. Gyn.*, 41: 329-333. 391, 400.
- Sill, E. M. 1909. A study of malnutrition in the school child. *J. Am. M. A.*, 52: 1981-1985. 83, 157, 263.
- Simmonds, M. 1913. Männlicher Geschlechtsapparat. In *Aschoff's Pathologische Anatomie.* 3. Aufl., Bd. 2, Jena. (Also Aufl. 5, 1921.) 404, 405.
- Simon, J. 1845. A physiological essay on the thymus gland. H. Renshaw, Lond., 100 pp. 287.
- . W. V. 1921. Spätrachitis und Hungerosteopathie. *Veröffentl. a. d. Geb. d. Medizinalverwaltung, Berl.*, 14: 351-443. (Abstr. in *Endocrinol.*, 1922, 6: 334.) 136.
- Simonnet, H. 1920. Obtention chez le pigeon des accidents de polynévrisme par l'emploi d'une alimentation synthétique. *Compt. rend. Soc. de biol., Par.*, 83: 1508-1510. 113.
- Simonowitsch (Simonovich), J. (I) 1896. (Ueber pathologisch-anatomische Veränderungen der Hoden bei vollständigem und unvollständigem Hungern der Thiere und Auffütterung nach dem Hungern.) *Russian Dissert., St. Petersburg.*, 64 pp. 1 pl. (Also abstr. by Mühlmann '99; in *Jahresb. d. Anat. etc.*, 1897, T. 3, pp. 735, 760; and in *Centralbl. f. path. Anat.*, 1899.) 407.
- Simpson, S. 1912. The food factor in hibernation. Preliminary communication. *Proc. Soc. Exp. Biol. & Med.*, 9: 92-93.
- Siperstein, D. M. 1921. The effects of acute and chronic inanition upon the development and structure of the testis in the albino rat. *Anat. Rec.*, 20: 355-391. 5 pl. 410, 411.

- Sison, A. G. 1920. Clinical observation on experimental starvation in human beings. Philip. J. Sc., Manila, 17: 415-420. 225, 272, 314, 326, 362.
- Sjöbring, N. 1900. Ueber das Formol als Fixierungsflüssigkeit. Anat. Anz., 17: 273-304. 3 Abb. 335, 383.
- Skoritschenko. 1883. (Untersuchungen über einige Factoren des Hungerns.) Protokolle der Konferenzsitungezun d. K. mil. med. Akad., pp. 175-233. (Abstr. by Mühlmann '99 and Bardier '13.) 115, 235, 274, 332, 344, 365, 377.
- . G. 1891. Lebensunterdrückung: altes und neues über den Winterschlaf. Thèse, St. Petersburg. (Abstr. by Mühlmann '99 and Bardier '13.)
- Slavjansky, K. 1870. Zur normalen und pathologischen Histologie der Graff'schen Bläschen des Menschen. Arch. f. path. Anat. etc., 51: 470-495. 1 Taf. 390, 399.
- Slonaker, J. R. & Card, T. A. 1918. The effect of omnivorous and vegetarian diets on reproduction in the albino rat. Science, N. S., 47: 223-224. 398, 413.
- . 1923. Effect of a restricted diet. I. On growth. Am. J. Physiol., 63: 503-511. 80, 102.
- . 1923a. Effect of a restricted diet. II. On pubescence and the menopause. *Ibid.*, 64: 35-43. 102, 398, 413.
- . 1923b. Effect of a restricted diet. III. On the number of litters and young born. *Ibid.*, 64: 167-180. 12 figs. 102, 398.
- . 1923c. Effect of a restricted diet. IV. On the age of greatest productivity. *Ibid.*, 64: 203-209. 102, 398.
- . 1923d. Effect of a restricted diet. V. On mortality, cannibalism and the sex ratio. *Ibid.*, 64: 297-310. 102.
- Slowtsoff (Slovtoff or Slovzov), B. L. 1903. Beiträge zur vergleichenden Physiologie des Hungerstoffwechsels. Erste Mitth. Der Hungerstoffwechsel der Insekten. Beitr. z. chem. Physiol. etc., 4: 23-39. 64.
- . 1903a. Zweite Mitth. Der Hungerstoffwechsel der Weinbergschnecke. *Ibid.*, 4: 460-475. 54.
- . 1904. Dritte Mitth. Der Hungerstoffwechsel bei Libellen. *Ibid.*, 6: 163-169. 60.
- . 1904a. Vierte Mitth. Der Hungerstoffwechsel von Hammeln (*Bombus terrestris*). *Ibid.*, 6: 170-174. 65.
- . 1904b. Der Hungerstoffwechsel der Eidechsen. Salkowski Festschr., pp. 365-374. (Abstr. in Physiol. Jahrb., 1904.)
- . 1905. (Comparative pathology of hunger.) Izviest. Imp. Voenno-Med. Akad. St. Petersburg, 11: 189-198. (Abstr. by Weinberg in Ergeb. d. allg. Path. etc., 1907, 11: 756.)
- . 1909. Beiträge etc. V. Mitth. Der Hungerstoffwechsel der Mistkäfer (*Geotrupes stercoralis*). Biochem. Ztschr., 19: 504-508.
- Smallwood, W. M. 1916. Twenty months of starvation in *Amia calva*. Biol. Bull., 31: 453-464. 169, 250, 462.
- & Rogers, C. G. 1908. Studies on nerve cells. I. The molluscan nerve cell, together with summaries of recent literature on the cytology of invertebrate nerve cells. J. Comp. Neur. & Psychol., 18: 45-86. 1 pl. 3 figs. 54, 204.
- . 1909. Studies on nerve cells. II. The comparative cytology and physiology of some of the metabolic bodies in the cytoplasm of invertebrate nerve cells. Folia Neuro-Biol., 3: 11-20. 54, 204.
- . 1910. Studies on nerve cells. III. Some metabolic bodies in the cytoplasm of nerve cells of gasteropods, a cephalopod, and an annelid. Anat. Anz., 36: 226-232. 3 Fig. 47, 54, 204.
- . 1911. Effects of starvation upon *Necturus maculatus*. (Preliminary report.) Anat. Anz., 39: 136-142. 197, 204, 307, 319.
- Smirnow, M. R. 1913. The effect of water ingestion on the fatty changes of the liver in fasting rabbits. Am. J. Physiol., 32: 309-314. 338.

- Smith, C. H. 1918. Methods used in a class for undernourished children. *Am. J. Dis. Child.*, vol. 15, No. 6.
- G. E. 1917. Fetal athyrosis. A study of the iodine requirement of the pregnant sow. *J. Biol. Chem.*, 29: 215-225. 106, 131, 443.
- W. J. 1909. Scurvy. In Allbutt & Rolleston's *System of Med.*, 5: 879-898.
- Snyder, J. R. 1923. Pellagra. In *Abt's Pediatrics*, 2: 876-906. Saunders Co., Phila. 103.
- Sobotta, J. 1914. Anatomie der Bauchspeicheldrüse (Pankreas). In *Bardeleben's Handb. d. Anat.*, Lief. 26. Jena. 347.
- Soergel, C. 1918. Hat die Kriegsernährung einen Einfluss auf die Entwicklung des Neugeborenen? *Münch. med. Wchnschr.*, 65: 743-744. 79.
- Sokoloff, A. A. 1876. (Ueber die Nervenendigungen in den Muskeln ausgehungertcr Frösche.) *Med. Bote*, No. 11, 15, 16. (Abstr. in *Jahresb. d. Anat. etc.*, 1876, pp. 130; 161-162.) 167, 205.
- Soler. 1791. Osservazione medico-pratiche che formano la storia esatta di una particolar malattia chiamato pellagra, etc. Venezia. (Cited by Harris '19.) 103.
- Soltz (Solts), O. S. 1894. (On the anatomical changes in the bone marrow during complete inanition and subsequent refeeding; experimental research.) *Russian Dissert.*, St. Petersburg. *Trudi V syezda Obsh. russk. vrach. v. pamyat Pirogova*, St. Petersburg, 1: 139-143. 136, 139.
- Sommerfeld, P. 1900. Zur Kenntnis der chemischen Zusammensetzung des Körpers im ersten Lebensjahr. *Arch. f. Kinderh.*, 30: 253-263.
- Soranus (Ephesius). 1894. Die Gynäkologie, Geburtshilfe, Frauen- und Kinderkrankheiten, Diätetik der Neugeborenen. Uebers. v. H. Lüneburg. 173 pp. J. F. Lehmann, München.
- Sorg, F. L. A. W. 1805. *Disquisitiones physiologicae circa respirationem insectorum et vermium, etc.* Rudolstadtii. 2 pts., 164 and 61 pp. (Cited by Lucas 1826.) 53, 57, 64.
- Sosnowsky, J. 1899. (Ueber die Beziehungen des Kerns zum Zellkörper bei Protozoen.) (*Russian.*) *Arb. aus zootom. Lab. d. Warschauer Univ.*, 20: 1-47. 1 Taf. (Abstr. in *Jahresb. d. Anat. etc.*, 1899, T. 1, pp. 32; 65-67; and by Lipska '10.) 19.
- Souba, A. J. 1923. Influence of the antineuritic vitamin upon the internal organs of single comb white leghorn cockerels. *Am. J. Physiol.*, 64: 181-201. 234, 284, 343, 354, 386, 415, 444.
- & Dutcher, R. A. 1922. Further observations on the influence of vitamin B on the development of organs in Single Comb White Leghorn cockerels. (Abstr.) *Science*, 61: 396. 234, 343, 386, 415.
- Soukhanoff, S. 1898. Contribution à l'étude des modifications que subissent les prolongements dendritiques des cellules nerveuses sous l'influence des narcotiques. *Cellule*, 14: 387-395. 1 fig. 184.
- . 1898a. L'anatomie pathologique de la cellule nerveuse en rapport avec l'atrophie variqueuse des dendrites de l'écorce cérébrale. *Ibid.*, 14: 397-417. 4 figs. 184.
- Spaeth, F. 1917. Zur Frage der Kriegsamorrhöe. *Zentralbl. f. Gyn.*, 41: 664-668. 391, 400.
- Spiegler, A. 1901. Ueber den Stoffwechsel bei Wasserentziehung. *Ztschr. f. Biol.*, 41: 239-270. 116.
- Springer, A. 1909. A study of growth in the salamander, *Diemyctylus viridescens*. *J. Exp. Zool.*, 6: 1-68. 94.
- Ssobolew, L. W. 1902. Zur normalen und pathologischen Morphologie der inneren Sekretion der Bauchspeicheldrüse. *Arch. f. path. Anat. etc.*, 168: 91-128. 2 Taf. 351.
- von Starck. 1896. Ueber die Bedeutung des Milztumors bei Rachitis. *Deut. Arch. f. klin. Med.*, 57: 265-278. 282.
- Starling, E. H. 1920. The food supply of Germany during the war. *J. Roy. Statis. Soc.*, Lond., 83: 225-254.
- Stassano, H. et Hass, E. 1900. Contribution à la physiologie des clasmatoctes. *Compt. rend. Soc. de biol., Par.*, 52: 807-808.

Statkewitsch, P. 1894. Ueber Veränderungen des Muskel- und Drüsengewebes, sowie der Herzganglien beim Hungern. Arch. f. exp. Path. u. Pharm., Lpz., 33: 415-461. 1 pl. 168, 205, 231, 331, 334, 345, 349, 357, 377.

Steenbock, H., Nelson, E. M. & Hart, E. B. 1921. Fat soluble vitamin. IX. Incidence of ophthalmic reaction in dogs fed fat soluble vitamin deficient diet. Am. J. Physiol., 58: 14-19. 218.

Stefani. 1910. Sul consumo degli organi nel digiuno. (Internat. Physiologenkongress, Wien.) Lavori del lab. fisiol. di Padova, vol. 15. (Abstr. in Zentralbl. f. Physiol., 24: 812.) 380.

Stefko, W. H. 1923. Der Einfluss des Hungerns auf Blut und blutbildende Organe. Arch. f. path. Anat. etc., 247: 86-117. 136, 137, 236, 244, 272, 277, 327, 329, 392.

———. 1923a. Der Einfluss des Hungerns auf das Wachstum und die gesamte physische Entwicklung der Kinder (im Zusammenhang mit anatomischen Veränderungen beim Hungern). Ztschr. f. Konstitutionsl., 9: 312-355. 17 Fig. 83, 292, 400, 406, 421, 437, 460.

———. 1924. Die Herzensänderungen beim Hungern im Zusammenhang mit seinen konditionellen Besonderheiten als eines Organs. *Ibid.*, 9: 501-516. 3 Fig. 227, 392, 406, 421.

Steinberg, R. A. 1919. A study of some factors in the chemical stimulation of the growth of *Aspergillus niger*. Am. J. Bot., 6: 330-372. 5.

Steinhardt. 1917. Vom Stillen in der Kriegszeit. Münch. med. Wchnschr., 64: 943. (Cited by Lusk '21.) 129.

Steinitz, F. 1904. Ueber den Einfluss von Ernährungsstörungen auf die chemische Zusammensetzung des Säuglingskörpers. Jahrb. f. Kinderh., 59: 447-461.

——— u. Weigert, R. 1905. Ueber die chemische Zusammensetzung eines ein Jahr alten atrophischen und rachitischen Kindes. Monatschr. f. Kinderh., 4: 301-307.

Stephani, E. 1923. (Anatomical findings in nutritional disturbances of infants.) Jahrb. f. Kinderh., 101: 201-220. Abstr. in Internat. Surv. Pediatr., 1923, 5: 480-481. 278, 292, 329, 421.

Stephenson, M. & Clark, A. B. 1920. A contribution to the study of keratomalacia among rats. Biochem. J., 14: 502-521. 2 pl. 218.

Stepp, W. 1917. Einseitige Ernährung und ihre Bedeutung für die Pathologie. Ergeb. d. inn. Med. u. Kinderh., 15: 257-364. 104, 110.

———. 1922. Ueber den derzeitigen Stand der Vitaminlehre mit besonderer Berücksichtigung ihrer Bedeutung für die klinische Med. Klin. Wchnschr., 1: 881-885; 931-935. 111.

Sternberg. (Cited by Benzançon et Labbé '04.)

——— C. 1913. Leber, Pancreas, etc. In Aschoff's Pathologische Anatomie, 3. Aufl., Bd. 2, Jena. (Also 5. Aufl., 1921.) 326, 346.

Stevens, N. M. 1901. Notes on regeneration in *Planaria lugubris*. Arch. f. Entw. d. Org., 13: 396-409. 41.

Stewart, C. A. 1916. Growth of the body and of the various organs of young albino rats after inanition for various periods. Biol. Bull., 31: 16-51. 4 charts. Also (abstr.) in Anat. Rec., 1916, 10: 245. 70, 89, 94, 95, 96, 119, 135, 139, 165, 166, 180, 193, 212, 228, 276, 297, 340, 366, 380, 395, 409, 429, 438, 451.

———. 1918. Changes in the relative weights of the various parts, systems and organs of young albino rats underfed for various periods. J. Exp. Zool., 25: 301-353. 1 fig. 75, 89, 119, 135, 157, 165, 180, 193, 212, 214, 228, 275, 297, 307, 338, 366, 380, 395, 409, 429, 438, 451, 467.

———. 1918a. Weights of various parts of the brain in normal and underfed albino rats at different ages. J. Comp. Neurol., 29: 511-528. 1 fig. 180, 187, 228, 451.

———. 1919. Changes in the weight of the various parts, systems and organs in albino rats kept at birth weight by underfeeding for various periods. Am. J. Physiol., 48: 67-78. 75, 89, 119, 135, 193, 212, 228, 297, 307, 338, 366, 380, 395, 409, 429, 438, 451, 467.

- Stheeman, H. A. 1921. Adynamie und Blutkalkspiegel (die calciprive Konstitution). *Jahrb. f. Kinderh.*, 3. F., 94: 27-54. 105.
- Stickel, M. 1910. Untersuchungen am menschlichen Neugeborenen. Über das Verhalten des Darmepithels bei verschiedenen funktionellen Zuständen. Ein Beitrag zur Physiologie des Neugeborenen. *Arch. f. Gyn.*, 92: 607-658. 2 Taf. 315, 321, 338.
- . 1917. Zur Amenorrhöefrage. *Zentralbl. f. Gyn.*, 41: 689-696. 391, 400.
- Stieve, H. 1918. Ueber experimentell, durch veränderte äussere Bedingungen hervorgerufene Rückbildungsvorgänge am Eierstock des Haushuhnes (*Gallus domesticus*). *Arch. f. Entw. d. Org.*, 44: 530-588. 10 Fig. 396.
- . 1921. Ueber den Einfluss der Umwelt auf die Eierstöcke der Tritonen. *Ibid.*, 49: 179-267. 2 Taf. 396.
- . 1922. Untersuchungen über die Wechselbeziehungen zwischen Gesamtkörper und Keimdrüsen. I. Mastversuche an männlichen Gänsen. *Ibid.*, 52: 313-364. 2 Taf. u. 3 Kurven. 77, 412.
- Stilling, H. 1898. Zur Anatomie der Nebennieren. II. *Arch. f. mikr. Anat.*, 52: 176-195. 1 Taf. 418, 423, 430.
- & von Mering, J. 1889. Ueber experimentelle Erzeugung der Osteomalacie. *Centralbl. f. d. med. Wiss.*, 27: 803-804. 147.
- Stinzing, R. 1899. Zur Struktur der Magenschleimhaut. *Festschr. zum 70. Geburtstag v. Kupffers*. Jena. Pp. 53-56. 1 Taf. 309.
- Stockard, C. R. 1910. Studies of tissue growth. 3. The rates of regenerative growth in different salt solutions. 4. The influence of regenerating tissue on the animal body. *Arch. f. Entw. d. Org.*, 29: 15-32. 4 Fig. 39.
- Stoeltzner, W. 1899. Die Stellung des Kalks in der Pathologie der Rachitis. *Jahrb. f. Kinderh.*, 50: 268-279. 147.
- . 1903. Pathologisch-anatomische Befunde an den Weichteilen Rhachitischer. Gibt es eine viscerale Rhachitis? *Charité-Annalen*. (Abstr. in *Monatschr. f. Kinderh.*, 1904. (Bd. II f. 1903), pp. 149-150.) 188, 282, 342.
- . 1904. Pathologie und Therapie der Rachitis. Berlin. 431.
- . 1908. Die zweifache Bedeutung des Calciums für das Knochenwachstum. *Arch. f. d. ges. Physiol.*, 122: 599-604. 147, 148
- . 1909. Korreferat über Rachitis und Osteomalacie. *Centralbl. f. allg. Path. etc.*, Erg. zum Bd. 20. *Verh. d. Deut. path. Ges.*, 13: 20-32. 109, 145, 170, 282, 431.
- . 1909a. Gilt v. Bunge's Gesetz des Minimums für Ca und Fe? *Med. Klinik*, 5: 808-809. 105, 256.
- . 1921. Die Rachitis als Avitaminose. *Münch. med. Wchnschr.*, 68: 1481-1482. 107.
- u. Salge, B. 1901. Beiträge zur Pathologie des Knochenwachstums. Kap. V. Die pseudorachitische Osteoporose infolge kalkarmer Fütterung. Verlag. S. Karger, Berl. 148.
- Stohmann, F. 1862. Ueber einige Bedingungen der Vegetation der Pflanzen. *Ann. d. Chem. u. Pharm.*, 121: 285-338. 7.
- Stokes, W. R., Rurah, J. & Rohrer, C. W. G. 1902. The relation of the thymus gland to marasmus. *Am. J. Med. Sc.*, 124: 847-864. 7 figs. 287.
- Stolc, A. 1906. Plasmodiogenie, eine Vermehrungsart der niedersten Protozoen. *Arch. f. Entw. d. Org.*, 21: 111-125. 18.
- Stolnikow. 1887. Vorgänge in den Leberzellen insbesondere bei der Phosphorvergiftung. *Arch. f. Anat. u. Physiol.*, Phys. Abt., Suppl. Bd., pp. 1-27. 2 Taf. 333.
- Stolte, K. 1913. Ueber Störungen des Längenwachstums der Säuglinge. *Jahrb. f. Kinderh.*, 78: 399-425. 91, 135.
- . 1922. Ueber Keratomalazie. *Klin. Monatsbl. f. Augenh.*, Stuttgart, 68: 739-743. 211, 220.
- Stone, L. 1897. The artificial propagation of salmon on the Pacific coast of the United States, with notes on the natural history of the Quinnot salmon. *Bull. U. S. Fish Commission*, vol. 16 (for 1896), pp. 203-235. 77, 310, 397, 412.

- Stoppenbrink, F. 1905. Der Einfluss herabgesetzter Ernährung auf den histologischen Bau der Süßwassertricladen. *Ztschr. f. wiss. Zool.*, 79: 496-547. 1 Taf. 1 Fig. **43, 204.**
- Strahl, H. 1908. Polyphemusbologie. Cladocereciere und Kernplasmarelation. *Int. Rev. Ges. Hydrobiol. u. Hydrogr.*, 1: 821-832. (Cited by Shull '11 and Green '19.)
- Stransky, E. 1922. Ernährungsprobleme bei *Lues congenita*. *Ztschr. f. Kinderh.*, 32: 199-214. **81.**
- Strassburger, E. 1900. Versuche mit diöcischen Pflanzen in Rücksicht auf Geschlechtsverteilung. *Biol. Zentralbl.*, No. 20-24. **3, 4.**
- Straub, W. 1899. Ueber den Einfluss der Wasserentziehung auf den Stoffwechsel und Kreislauf. *Ztschr. f. Biol.*, 38: 537-566. **116, 172, 260.**
- Strauss. 1915. (Cited by Maver '20.) **71.**
- Streicher, M. H. & Emmel, V. E. 1924. Comparative analysis of acute inanition and lactation leucopenia. (Abstr.) *Anat. Rec.*, 27: 188. **253.**
- Strelzoff, 1864. L'influence de l'inanition sur la tension du sang. (Rev. in *Canst. Jahresb.*, 1865, II, p. 91; cited by Falck '81 and Dünschmann '00.) **235.**
- . 1873. Zur Lehre von der Knochenentwicklung. *Centralbl. f. d. med. Wiss.*, Berl., Bd. 11. (Cited by Pommer '85.) **146.**
- Strong, R. P. & Crowell, B. C. 1912. The etiology of beriberi. *Philip. J. Sc., B.*, 7: 271-413. 7 pl. **206, 233, 268, 283, 312, 343, 367, 385, 432.**
- Stschastny (Shtshastny), S. 1898. (Veränderungen der inneren Organe eines Menschen; der nach 35 tägiger Hungerdauer gestorben war.) (Russian.) *Arch. f. Path., klin. Med. u. Bakt., St. Petersburg.*, 5: 694-705. 1 pl. (Abstr. by *Jahresb. d. Anat. etc.*, 1898, T. 1, p. 32, and by Mühlmann '99.) **229, 277, 304, 326, 346, 372.**
- Subbotin, V. 1871. Mittheilung über den Einfluss der Nahrung auf den Haemoglobingehalt des Blutes. *Ztschr. f. Biol.*, 7: 185-196. **254.**
- Sugita, N. 1918. Comparative studies on the growth of the cerebral cortex. VII. On the influence of starvation upon the development of the cerebral cortex. Albino rat. *J. Comp. Neurol.*, 29: 177-240. 2 charts. **180, 186.**
- Sugiura, K. & Benedict, S. R. 1923. A study of the adequacy of certain synthetic diets for the nutrition of pigeons. *J. Biol. Chem.*, 55: 33-44. 1 pl. **111.**
- Sulli, G. 1906. Sul potere di riduzione dei tessuti nella inanizione. *Arch. di psichiatri. etc.*, Torino, 27: 611-620.
- Sullivan, M. X. 1920. A biological study of a diet resembling the Rankin Farm diet. *Bull. No. 120, U. S. Hyg. Lab., Washington*, pp. 127-140. **103.**
- . 1920a. Feeding experiments with the Rankin Farm pellagra-producing diet. *Ibid.*, pp. 141-156. **103.**
- Sundwall, J. 1917. Tissue alteration in malnutrition and pellagra. *Bull. No. 106, U. S. Hyg. Lab., Washington*, pp. 5-73. 7 pl. 21 figs. **103, 104, 185, 187, 197, 199, 233, 280, 281, 283, 307, 311, 340, 342, 366, 380, 431, 461.**
- Sure, B. 1924. Dietary requirements for reproduction. II. Existence of a specific vitamin for reproduction. *J. Biol. Chem.*, 58: 693-709. 11 charts.
- Susamiki, J. 1896. (Consumption of substance in inanition of the domestic hare.) (Japanese.) *Okayama Igaku Kwai Zasshi*, pp. 253; 333. (Ind. Cat. S. G. L.)
- Suski, P. M. 1923. Ueber die Zusammensetzung des Blutes bei experimenteller Avitaminose. *Biochem. Ztschr.*, 137: 405-412. **257.**
- Suzuki, T. 1912. Zur Morphologie der Nierensekretion unter physiologischen und pathologischen Bedingungen. 252 pp. Verlag G. Fischer, Jena. (Cited by Arnold '14.) **384, 388.**
- Sweet, C. B. 1921. The etiology of rickets. *Brit. Med. J.*, 2: 1067-1068. **109, 298.**
- Swingle, W. W. 1918. The effect of inanition upon the development of the germ glands and germ cells of frog larvae. *J. Exp. Zool.*, 24: 545-565. 14 figs. **75, 77, 396, 409.**
- . 1922. Experiments on the metamorphosis of the neotenen amphibians. *Ibid.*, 36: 397-421. **106.**
- Swirski, G. 1902. Ueber das Verhalten des festen Magendarminhaltes bei absoluter Karenz des Kaninchen. *Arch. f. exp. Path. etc.*, 48: 282-301. **307.**

Szenes, A. 1921. Ueber alimentär entstandene Spontanfrakturen und ihren Zusammenhang mit Rachitis tarda und Osteomalacie. Mitt. a. d. Grenzgeb. d. Med. u. Chir., 33: 618-648. 136.

Szwajsówna, P. 1916. Le métabolisme physiologique chez les larves du *Tenebrio molitor*. Compt. rend. Soc. Sc. de Varsovie, vol. 9. (Cited by Kopeć '24.) 64.

Takaki, K. 1907. Ueber die Stäbchenstrukturen der Niere. Arch. f. mikr. Anat., 70: 245-265. 1 Taf. 379, 383, 388.

Takasu, K. 1903. Ueber das Blut der an Kakke leidenden Säuglinge. Mitt. d. Med. Ges. z. Tokyo, 17: 395-404. 257.

Talbot, E. S. et al. 1909. A study of malnutrition in the school child. (Abstr. of discussion.) J. Am. M. A., 53: 712-714. 157, 182.

———. 1919. Pathology of the mouth in scurvy. *Ibid.*, 73: 853-854. 160.

———. 1921. Severe infantile malnutrition. Energy metabolism with report of a new series of cases. Am. J. Dis. Child., 22: 358-370. 6 figs. 81.

——— F. B., Dodd, W. T. & Peterson, H. O. 1913. Experimental scorbutus and the roentgen-ray diagnosis of scorbutus. Bost. Med. & Surg. J., 169: 232-238. 154.

Tallquist, T. W. 1922. Unterernährung und innere Sekretion. Acta med. scand., Stockholm, 56: 640-657. 1 Fig. (Also in Finska Läkaresällskapets Handlingar, Helsingfors, 64: 1-17.) 71, 255, 431, 437, 442.

Tanberg, A. 1910. Om Virkungen of ensidig Kjødernoering, soerlig paa glandula thyroidea. Norsk Mag. f. Laegevidenskabem, pp. 156-ff. (Cited by Biedl.) 442.

Tang, E. H. 1922. Ueber die Panethschen Zellen sowie die gelben Zellen des Duodenums beim Schwein und den anderen Wirbeltieren. Arch. f. mikr. Anat., 96: 182-209. 3 Fig. 321.

Tangl, F. 1909. Zur Kenntnis des Stoff- und Energieumsatzes holometaboler Insekten während der Metamorphose. VI. Beitrag-zur Energetik der Ontogenese. Arch. f. d. ges. Physiol., 130: 1-54. 61.

Tapke. 1910. Die Geburtshilfe des Rindes. Braunmüller. (Cited by Bondi '13.) 77.

Tarasewitsch (Tarasevich), L. A. 1898. (Veränderungen des centralen Nervensystems (Gross- und Kleinhirn) in einem Falle von Tod nach 35-tägigem Hunger.) Russ. Arch. f. Path., etc., St. Petersburg, 5: 687-693. 1 pl. (Abstr. in Jahresb. d. Anat. etc., 1899, T. 1, p. 224; and by Mühlmann '99.) 181.

———. 1907. O golodanii. (On starvation.) Kiyev. (Ind. Cat., S. G. L.)

Tardieu, A.-A. 1880. Étude médicolegale sur l'infanticide. Par. 2. éd. (pp. 204-207). (Cited by Dünschmann '00.) 138, 182, 211, 216, 314, 362.

Tartakowsky, S. 1904. Ueber die Resorption und Assimilation des Eisens. Arch. f. d. ges. Physiol., 101: 423-553. 256.

Tasawa, R. 1915. Experimentelle Polyneuritis, besonders bei Vögeln, im Vergleich zur Beriberi des Menschen. Ztschr. f. exp. Path. u. Therap., 17: 27-46. 113, 131, 207, 233, 257, 268, 283, 312, 343, 354, 368, 386, 414, 432.

Tauszk, F. A. 1894. (Die Veränderungen im Centralnervensystem bei Inanition.) Magyar Orvosi Arch., Budapest, 3: 505-512. (Abstr. in Neurol. Centralbl., 13: 820-821.) 195.

———. 1894a. (Hämatologische Untersuchungen beim hungernden Menschen.) Orvosi hetilap., Budapest, p. 512. (Abstr. in Maly's Jahresb. üb. d. Thier-Chemie, etc., 24: 147, and by Ash '15.) 242.

———. 1896. Hämatologische Studien am hungernden Menschen. Wien. klin. Rundschau, 10: 306-308. 242.

Taylor, A. S. 1920. Principles and practice of medical jurisprudence. 7th ed., revised by F. J. Smith. 1: 608-619. Churchill, Lond. 72, 240.

——— C. K. 1922. The great underweight delusion. Outlook, Mar. 15. 87.

Tello. 1903. Sobre la existencia de neurofibrillas colosales en las neuronas de los reptiles. Trab. Lab. investig. de la Univ. de Madrid, 2: 223-ff. (Cited by Cutore '08.) 198.

———. 1904. Las neurofibrillas en los vertebrados inferiores. *Ibid.*, T. 3. (Cited by Cutore '08.)

Terroine, E. F. 1920. Contribution à la connaissance de la physiologie des substances grasses et lipidiques. *Ann. d. sc. nat. d. zool., Par., 10. ser., 4: 1-397.* 30, 170, 231, 280, 340, 366, 381.

Teuscher, R. 1867. *Jenaische Ztschr. f. Med. u. Naturwiss., 3: 103.* (Cited by Blegvad '24.) 211, 216.

Thalberg. 1883. *Arch. f. Augenh., 12: 315.* (Cited by Blegvad '24.) 211, 216.

Thaon. 1872. *Der thymus aux différents âges. Mouvem. méd. (Cited by Farret '96.) 287.*

Theile, F. W. 1884. *Gewichtsbestimmungen zur Entwicklung des Muskelsystems und des Skelettes beim Menschen. Nova Acta d. k. Leop.-Carol. Deut. Akad. d. Naturf., 46: 135-471.* 163, 165,

Theiler, A. 1912. Facts and theories about stijfziekte and lamziekte. *Agr. J. Union of S. Afr. (Cited by Funk '22.) 136.*

———. Green, H. H., du Foit, Meier & Viljoen. 1920. The causes and prevention of lamziekte. *Ibid., Reprint 13, July.* (Cited by Funk '22.) 136.

——— & Viljoen, P. R. 1915. Contribution to the study of deficiency diseases, etc. 3d & 4th Director Veter. Res. Rep., Dept. Agr. Union S. Afr. 9. (Cited by Funk '22.)

Théohari, A. 1899. Étude sur la structure fine des cellules principales, de bordure et pyloriques de l'estomac à l'état de repos et à l'état d'activité sécrétoire. *Arch. d'anat. micr., 3: 11-34.* 1 pl. 309.

Theremin, E. 1877. Ueber congenitale Occlusionen des Dünndarms. *Deut. Ztschr. f. Chir., 8: 34-71.* 69.

Thiemich, M. 1900. Ueber die Schädigung des Centralnervensystems durch Ernährungsstörungen im Säuglingsalter. *Jahrb. f. Kinderh., 52: 810-843; 895-917.* 194.

Thiercelin, E. 1904. Athrepsie. In *Traité des malades de l'enfance*, by Grancher et Comby, 2 ed., Par., 2: 290-325. 81, 82, 120, 138, 165, 176, 182, 226, 230, 247, 263, 273, 303, 304, 315, 328, 362, 373, 420.

Thjötta, T. & Avery, O. T. 1921. Studies on bacterial nutrition. II. Growth accessory substances in the cultivation of hemophilic bacilli. *J. Exp. Med., 34: 97-114.* 13.

Thompson, D. 1917. *On growth and form.* Cambridge Univ. Press. 18.

———. F. D. 1911. On the thyroid and parathyroid glands throughout vertebrates. *Phil. Trans. Roy. Soc. Lond., Ser. B, vol. 201.* 438.

———. H. B. & Mendel, L. 1918. An experimental study of alternating growth and suppression of growth in the albino mouse with special reference to the economy of food consumption. *Am. J. Physiol., 45: 431-460.* 10 figs. 89, 120, 135, 165.

———. R. L. 1907. Atrophy of the parathyroid glandules and other glandular structures in primary infantile atrophy. *Am. J. Med. Sc., 134: 562-576.* 289, 420, 437, 445.

Thomson, J. A. 1888. Synthetic summary of the influence of environment upon the organism. *Proc. Roy. Physical Soc. Edinb., 9: 446-499.* 3.

Thon, K. 1905. Ueber den feineren Bau von *Didinium nasutum* O. F. M. *Arch. f. Protistenk., 5: 281-321.* 20.

Tiedemann, F. 1836. *Physiologie des Menschen. Bd. 3. Untersuchungen über das Nahrungs-Bedürfniss, den Nahrungs-Trieb und die Nahrungs-Mittel des Menschen. Darmstadt.* 120, 132, 163, 240, 264, 278, 302, 303, 316, 325, 331, 348, 356.

Tirelli, V. 1903. Studi ematologici sulla morte per fame e sul digiuno seguito da rialimentazione. *Ann. di freniatr. etc., Torino, 13: 137-152.*

Tixier, L. et Feldzer. 1910. La regression pathologique de thymus dans la jeune âge. *Compt. rend. Soc. de biol., Par., 68: 279-281.* 289, 290.

Tobler, L. 1910. Zur Kenntnis des Chemismus akuter Gewichtsstürze. Beziehungen zwischen Wasser und Salzen im Organismus. *Arch. f. exp. Path., 62: 431-468.* 172.

———. 1911. Ueber Veränderungen im Mineralstoffbestand des Säuglingskörpers bei akuten und chronischen Gewichtsverlusten. *Jahrb. f. Kinderh., 73: 566-585.* 170.

———. 1913. (Discussion following Aron '13.) 97.

- u. Bessau, G. 1914. Krankheiten durch abnormen Ablauf der Ernährungsvorgänge und des Stoffwechsels. In Brüning und Schwalbe's Handbuch der allgemeinen Pathologie und pathologischen Anatomie des Kindesalters. Bd. 1, Abt. 2, Kap. 9, pp. 650-749. **91, 94, 132.**
- Toldt, C. 1870. Beiträge zur Histologie und Physiologie des Fettgewebes. Sitzber. d. Wien. Acad. d. Wiss., Bd. 62, Abt. II. Juliheft. (Cited by Flemming '71a.) **124.**
- Tonin, R. 1919. Edemi da fame e poliuria. Gazz. d. osp., Milano, 40: 636. (Cited by Maver '20.)
- Tonninga, K. 1893. Ueber den Verbrauch an stickstoffhaltigen Substanzen in verschiedenen Organen der Tiere. Centralbl. f. Physiol., 7: 381-382. **170, 186, 280, 333, 365, 377.**
- Tonnini. 1883. I disturbi spinali nei pezzi pellagrosi. Riv. sper. di fren. e. di med. leg., 9: 118-120; 208-236; 429-448. Also *ibid.*, 1884, 10: 63-72. (Cited by Harris '19.) **199.**
- Tornier, G. 1907. Experimentelles über Erythrose und Albinismus der Kriechtierhaut. Sitzber. d. Ges. Naturf. Freunde. Berl., Nr. 4, pp. 81-89. Cf. also Zool. Anz., 1907, 32: 284-288. (Cited by Kammerer '13.) **121.**
- . 1911. Ueber die Art, wie äussere Einflüsse den Aufbau des Tieres abändern. Verh. d. Deut. zool. Ges., 20. u. 21. Vers., 1910 u. 1911, pp. 21-90. (Cited by Jahresb. d. Anat. etc., 1911, T. 2, p. 51.)
- Tozer, F. M. 1918. On the histological diagnosis of experimental scurvy. Biochem. J., 12: 445-447. 1 pl. Also *ibid.*, 1920, 14: 212. **150, 154.**
- . 1921. The effect on the guinea pig of deprivation of vitamin A and of the antiscorbic factor. J. Path. & Bact., 24: 306-325. 2 pl. **150.**
- . 1921a. The effect of a diet deficient in animal fat on the bone tissue (rib junctions) of kittens. Biochem. J., 15: 28-29. **150.**
- Traina, R. 1904. Ueber das Verhalten des Fettes und der Zellgranula bei chromschem Marasmus und akuten Hungerszuständen. Beitr. z. path. Anat. etc., 35: 1-92. 2 Taf. **124, 136, 336, 348, 358, 378, 393, 407, 423, 438.**
- Treat, M. 1873. Controlling sex in butterflies. Amer. Naturalist, 7: 129-132. **29, 63.**
- Trembley, A. 1744. Mémoires pour servir à l'histoire naturelle d'un genre de polypes d'eau douce, à bras en forme de cornes. Leyde. (Cited by Marshall '82 and Schultz '06.) **34.**
- . Biologie. T. 1, f. 1, 3, 4. (Cited by Lucas '26.) **65.**
- Tria, P. 1909. Proprietà chimico-fisiche del sangue durante la inanizione. Arch. di farm. sper., Roma, 8: 359-366.
- . 1911. Propriétés chimico-physiques du sang durant l'inanition. Arch. ital de biol., 55: 49-56. **241.**
- Triboulet, Ribadeau-Dumas et Harvier. 1910. La sidérose du foie chez les nourrissons. Compt. rend. Soc. de biol., Par., 68: 516-518. **277, 328.**
- Trifiliey, S. P. 1901 (1902?). (Action de l'inanition incomplete sur la consolidation des fractures.) Thèse, St. Petersburg. (Cited by Bardier '13.) **139.**
- Trivius, I. L. 1899. (Changes in the thrombosed arteries of animals during complete starvation and upon refeeding.) St. Petersburg., 76 pp. 1 pl. 5 figs. **235.**
- Troizky. (Cited by Stefko '23a.) **79.**
- Trousseau et Lasegue. 1850. L'Union méd. (Cited by Beylard '52 and Comby '01.) **143.**
- Trowbridge, P. F., Moulton, C. R. & Haigh, L. D. 1915. The maintenance requirement of cattle as influenced by condition, plane of nutrition, age, season, time of maintenance, type and size of animal. Univ. of Mo. Agr. Exp. Sta. Bull. No. 18, 62 pp. **241, 253.**
- . 1918. Effect of limited food on growth of beef animals. *Ibid.*, Res. Bull. No. 28, 129 pp. **90, 119, 120, 135, 156, 165, 180, 193, 228, 241, 253, 297, 340, 353, 366, 381, 440.**
- . 1919. Composition of the beef animal and energy cost of fattening. *Ibid.*, Res. Bull. No. 30, 106 pp. **90, 135, 228, 241, 253, 366.**
- True, R. H. 1922. The significance of calcium for higher green plants. Science, 55: 1-6. **7.**

- Tschirch, A. 1916. Zur Frage der Kriegsneugeborenen. Münch. med. Wchnschr., 63: 1650-1651. **79, 129.**
- Tschirvinsky, N. 1910. Die Entwicklung des Skelets bei Schafen unter normalen Bedingungen, bei unzulänglicher Ernährung und nach Kastration der Schafböcke in frühem Alter. Arch. f. mikr. Anat., 75: 522-561. Also in Nachrichten des Kiewer Polytechnischen Institutes, 1909. 103 Fig. **89, 135, 157.**
- Tschudnowsky (Chudnovski). 1890. (Material zum Studium des Heilungsprocesses von Hautwunden bei Erschöpfung des Organismus durch Inanition, Aderlass, Eiterung.) Dissert., St. Petersb.
- Tsuji, K. 1920. On the function of thyroid gland with special reference to the effect of variations of diet upon it. Acta Scholae Med. Univ. Imp. Kioto, 3: 713-729. 3 pl. **343, 354, 360, 399, 414, 444.**
- Tuczek, F. 1893. Klinische und anatomische Studien über Pellagra. G. Fischer, Berl., 113 pp. 9 pl. (Cf. also Deut. med. Wchnschr., 1888, 14: 222.) (Cited by Raubitschek '15 and Niles '16.) **104, 140, 170, 187, 199, 206, 232, 281, 322, 342, 367, 385.**
- Tuerk, W. 1912. Vorlesungen über klinische Haematologie. 2. Teil, 1. Hälfte. Wien u. Lpz. (Pp. 356-357.) **243.**
- Tugendreich, G. 1904. Beiträge zur pathologischen Anatomie der Magendarmkrankheiten des Säuglings. Arch. f. Kinderh., 39: 133-162. **315.**
- Ugromow (Ugryumoff or Ugriumov), P. K. 1904. (Ueber chemische Organveränderung bei Früchten hungernder Muttertiere.) Verh. d. IX Pirogow-Kongr., Sekt. f. allg. Path. Russki Vrach (Wratsch), 3: 41-43. (Abstr. in Ergeb. d. allg. Path. etc., 1906, 10: 43.) **407.**
- Urbain, A. 1920. Influences des maitères de reserve de l'albumen de la graine sur le developpement de l'embryon. Rev. Gén. Bot., 32: 125-139; 165-191. 24 figs. **5, 11, 13.**
- Urban, F. 1910. Zur Kenntnis der Biologie und Cytologie der Kalkschwämme (Fam. Clatherinidae Minch.) Intern. Rev. Ges. Hydrobiol., 3: 37-43. 6 Fig. **34.**
- Uspenski. 1896. (Pathologo-anatomische Veränderungen einiger peripherer Nervenganglien bei der Inanition. Veränderungen des Gangl. nodosum n. vagi, Gangl. cervic. super. u. sympathici, Gangl. coeliaci und automatischen Herzganglien. Eine experimentelle Untersuchung.) Dissert, St. Petersb., 99 pp., 2 Taf. (Abstr. in Jahresb. d. Anat. etc., 1896, T. 1, pp. 158, 164-165; and Mühlmann '99.) **205, 231.**
- Uthelm, K. 1921. (Changes in blood on different diets.) Norsk. mag. f. Laegevidenskaben, Christiana, 82: 96-104. **253.**
- . 1922. Advanced chronic nutritional disturbance in infancy. J. Metab. Res., 1: 803-917. **81, 82, 116, 249, 253.**
- Vacker. 1871. La mortalité à Paris en 1870. Gaz. méd. de Par., 26: 9-12. **71, 254.**
- Vaerting, M. 1918. Kriegsamennorrhöe und Sterilität. Zentralbl. f. Gyn., 42: 367-370. **391, 400.**
- Valenciennes. 1848. Histoire naturelle des Poissons, 21: 294-ff. (Cited by Nussbaum '14.) **77.**
- Valentin, G. 1838. Repert. f. Anat. u. Physiol., 3: 156-ff. (Cited by Rasmussen & Rasmussen '17.) **253.**
- . 1857. Beiträge zur Kenntniss des Winterschlafes der Murmelthiere. (Moleschott's) Unters. z. Naturl. d. Mensch. u. d. Thiere, 2: 1-55. Also *ibid.*, 1857, 1: 206-ff; 2: 222-ff, 285-ff; 3: 195-ff; 1858, 4: 58-ff; 5: 11-ff, 259-ff; 1860, 7: 39-ff; 1862, 8: 121-ff; 1865, 9: 129-ff, 227-ff, 632; 1870, 10: 265-ff, 526-ff, 590; 1876, 11: 149-ff, 392-ff, 450; 1881, 12: 31-ff, 237-ff, 466; 1882, 13: 34-ff. **70, 122, 126, 134, 164, 167, 178, 192, 213, 253, 276, 310, 356, 365, 430, 462.**
- Valisnieri. (Cited by Lucas 1826 from Haller 1771.) **47.**
- Valtorta. 1912. Sindromi distiroidee nella psicosi pellagrosa. Atti del Quinto Cong. Pel. Ital. Bergamo, p. 383. (Cited by Harris '19.) **200, 442.**
- Van der Loo, C. J. 1922. (Standard of nutrition for children.) Nederl. Tijdschr. v. Geneesk., No. 16, Apr. 22, 1: 1611-1620. (Abstr. in J. Am. M. A., 79: 511.) **85, 86, 87.**
- Van der Stricht, O. 1912. Sur le processus de l'excrétion des glandes endocrines: le corps jaune et la glande interstitielle de l'ovaire. Arch. de biol., 27: 585-722. 7 pl. **398.**

- Vandervelde, P. et Cantineau, G. 1919. La deportation des civils flamands en 1916. Considérations médicales. Bull. Acad. roy. de méd. de Belg., 4. s., 29: 129-208. (Abstr. in J. Am. M. A., 1919, 73: 1229.) **71, 120.**
- Van der Weyde, P. H. 1879 (?). Dr. Tanner's blood after starvation. Med. Tribune, N. Y., 2: 462-464. (Ind. Cat., S. G. L.) **241.**
- Van Ewing, P. and Wells, C. A. 1914. Digestion and metabolism of a steer when placed on a continuous ration of corn silage. Georgia Agr. Exp. Sta. Bull. 109, 14 pp. **90, 120.**
- de Varigny, H. 1887. Gewichtsverlust durch Nahrungsmangel bei *Aurelia aurita*. Centralbl. f. Physiol., 1: 389-390. **39.**
- Variot, G. 1904. Sur les formes prolongées de l'atrophie infantile d'origine gastro-intestinale. Bull. Soc. de pédiatr. de Par., 6: 153-159.
- . 1904a. Observations et remarques sur les stagnations de poids dans l'élevage des enfants atrophiques. Ann. de méd. et chir. inf., Par., 8: 361-366.
- . 1905. Rapport au Congrès international des Gouttes de lait, Par., 20. Oct. (Cited by Lascoux '08.)
- . 1905a. Étude radiographique du squelette des mains et des pieds dans trois cas d'hypotrophie infantile (atrophie infantile prolongée). Bull. et mém. Soc. méd. d. hôp. de Par., 3. s., 22: 31-38. Also in Bull. Soc. de pédiatr. de Par., 7: 14-19. **138.**
- . 1906. Nouvelles recherches radiographiques sur l'ossification des métacarpiens et des phalanges chez les enfants normaux et chez les hypotrophiques. Erreur d'un anatomiste français sur l'époque d'apparition des points complémentaires. Bull. Mém. Soc. d'anthrop., Par., sér. 5, 7: 405-415. 6 figs. Also in J. de la clin. inf., Nov. 1906. (Abstr. in Jahresb. d. Anat. etc., 1907, T. 3, pp. 116, 132.) **138.**
- . 1907. Remarques sur l'indépendance du développement du cerveau dans l'hypotrophie infantile. Bull. Soc. de pédiatr. de Par., 9: 62-65. **91, 176.**
- . 1907a. Sur les caractères spéciaux de l'hypotrophie chez les prématurés; atrophie pondérale; atrophie staturale. *Ibid.*, 9: 363-369. **91, 135.**
- . 1907b. Croissance infantile et hypertrophie. Méd. mod., Par., 18: 295 (?). **91.**
- . 1907c. La dissociation de la croissance dans l'atrophie et l'hypotrophie infantiles; atrophie pondérale, atrophie staturale. Bull. et Mém. Soc. méd. d. hôp. de Par., 3. s., 24: 1374-1376. **91, 135.**
- . 1907d. Anticipation du développement des points d'ossification complémentaires des premières phalanges et des métacarpiens chez un enfant hypernormal de douze mois. Bull. Mém. Soc. d'anthrop., Par., sér. 5, 8: 104-105. 1 fig. **138.**
- . 1907e. La dissociation de la croissance dans l'atrophie et l'hypotrophie infantile. Atrophie pondérale; atrophie staturale. J. de la clin. inf., 15 déc. (Cited by Lascoux '08.) **91, 135.**
- . 1908. La dissociation de la croissance dans l'atrophie et l'hypotrophie infantiles. Atrophie pondérale; atrophie staturale. Rev. internat. de méd. et de chir., 19: 41-42. **91.**
- . 1908a. L'accroissement statural et l'accroissement pondéral chez le nouveau-né. J. de la clin. inf., 1 Mai. (Cited by Lascoux '08.) **91.**
- . 1908b. L'accroissement statural et l'accroissement pondéral chez le nouveau-né. Dissociation physiologique de la croissance. Bull. Mém. Soc. d'anthrop., Par., sér. 5, 9: 283-289. **91.**
- . 1910. Traité d'hygiène infantile. O. Doin, Par.
- . 1921. Traité pratique des malades des enfants du premier âge. I. O. Doin, Par. **81.**
- et Cailliau. 1912. Recherches sur le processus de vacuolisation des fibres musculaires du coeur, dans la cours de l'atrophie et de l'hypotrophie infantiles. Bull. et mém. de la Soc. méd. d. hôp. de Par., 7 juin, pp. 781-792. **230.**
- et Ferrand, M. (Cited by Nobécourt '16.) **169.**
- et Guyarder. 1904. Atrophie infantile prolongée liée à l'hérédité tuberculeuse maternelle et à l'insuffisance de l'alimentation, poids de 13 livres 100 grammes à deux ans

- onze mois. Bull. et mém. Soc. méd. d. hôp. de Par., 3. s., 21: 947-949. Also in Bull. Soc. de pédiatr. de Par., 1904, 6: 276-284; and in Ann. de méd. et chir. inf., Par., 8: 802-808. 81.
- et Lassablière, P. 1909. Autonomie du développement de l'encéphale, dans les retards de la croissance chez les jeunes enfants. Compt. rend. Soc. de biol., Par., 66: 106-108. 177.
- Vaughan, V. C. 1923. Epidemiology and public health. Vol. 2, 917 pp. C. V. Mosby, St. Louis. 103, 108, 112, 113.
- Vedder, E. B. 1913. Beriberi. Wm. Wood & Co., N. Y., 427 pp. 5 pl. (Cf. also Proc. 2nd Pan Am. Sci. Congr., Sec. 8, pt. 2, p. 27.) 112, 206, 233.
- . 1923. Beriberi. In Abt's Pediatrics, 2: 815-826. Saunders Co., Phila. 112.
- & Clark, E. 1912. A study of polyneuritis gallinarum. A fifth contribution to the etiology of beriberi. Philip. J. Sc., Sec. B, 7: 423-461. 11 pl. 200, 201, 207, 233.
- & Williams, R. R. 1913. Concerning the beriberi-preventing substances or vitamins contained in rice polishings. *Ibid.*, 8: 175-195. (Cited by Maver '20.)
- Venulet, F. u. Dmitrosky, G. 1910. Ueber das Verhalten des chromaffinen Substanz der Nebennieren beim Hungern und unter dem Einfluss von Iodkali. Arch. f. exp. Path. u. Pharm., 63: 460-464. 427.
- Verdeil. 1849. Liebig's Annalen d. Chem. u. Pharm., 59: 89-ff. (Cited by Benzançon et Labbé '04.) 254.
- Ver Eecke, A. 1899. Nouvelle contribution à l'anatomophysiologie du thymus chez la grenouille. Ann. de la Soc. de méd. de Gand. (Cited by Hammar '05a.) 293, 297.
- . 1899a. Structure et modifications fonctionnelles du thymus de la grenouille. Bull. Acad. roy. de méd. de Belg., 4. s., 13: 67-86. 3 pl. 293.
- . 1901. Les échanges matériels dans leur rapports avec les phases de la vie sexuelle. Mém. cour. et autres mém. publ. par l'Acad. roy. de méd. de Belg., T. 15, fasc. 7. (Cited by Reeb '05 and Jägerroos '02.) 77.
- von Veress, F. 1906. Ueber Pellagra, mit besonderer Berücksichtigung der Verhältnisse in Ungarn. Arch. f. Derm. u. Syph., 81: 233-258. 130.
- Verheyen, P. 1710. Corporis humani anatomia. Ed. 2. Bruxelles (p. 159). (Cited by Hammar '06.) 286.
- Vernoni, G. 1912. Contribuzione all'anatomia patologica e patologia sperimentale della pellagra. Arch. per les sc. med., 36: 135-205. 7 pl. (Cited by Raubitschek '15.)
- Verworn, M. 1900. Das Neuron in Anatomie und Physiologie. Gemeinsch. Sitz. d. med. Hauptgr. d. 72. Versamml. deut. Naturf. u. Aerzte, Aachen. G. Fischer, Jena, 54 pp. (Cited by Wallengren '02.) 20.
- Vève, A.-J.-A. 1902. Malformations et lésions dentaires chez les rachitiques. Thèse, Par., No. 373, 73 pp. (Cited by Wohlauer '11.) 158.
- Victoroff, K. 1908. Zur Kenntnis der Veränderungen des Fettgewebes beim Frosche während des Winterschlafes. Arch. f. d. ges. Physiol., 125: 230-236.
- . 1909. (Changes in the fatty tissue during hibernation.) Uchen zapiski Kagan. vet. inst., 26: 143-149. (Ind. Med.)
- Vierordt, H. 1906. Anatomische, physiologische und physikalische Daten und Tabellen. 3. Aufl., Jena. 81, 373, 405, 419.
- Vigor, E. 1911. Étude clinique de l'hypoalimentation chez le nourrisson. Thèse, méd., Par., 1910-11, No. 309, 103 pp. 81, 91, 305.
- Villa, G. 1918. Contribucion al estudio de la sangre en la atrofia infantil, atrepsia de Parrot. La med. de los niños, Août, p. 233-ff. (Abstr. in Nourrisson, 1918, p. 223.) (Cited by Marfan '21.) 247.
- Ville, G. 1861. De l'importance comparée des agents de la production végétale. Des composés phosphorés utiles pour la végétation et des composés phosphorés qui ne le sont pas. Compt. rend. Acad. des sc., Par., 53: 832-ff. (Cited by Reed '07.) 10.
- Vincent, R. 1904. The nutrition of the infant. 2nd ed., Lond., 321 pp. 109, 120, 142, 151, 170, 282, 342.
- S. 1912. Internal secretion and the ductless glands. Lond. 438.

- & Hollenberg, M. S. 1920. The effects of inanition upon the adrenal bodies—preliminary communication. *Endocrinol.*, 4: 408-410. **428, 429.**
- . 1921. Changes in the adrenal bodies and in the thyroid resulting from inanition. *J. Physiol.*, 54: lxxix-lxxi. **428, 429, 438.**
- & Thompson, F. D. 1907. On the relation between the "islets of Langerhans" and the zymogenous tubules of the pancreas. *Internat. Monatschr. f. Anat. u. Physiol.*, 24: 61-102. 2 pl. **345, 352.**
- Vinokuroff, S. I. 1922. (Materials on the physiology of nutrition. Physiology of nutrition of the domestic fly.) Hunger (Famine). In memory of V. G. Korolenko. Kharkoff, pp. 74-78. (In Russian.) (Cited by Pearl & Parker '24.) **62.**
- Virchow, R. 1854. *Handbuch der speziellen Pathologie und Therapie.* Bd. 1. (Cited by Friebleben '60.) **143.**
- . 1859. Die Bindegewebsfrage. *Arch. f. path. Anat. etc.*, 16: 1-20. **124.**
- Voegtlin, C. & Lake, G. C. 1919. Experimental mammalian polyneuritis produced by a deficient diet. *Am. J. Physiol.*, 47: 558-589. **207, 234, 283, 323, 368, 386.**
- Voelkel, A. 1886. *Freiwilliger Hungertod.* *Deut. med. Wchnschr.*, 12: 523-534. **69, 122, 229, 240, 271, 303, 325, 362, 371.**
- Voigt, W. 1894. *Planaria gonocephala* als Eindringling in das Verbreitungsgebiet von *Planaria alpina* und *Polycelis cornuta*. *Zool. Jahrb., Abt. f. Syst. Geogr. u. Biol.*, 8: 131-176. **41.**
- Voit, C. 1866. Ueber die Verschiedenheiten der Eiweisszersetzung beim Hungern. *Ztschr. f. Biol.*, 2: 308-365. **134, 164, 179, 192, 217, 316, 331, 364, 376, 406.**
- . 1881. *Physiologie des allgemeinen Stoffwechsels und der Ernährung.* Hermann's Handb. d. Physiol., Bd. 6, T. 1, 575 pp. (Cited by Morgulis '11.) **141, 240.**
- . 1894. Gewichte der Organe eines wohlgenährten und eines hungernden Hundes. *Ztschr. f. Biol.*, (n. F. Bd. 12) 30: 510-522. **118, 134, 164, 186, 192, 213, 227, 249, 274, 293, 332, 349, 357, 365, 437.**
- . E. 1877. *Ber. d. 50. Versamml. deut. Naturf. u. Aerzte, München*, p. 242. (Cited by Hirsch '99 ?) **141, 145.**
- . 1880. Ueber die Bedeutung des Kalks für den thierischen Organismus. *Ztschr. f. Biol.*, 16: 55-118. **105, 109, 144, 145, 159, 171, 188, 233, 343.**
- . 1901. Ueber die Grösse des Energiebedarfes der Thiere im Hungerzustande. *Ibid.*, 41: 113-154.
- . 1901a. Die Bedeutung des Körperfettes für die Eiweisszersetzung des hungernden Tieres. *Ibid.*, 41: 502-549. **104.**
- . 1905. Welchen Schwankungen unterliegt das Verhältnis Organgewichte zum Gesamtgewicht des Tieres? *Ibid.* (n. F. Bd. 28) 46: 153-166. **118, 164.**
- . 1905a. Die Abnahme des Skeletts und der Weichteile bei Hunger. *Ibid.* (n. F. Bd. 28), 46: 167-197. **118, 134, 164.**
- de Vries, H. 1900. Ernährung und Zuchtwahl. Vorläufige Mitteilung. *Biol. Centralbl.*, 20: 193-198. (Complete work: *Alimentation et Sélection.* Volume jubilaire du Cinquantenaire de la Soc. de biol., Par., pp. 17-30.) **3, 4.**
- Wagner, R. 1921. Die zahlenmässige Beurteilung des Ernährungszustandes durch Indices. *Ztschr. f. Kinderh.*, 28: 38-51. **85.**
- Walbaum, O. 1899. Untersuchungen über die quergestreifte Muskulatur mit besonderer Berücksichtigung der Fettinfiltration. *Arch. f. path. Anat. etc.*, 158: 170-187. **169.**
- Walcott, F. C. 1918. Forerunners of famine. *Nat. Geogr. Mag.*, 33: 336-347.
- Walker, S. Jr. 1922. The relationship between xerophthalmia and fat-soluble A. *J. Am. M. A.*, 78: 273-274. **218.**
- Wallengren, H. 1902. Inanitionserscheinungen der Zelle. Untersuchungen an Protozoen. *Ztschr. f. allg. Physiol.*, 1: 67-128. 2 Taf. u. 2 Fig. **17, 19, 20, 21, 24.**
- Wallgren, A. 1921. Zur Symptomatologie und Pathogenese des Oedema scorbuticum invisibile. *Ztschr. f. Kinderh.*, 31: 35-50. (Abstr. in *J. Am. M. A.*) **237.**
- Walshe, F. M. R. 1918. On the "deficiency" theory of the origin of beri-beri in the light of clinical and experimental observations on the disease, with an account of a series of forty cases. *Quart. J. Med.*, 11: 320-338. **189.**

- . 1920. The nervous lesion of beriberi, and its bearing on the nature and cause of the disease. *Med. Sc. Abstr. & Rev.*, 2: 41-46. 189.
- Waser, B. 1920. Beobachtungen über das Längenwachstum gesunder und ernährungs-gestörter Säuglinge. *Ztschr. f. Kinderh., Orig.*, 27: 1-43. (Abstr. in *Ber. ges. Physiol.*, 1921, 6: 379.) 91, 135.
- Wason, I. M. 1921. Ophthalmia associated with a dietary deficient in fat soluble vitamin A. A study of the pathology. *J. Am. M. A.*, 76: 908-912. 5 figs. 218.
- Wassermann, S. 1918. Ueber hochwertige Erythrocyten- und Hemoglobinbefunde bei Kriegern. *Münch. med. Wchnschr.*, 65: 927. Also in *Fol. haematol.*, 1918-19, 23: 1-10. (Cited by Hess '20.) 258.
- Waters, H. J. 1908. The capacity of animals to grow under adverse conditions. *Proc. Soc. for the Promotion of Agr. Sc.*, 29th Ann. Meeting, Washington, D. C., pp. 71-96. 5 figs. 89, 125, 135.
- . 1909. The influence of nutrition upon the animal form. *Ibid.*, 30: 70-98. (Cf. also in *Kan. State Board Agr.*, 17th Bien. Rep., 1911, p. 199-ff.) 89.
- Watson, C. 1899. Article "Atrophy" in *Encycl. med.*, 1: 401-405. Longmans, Green & Co., N. Y.
- . 1910. Food and feeding in health and disease. Edinb. & Lond. (Appendix contains reprints of articles in *J. Physiol.*, etc.) 442.
- Weber, M. 1914. *Biologie der Tiere*. In *Lehrb. d. Biol. f. Hochschulen*, von Nussbaum, Karsten u. Weber. 2. Aufl. Lpz. u. Berl. 47, 60, 121.
- O. 1921. Der Einfluss des Krieges auf die Organgewichte. *Frankf. Ztschr. f. Path.*, 25: 35-52. 176, 225, 272, 327, 373.
- S. 1902. Ueber Hungerstoffwechsel. *Ergeb. d. Physiol.*, 1. Jahrg., 1. Abt. Biochemie. Wiesb. pp. 702-746. 72, 241.
- Wegelin, C. 1913. Ueber alimentäre Herzmuskelverfettung. *Berl. klin. Wchnschr.*, 50: 2125-2129; 2190-2192. 231, 338, 423.
- Wegner, G. 1872. Der Einfluss des Phosphors auf den Organismus. Eine experimentelle Studie. *Arch. f. path. Anat. etc.*, 55: 11-45. 3 Taf. 144, 145, 148.
- Weichselbaum u. Erdheim. 1909. Ueber die Veränderungen der Zähne bei Rachitis weisser Ratten. *Centralbl. f. allg. Path. etc.*, Bd. 20. *Verh. d. Deut. path. Ges.*, 13: 49-51. 159.
- Weigert, R. 1905. Ueber den Einfluss der Ernährung auf die chemische Zusammensetzung des Organismus. *Jahrb. f. Kinderh.*, 61: 178-198.
- Weill, E., Arloing, F. et Dufour, A. 1922. Sur l'hémalogie du pigeon carencé par alimentation au riz décortiqué. *Compt. rend. Soc. de biol., Par.*, 86: 1175-1176. 257.
- et Mouriquand, G. 1916. Inanition et carence. *Ibid.*, 79: 382-384.
- ———. 1917. Neurologie expérimentale. Les paralysies par carence. *Soc. de neurol., Mai*. (Cited by Funk '22.) 207.
- ———. 1919. La notion de carence en pathologie. *Gaz. des hôp.*, 92: 713-722. 98.
- Weinland, E. 1901. Ueber Kohlehydratzersetzung ohne Sauerstoffaufnahme bei *Ascaris*; einen tierischen Gärungsprozess. *Ztschr. f. Biol.*, 42: 55-90. 46.
- Weiske, H. 1871. Ueber den Einfluss von kalk- oder phosphorsäurearmer Nahrung auf die Zusammensetzung der Knochen. 1. u. 2. Abh. *Ibid.*, 7: 179-184; 333-337. 141, 142.
- . 1874. Ueber Knochenzusammensetzung bei verschiedenartiger Ernährung. 4. Abh. *Ibid.*, 10: 410-438. 105, 141, 462,
- . 1875. *J. f. Landwirtsch.*, p. 306. (Cited by Thompson & Mendel '18.) 120.
- . 1895. Weitere Beiträge zur Frage über die Wirkung eines Futters mit sauren Eigenschaften auf den Organismus, insbesondere auf das Skelett. *Ztschr. f. physiol. Chem.*, 20: 595-605.
- . 1897. Ueber den Einfluss der Nahrungsentziehung auf das Gewicht und die Zusammensetzung der Organe, insbesondere der Knochen und Zähne. *Ibid.*, 22: 485-499. 118, 134, 156, 164, 228, 275, 306, 335, 365, 378.

- u. Wildt, E. 1873. Untersuchungen über die Zusammensetzung der Knochen bei kalk- oder phosphorsäurearmer Nahrung. 3. Abh. Ztschr. f. Biol., 9: 541-549. **141, 142.**
- Weismann, A. 1879. Beiträge zur Naturgeschichte der Daphnoiden. VI. Samen und Begattung der Daphniden. VII. Die Entstehung der cyklichen Fortpflanzung bei den Daphniden. Ztschr. f. wiss. Zool., 33: 55-270. (Cited by Green '19.)
- Weitbrecht, E. 1922. Experimentelle Untersuchungen über den Einfluss vitaminfreier Kost auf das Blut wachsender Ratten. Arch. f. Kinderh., 71: 192-208. 7 Taf. **258.**
- Welcker, H. 1902. Gewichtswerte der Körperorgane bei dem Menschen und den Tieren. (Nach dem Tode des Verfassers geordnet und eingeleitet von. A. Brandt.) Arch. f. Anthropol., Bd. 28, H. 1.
- Wellmann, O. 1908. Untersuchungen über den Umsatz von Ca, Mg, und P bei hungerten Tieren. Arch. f. d. ges. Physiol., 121: 508-533. **135, 140.**
- Wells, F. M. 1919. Food deficiencies as a factor influencing the calcification and fixation of the teeth. Proc. Roy. Soc. Med., (Sec. Odontology), 12: 23-37. **158, 161.**
- . 1921. Food deficiencies as a factor influencing the calcification and fixation of the teeth. Brit. J. Dent. Sc. 64: 135-150. **161.**
- H. G. 1918. (Discussion in symposium on nutritional deficiency diseases.) J. Am. M. A., 71: 954. **71, 102.**
- Wesëlkin. 1904. (Untersuchungen über Mineralhunger.) Verh. IX Pirogow-Kongr., Sekt. f. allg. Path. Wrcebn. gas., Nr. 23, p. 686. (Cited by Weinberg in Ergeb. d. allg. Path. etc., 1906, 10: 43.)
- Wesselkin, N. W. 1913. Ueber den Einfluss von Sauerstoffmangel auf das Wachstum und die Entwicklung von Hühnerembryonen. Vorl. Mitt. Russky Wratsch, Bd. 12, H. 28. (Abstr. in Jahresh. d. Anat. etc., 1913, T. 2, pp. 206, 208.)
- Weygandt. 1904. Ueber den Einfluss von Hunger und Schlaflosigkeit auf die Gehirnrinde. 29. Vers. südwestdeut. Neurol. u. Irrenärzte, Baden-Baden. (Abstr. in Deut. med. Wehnschr. 1904, Vereinsbeilage, 30: 1088.) Also in Monatschr. f. Psychiatr. u. Neurol., 1904, 16: 288. **184.**
- Wharton, T. 1659. Adenographia. Amsteledami. (P. 93.) (Cited by Hammar '06.) **293.**
- Wheeler, R. 1913. Feeding experiments with mice. J. Exp. Zool., 15: 209-223. 6 charts. **101, 129.**
- Whipple, G. H. & Hooper, C. W. 1918. Blood regeneration after simple anemia. II. Curve of regeneration by starvation, sugar, amino acids and other factors. Proc. Am. Physiol. Soc. (1917), Am. J. Physiol., 45: 576-577. **253, 254.**
- & Robscheit, F. S. 1920. Blood regeneration following simple anemia. *Ibid.*, 53: 151-282. **253, 254.**
- Whistler, D. 1645. De morbo puerili anglorum, quem patrio idiomate indigenae vocant The Rickets. Disputatio med. inaug., Leyden, 18 pp. Also reprinted in London, 1684. (Cited by v. Starck '96 and Moore '84.) **108, 142, 157, 170, 188, 267, 282, 342.**
- Whitney, D. D. 1907. The influence of external factors in causing the development of sexual organs in *Hydra viridis*. Arch. f. Entw. d. Org., 24: 524-537. **28, 36.**
- . 1908. Determination of sex in *Hydatina senta*. J. Exp. Zool., 5: 1-26. **28, 58.**
- Wiazemsky (Wiasemsky), N. W. 1907. Influence de différents facteurs sur la croissance du corps humain. Thèse (Sci.), Par., A. Maloine, 394 pp. (Index Med.)
- Wieland, E. 1910. Die Frage der angeborenen und der hereditären Rachitis. Ergeb. d. inn. Med. u. Kinderh., 6: 64-119. **108.**
- . 1913. Spezielle Pathologie des Bewegungsapparates (Stützapparates) im Kindesalter. In Brüning u. Schwalbe's Handb. d. allg. Path. u. d. path. Anat. d. Kindesalters, Bd. 2, Abt. 1, Kap. 4, pp. 148-155. **105, 141.**
- Wiesmann. (Unpublished observations cited by Lucas 1826.)
- Wilckens, M. 1886. Untersuchung über das Geschlechtsverhältniss und die Ursachen der Geschlechtsbildung bei Haustieren. Landw. Jahrb., 15: 607-651. (Abstr. in Biol. Centralbl., 6: 503-510.) **80.**

- Wild, E. R. 1901. Anatomische Untersuchungen über das puerperale Osteophyt etc. Dissert., Lausanne, 60 pp. 1 Taf. (Cited by Funk '22.) 145.
- Wilkins, S. D. & Dutcher, R. A. 1920. The relation of vitamins to the development of sex organs in cockerels. (Abstr.) Proc. Am. Chem. Soc., Div. Biol. Chem., Science (N. S.), 52: 393.
- Willcock, E. G. & Hopkins, F. G. 1906. The importance of individual amino-acids in metabolism. J. Physiol., pp. 88-102.
- Williams, R. R. & Crowell, B. C. 1915. The thymus gland in beriberi. Philip. J. Sc., B, 10: 121-125. 298, 299.
- Willien, J. L. 1836. De la faim considérée sous la rapport physiologique, pathologique et thérapeutique. Thèse, Strassbourg, 48 pp. 163, 270, 303, 325, 346, 371.
- Willstaetter, R. 1906. Zur Kenntniss der Zusammensetzung des Chlorophylls. Liebig's Ann. d. Chem. u. Pharm., 350: 48-82. (Cited by Palladin '18.) 9, 10.
- Wilms, M. u. Sick. 1902. Die Entwicklung der Knochen der Extremitäten von der Geburt bis zum vollendeten Wachstum. Hamburg. (Cited by Wohlauer '11.) Cf. also Fortschr. a. d. Geb. d. Röntgenstr., Erg.-Bd. 9, 1902. 144.
- Wilson. 1916. Appendix to Report No. 2 on a pellagra epidemic at Armenian refugees' camp. Port Said Publ. Health Dep't., Egypt. (Cited by Funk '22.) 431.
- E. B. 1900. The cell in development and inheritance. 2nd ed. Macmillan Co., N. Y., 483 pp. 29.
- H. V. 1907. A new method, by which sponges may be artificially reared. Science (N. S.), 25: 912-915. 34.
- Wiltshire, H. 1919. Hyperkeratosis of the hair follicles in scurvy. Lancet, 197: 564-565. 132.
- Winckel. 1862. Recherches sur les rapports de poids des nouveau-nés. Monatschr. f. Geburtsh., Berl. (Cited by Lascoux '08.) 81.
- Winkler, H. 1913. Entwicklungsmechanik oder Entwicklungsphysiologie der Pflanzen. In Handb. d. Naturwiss., 3: 642-644. 2, 3, 5, 6, 7, 11.
- Withington, F. 1904. Article "Starvation-Fasting" in Buck's Ref. Handb. of the Med. Sc., N. Y., Vol. 7.
- Wodsedalek, J. E. 1917. Five years of starvation of larvae. Science (N. S.), 46: 366-367. 64.
- . 1921. Longevity of *Trogoderma tarsale* larvae without food. (Abstr.) Anat. Rec., 20: 222-223. 64.
- Wohlauer, F. 1911. Atlas und Grundriss der Rachitis. Lehmann's Med. Atl., Bd. 10. München. 154 pp., 120 Fig. 109, 142, 143, 146, 147, 158, 170, 233, 256, 267, 282, 322, 367, 385.
- Woltreck, R. 1908. Ueber natürliche und künstliche Varietätenbildung bei Daphniden. Verh. d. Deut. zool. Ges., 18: 234-240. 1 Fig. 27, 58.
- . 1909. Weitere experimentelle Untersuchungen über Artsveränderung, speziell über das Wesen quantitativer Artsunterschiede bei Daphniden. *Ibid.*, 19: 110-173. 18 Fig. (Cf. also *ibid.*, Bd. 21, 1911.) 27, 58.
- . 1911. Ueber Veränderung der Sexualität bei Daphniden. Internat. Rev. d. ges. Hydrobiol. u. Hydrographie, 4: 91-ff. (Abstr. in Biol. Centralbl., 31: 708-712.) 29, 58.
- Wolterstorff, W. 1896. Ueber die Neotenie der Batrachier. Zool. Garten, Bd. 37. (Cited by Kopeć '24.) 77.
- Woltmann. 1916. Wien. klin. Wchnschr. (Cited by Funk '22.) 254, 255.
- Woodbury, R. M. 1921. Statures and weights of children under six years of age. U. S. Dep't Labor, Children's Bureau, Community Child-Welfare Series No. 3. Bureau Publ. No. 87, 117 pp. 84.
- Woronichin, N. 1876. Ueber den Einfluss des Körperbaues, des Ernährungszustandes und des rachitischen Processes auf den Durchbruch der Milchzähne. Jahrb. f. Kinderh., 9: 91-105. 158.
- Wright, R. E. 1922. Keratomalacia in Southern India. Brit. J. Ophth., 4: 164-175. (Cited by Blegvad '24 and Index Med.) 220.

Yarotski—see Jarotzky.

Yudkin, A. M. 1922. Ocular manifestations of the rat which result from deficiency of vitamin A in the diet. *J. Am. M. A.*, 79: 2206-2208. **218, 219.**

——— & Lambert, R. A. 1922. Location of the earliest changes in experimental xerophthalmia of rats. *Proc. Soc. Exp. Biol. & Med.*, 19: 375. **218, 219.**

——— ———. 1922a. Lesions in the lacrimal glands of rats in experimental xerophthalmia. *Ibid.*, 19: 376-377. **218, 219.**

——— ———. 1923. Pathogenesis of the ocular lesions produced by a deficiency of vitamin A. *J. Exp. Med.*, 38: 17-24. 4 pl. **219.**

Yung, E. 1878. Contributions à l'histoire de l'influence des milieux physiques sur les êtres vivants. *Arch. de zool. exp.*, 7: 251-282; 1883, *ibid.*, pp. 31-55. Also in *Arch. sc. phys. nat.*, 1883, 6: 310-312; 1885, 14: 502-522. (Cited by Geddes & Thomson '01.) **77, 80.**

———. 1881. De l'influence de la nature des aliments sur la sexualité. *Compt. rend. Acad. des sc., Par.*, T. 93. (Cited by Geddes & Thomson '01.)

———. 1881a. Der Einfluss des farbigen Lichts auf die Entwicklung der Thiere. *Kosmos*, 10: 107-117. (Abstr. in *Jahresb. d. Anat. etc.*, 1881, pp. 383, 394-395.)

———. 1884. Ueber den Einfluss verschiedener Nahrungsmittel auf die Entwicklung von *Rana esculenta*. *Ibid.*, Bd. II. (?), H. 1, S. 18-34. (Cited in *Jahresb. d. Anat. etc.*, 1884, p. 431.)

———. 1900. De l'influence des facteurs déterminant le sexe. *Rev. de Morale Soc.*, II, No. 5, pp. 88-110. (Cited by Geddes & Thomson '01.)

———. 1905. De la cause des variations de la longueur de l'intestin chez les larves de *Rana esculenta*. *Compt. rend. Acad. des sc., Par.*, 140: 878-879. **318.**

———. 1905a. De l'influence de l'alimentation sur la longueur de l'intestin. Expériences sur les larves de *Rana esculenta*. *Compt. rend. Séances d. 6. Congr. internat. zool.*, Berne (1904); publ. Bâle, pp. 297-314. (Cited by *Jahresb. d. Anat. etc.*, 1906, T. 2. p. 124.) **318.**

———. 1912. Influence d'un jeûne expérimental prolongé sur la longueur de l'intestin chez *Rana fusca* et *Rana esculenta*. *Verh. d. 8. internat. zool. Kongr. Graz* (1910), pp. 602-604. *Jena.* **318.**

———. (Date?) Ueber anatomische Veränderungen infolge fortgesetzter Nahrungsentziehung. *Arch. sc. physiol.*, Genève, T. 10, p. 572. (Cited by Weber '02.)

——— et Fuhrmann, O. 1899 (?). De l'influence d'un jeûne prolongé sur les éléments histologiques de l'intestin chez les poissons. *Soc. helvét. d. sc. nat. Arch. sc. phys. et nat.*, 8: 483-485. (Abstr. in *Physiol. Jahresb.*, 1899.) **317.**

Zabaver, D. 1904. La mort par la soif. Thèse. méd., Lyon. (1903-'04, No. 15, 51 pp.)

Zacharias, O. 1886. Ueber Fortpflanzung durch spontan Quertheilung bei Süßwasserplanarien. *Ztschr. f. wiss. Zool.*, 43: 271-276. **41.**

Zak, E. 1917. Beobachtung an Hemeralopie- und Skorbutkranken. *Wien. klin. Wchnschr.*, 30: 592-595. **216, 221.**

Zalla, M. 1910. Recherches expérimentales sur les modifications morphologiques des cellules nerveuses chez les animaux hibernants. *Arch. ital. de biol.*, 54: 116-126. 7 figs. (Abstr. of orig. in *Riv. patol. nerv. e ment.*, 1910, 15: 211-221.) **185, 198.**

Zander, R. 1879. Die Folge der Vagusdurchschneidung bei Vögeln. *Centralbl. f. d. med. Wiss.*, 17: 99; 113-115. **230.**

Zanier, G. 1896. I. bioplasti di Altmann negli stati di attività e di riposo. *Gaz. d. osp.*, 17: 315-316. **334, 383.**

Zillenbergs-Paul, O. 1909. Fortgesetzte Untersuchungen über das Verhalten des Darmepithels bei verschiedenen funktionellen Zuständen. III. *Mitt. Ztschr. f. Biol.*, 52: 327-354. 1 Taf. **321.**

Zilva, S. S. & Wells, F. M. 1919. Changes in the teeth of the guinea pig, produced by a scorbutic diet. *Proc. Roy. Soc. Lond., Ser. B*, 90: 505-512. 1 pl. **160, 161.**

Zoccoli, F. 1865. Studi sull' inanizione. (Cited by Pagliani '15.)

Zuboff, I. O. 1903. (Changes in the nerve cells of the abdominal sympathetic glands in starvation, with remarks on the importance of these changes in the formation of round ulcer of the stomach; experimental investigation.) Thesis, Yuryev. (*Index Cat.*, S. G. L.) **205.**

Zuntz, E. 1920. Les facteurs accessoires de la croissance et de l'équilibre. *Scalpel*, June 19, No. 25, pp. 10. (*Physiol. Abstr.*, 1921, 5: 556.)

——— L. 1919. Experimentelle Untersuchungen über den Einfluss der Ernährung des Muttertieres auf die Frucht. *Arch. f. Gyn.*, 110: 244-273. **77, 139.**

——— N. 1913. Einfluss chronischer Unterernährung auf den Stoffwechsel. *Biochem. Ztschr.*, 55: 341-354.

———. 1920. Beeinflussung des Wachstums der Horngebilde (Haare, Nägel, Epidermis) durch spezifische Ernährung. Ein Beitrag zur Kenntniss der Sondernährstoffe. *Deut. med. Wchnschr.*, 46: 145-146. (Abstr. in *Ber. ges. Physiol.*, 1920, 2: 529.) **130.**

Zweifel, P. 1900. Aetiologie, Prophylaxis und Therapie der Rhachitis. *Lpz.*, 1888 pp.



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